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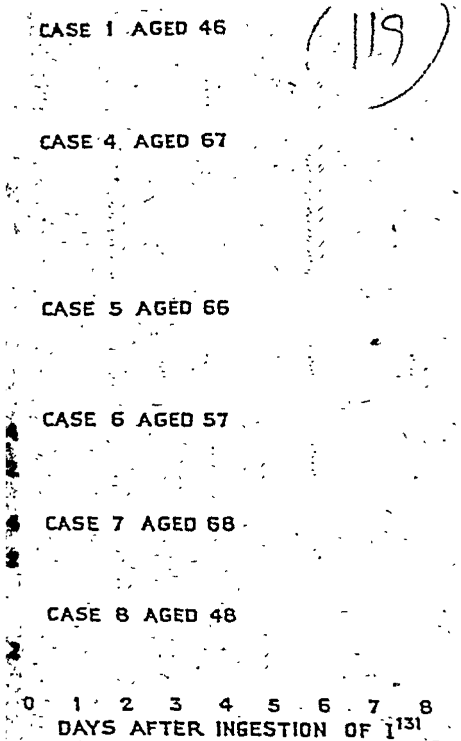

-bound I^{131} in plasma in duplicate tracer experiments in ...p of patients not given any antithyroid drug: stippled 1st experiment; hatched columns, 2nd experiment.

king together of urine collected during the nty-four hours following the tests is partly le for the large values of the standard deviation, e values are undoubtedly influenced by urine normal amounts of radioactivity before the had time to act. There is clearly a large in the daily output of radio-iodine following ation of both drugs. There is, however, no significant difference in daily output between ated and methylthiouracil-treated patients.

RADIO-IODINE IN PLASMA

lioactivity of the blood-plasma, both total and ound, was measured in terms of the percentage gested dose per litre of plasma. The liquid were counted generally to give at least 500 i.e., with a coefficient of variation of less than It is known that the techniques adopted for counting give results reproducible within error of counting, when the total activity in ma at a given time is measured. For measure- Protein-bound radioactivities, involving separate procedures on different specimens of blood, the reproducible generally to within 10%.

lts of the measurements of the protein-bound ity in the plasma in the three groups of patients out in figs. 4–6. In these diagrams, and in –VI, the plasma radioactivity levels have been o the thyroid radio-iodine levels. This has been cause methylthiouracil produced large changes hyroid radio-iodine levels, and the results of the a would not otherwise have been comparable. ma values quoted are therefore the amounts of ive iodine per litre of plasma, expressed as a ge of the total radioactivity in the gland at the h blood sample was taken.

Patients

illustrates the reproducibility of results obtained acer experiments are repeated at an interval of two weeks in untreated patients. The ratio of plasma activities at comparable times during the two tests was calculated, and table III gives the mean values of this rate for both total and protein-bound radioactivity.

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TABLE III—UNTREATED GROUP OF PATIENTS

Mean ratio of total plasma radioactivity (11 samples)	0·90 ± 0·13
Mean ratio of protein-bound radioactivity (11 samples)	0·93 ± 0·18

The standard deviation expressed here includes not only the real variation between plasma samples taken at comparable times in successive tracer experiments but also the counting errors and, in the case of chemical procedures, the pipetting and chemical errors.

Iodide-treated Patients

In patients treated with iodide (fig. 5) there is a considerable fall of the plasma levels in the second tracer experiment compared with the control values in the first experiment, the values of the ratio being set down in table IV.

TABLE IV—PATIENTS TREATED WITH IODIDE

Mean ratio of total plasma radioactivity (15 samples) ..	0·48 ± 0·28
Mean ratio of protein-bound radioactivity (15 samples)	0·52 ± 0·31

Though the protein-bound radioactivity comprises the major portion of the total activity, the standard deviatio for these measurements is higher than for the total plasm radioactivity measurements. This is partly because greater error in measurement and partly because th proportion of protein-bound iodine varied somewhat from patient to patient. Insufficient evidence is available

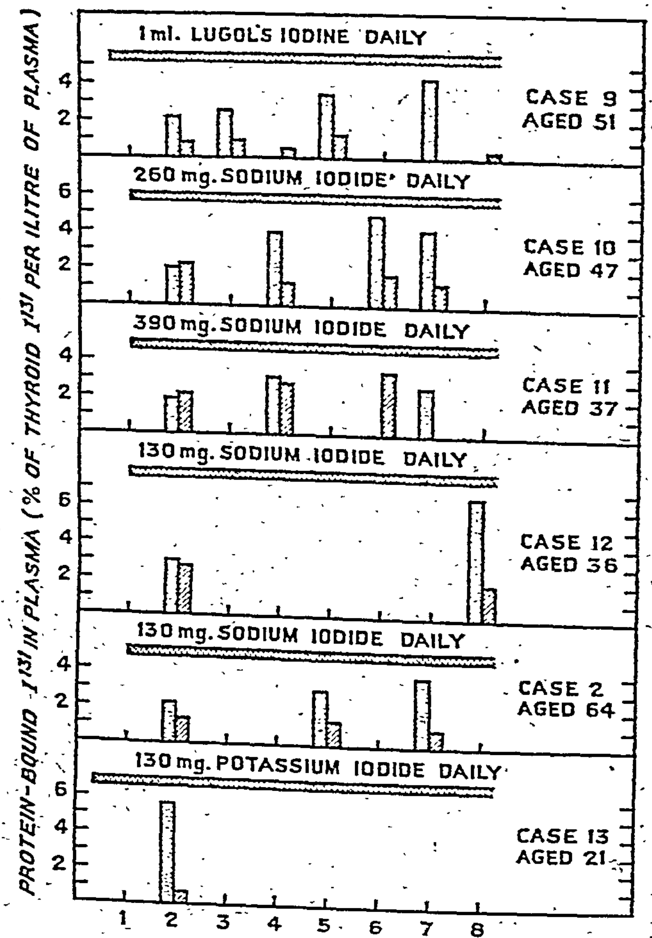

Fig. 5—Protein-bound I^{131} in plasma in duplicate tracer experiments in 4 patients given sodium iodide, 1 patient given Lugol's iodine, and 1 patient given potassium iodide during 2nd experiment: stippled columns, 1st experiment; hatched columns, 2nd experiment.

in our experiments to give a firm explanation of these variations.

The ratios cited above for the effects of iodide on plasma radioactivity include all the observations on plasmas [illegible] later than twenty-four hours after giving the I131 [illegible] o shows clearly that the values taken only one day after the start of the iodide (I^{127}) administration are less influenced than later plasma values. This is one reason for the large values of the standard deviation cited for these figures.

The ratios worked out using only plasma taken two days after the drug or later—i.e., three days or later after giving the tracer I^{131} dose—are shown in table V.

TABLE V—PLASMA RADIOACTIVITY TWO DAYS OR MORE AFTER TREATMENT WITH IODIDE

Mean ratio of total plasma radioactivity (9 samples)	0·36 ± 0·10
Mean ratio of protein-bound radioactivity (9 samples)	0·39 ± 0·19

It will be noted that in one case (case 11) in fig. 5 a reduction in plasma radioactivity following administration of iodide was not observed. These values were, however, included in the mean ratios cited above. In the 5 other patients there was a significant reduction in plasma radioactivity after the administration of iodide.

Methylthiouracil-treated Patients

The plasma radioactivity in the methylthiouracil-treated patients (fig. 6) showed less change compared with the control values; in fact the radioactivity observed was about proportional to the total radioactivity of the gland at the time the blood was taken. The ratios for this group are given in table VI.

TABLE VI—PATIENTS TREATED WITH METHYLTHIOURACIL

Mean ratio of total plasma radioactivity (13 samples)	1·04 ± 0·18
Mean ratio of protein-bound radioactivity (12 samples)	0·97 ± 0·18

The ratios obtained when the calculations are restricted to samples of blood taken after forty-eight hours from the start of the administration of the drug are shown in table VII.

TABLE VII—PLASMA RADIOACTIVITY TWO DAYS OR MORE AFTER ADMINISTRATION OF METHYLTHIOURACIL

Mean ratio of total plasma radioactivity (7 samples)	0·96 ± 0·20
Mean ratio of protein-bound radioactivity (6 samples)	0·88 ± 0·20

There is a suggestion, therefore, that the relative blood level may also be depressed by methylthiouracil after some time; but this is uncertain, and it is clearly much less than when iodide is used.

SUMMARY OF RESULTS

Iodide administered in the quantities described, after the peak of the uptake curve has been passed, has little influence on the rate of fall of the thyroid radio-iodine level, but does depress the level of radioactive thyroid hormone in the plasma. By contrast, the administration of methylthiouracil after the peak causes an increased rate of fall of thyroid radioactivity, but the plasma dioactivity remains unchanged relative to the thyroid-level. Finally, the urinary excretion of radio-iodine is ased by both iodide and methylthiouracil.

Discussion

ioactive iodine administered orally as sodium is rapidly absorbed into the blood-stream, from it is then removed mainly by the thyroid gland the kidneys. In untreated thyrotoxic patients 80% of the radio-iodine is taken up by the thyroid a few hours, and the greater part of the remaining excreted in the urine. The radio-iodine taken up thyroid rapidly enters into organic combination, radioactive monoiodotyrosine, diiodotyrosine, roxine (Taurog et al. 1950). By the time the take has been reached, the gland has already to liberate radioactive hormone into the blood. The level of radioactive hormone in the plasma nues to rise for several days, after which it usually reaches a plateau (Pochin 1950). This hor in the tissues, where it is eventually liberating radio-iodide. This liberated iodi the cycle again, being divided between t the kidneys in the same ratio as before.

The thyroid radio-iodine curve can be div into an uptake phase and a release ph here with the effect of drugs administer release phase. The shape of the curve i due in the main to the resultant of two o release of radioactive hormone, which ten the gland radioactivity; and (2) the reac the thyroid of radio-iodide from broken hormone, which tends to increase the gland. When methylthiouracil is administered du phase it prevents the synthesis of thyroid suppresses the reaccumulation in the gl iodide liberated by this breakdown of h tissues. The gland radioactivity therefo rapidly than it would otherwise do, a iodide not converted into protein-bound fo in the urine. The fact that there is no subst in the plasma-hormone radioactivity administration of methylthiouracil sugg increase in the rate of fall of the gland r not associated with an increased rate of rele hormone from the gland. While this

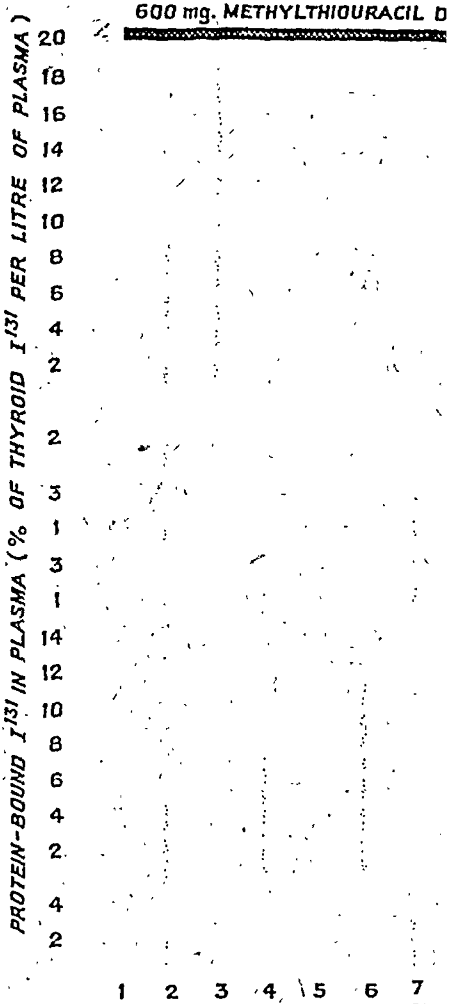

Fig. 6—Protein-bound I^{131} in plasma in duplicate trace 6 patients given methylthiouracil during 2nd exper columns, 1st experiment; hatched columns, 2nd

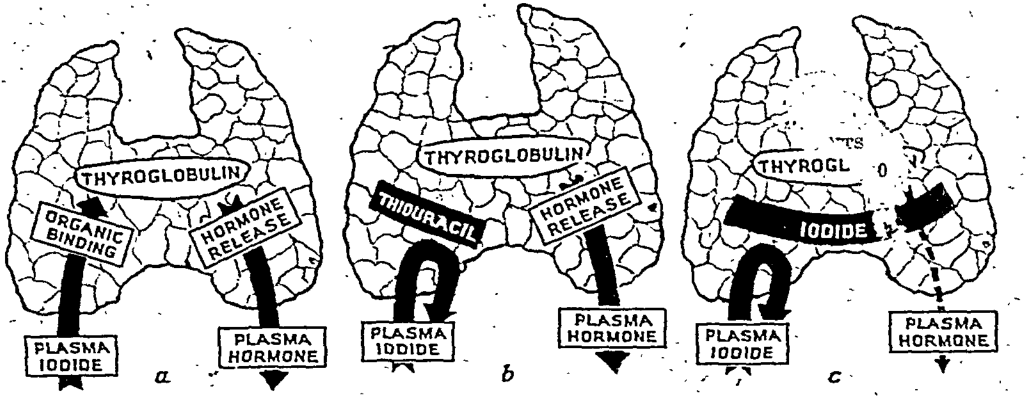

Fig. 7—Site of action of thiouracil and sodium iodide in thyrotoxicosis:

(a) In the untreated patient radioactive iodine is removed from the plasma by the thyroid and rapidly bound into an organic state, being stored in the gland as thyroglobulin. Subsequently the thyroglobulin is broken down, liberating thyroid hormone, which is secreted into the blood-stream.

(b) The thiouracil group o compounds block the organic binding of iodine with the result that radio-iodide picked up by the thyroid cannot be stored and is therefore rapidly returned to the plasma unchanged. The release mechanism is, however, not affected; hence hormone synthesised before the start of thiouracil therapy is secreted into the blood-stream until the supply of hormone in the gland has been exhausted.

(c) A possible way in which iodides may act in thyrotoxicosis by blocking both the organic binding of iodide and the release of preformed thyroid hormone. The arrow showing the release of thyroid hormone has been drawn as an interrupted line to indicate that the block is probably incomplete.

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e produced by the thiouracil drugs. In both
here is an increase in the urinary excretion of
dicating that the reaccumulation of radio-iodide
roken-down hormone has been suppressed. With
thiouracil this increased urinary excretion is
ted with an increased rate of fall in thyroid
tivity, whereas with sodium iodide there is no
decrease of thyroid radioactivity. In addition
sma radioactive hormone levels are lowered after
ministration of iodides. Our findings would be
ent with a mechanism whereby the sodium iodide,
suppressing the reaccumulation of radio-iodide,
ows the release from the thyroid of preformed
tive thyroid hormone, thereby preventing any
e in the rate of fall of gland radioactivity.
onsequence of the diminished delivery of radio-
thyroid hormone to the blood, the radioactive
ne in the blood is not replaced at a rate sufficient
mpensate for its breakdown, and the plasma
tivity levels therefore fall.

nterpretation of these effects is not easy without
dditional information that would be given by
measurements of both the radioactive and
oactive iodine compounds in the plasma

tempting to assume that the high iodide level in
sma reduces both the rate at which the iodide is
sised into thyroid hormone and the rate at which
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planation of the well-known clinical fact that the
tic effect of iodide is more rapid than that of
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body would be decreased immediately, whereas
case of thiouracil the stock of hormone in the
has first to be exhausted before the supply to the
s affected. The suggested mode of action of these
is shown diagrammatically in fig. 7.

fact that no significant change was observed in
te of fall of the level of radioactive iodine in the
when large doses of iodide were given, seems to
t that there is at least an approximate compensa-
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iodide from hormone breakdown and the inhibition
release of the radioactive thyroid hormone from
and.

e must be taken, however, in assuming that the
iour of I^{131} accurately indicates the behaviour of the normal iodine atom when the iodine cycle is disturbed by the administration of large amounts of inactive iodide. For example, if appreciable quantities of the newly administered I^{127} were synthesised into thyroid hormone in the gland, the specific activity of the gland hormone would decrease. If the gland, therefore, could secrete a fixed quantity of the hormone per unit time into the plasma, the amount of radioactive hormone put out by the gland would decrease. This possibility cannot be eliminated with certainty until more complete chemical analyses of the active and inactive components of the iodine cycle are available. Nevertheless it should be remembered that the clinical remission shown by patients receiving I^{127} suggests that the output of thyroid hormone is in fact decreasing.

The possibility was also considered that the high plasma-iodide level might in some way have increased the rate of breakdown of the thyroid hormone peripherally and thereby have increased the rate of excretion. To test this possibility measurements were made of the rate of disappearance from the plasma of biologically synthesised radioactive thyroid hormone injected into two groups of thyroidectomised rabbits. One group was given large doses of iodide, and the other was fed on a low-iodine diet. These measurements showed no significant difference in the rate of decrease of plasma radioactivity in the two groups. We conclude therefore that a peripheral effect of iodides of this nature probably does not contribute significantly to the results described with thyrotoxic patients.

In conclusion, therefore, it can be stated that the experimental results indicate that large doses of I^{127} do reduce the rate at which the radioactive hormone is lost from the gland to the plasma. This may point to a real reduction in hormone output from the gland when the plasma-iodide level is high. The possibility, however, that changes of specific activity of the hormone play an important rôle has not been entirely eliminated.

Summary

Tracer experiments using radioactive iodine (I^{131}) were made in duplicate on three groups of thyrotoxic patients. One group was given no drugs and was used as a check on the reproducibility of the results. A second group was given methylthiouracil, and the third group sodium iodide, during the second tracer experiment. The drugs were administered in each case after the peak uptake of the radio-iodine in the gland had been passed.

The rate of fall of the gland radioactivity was much increased by the administration of methylthiouracil but was unaffected by sodium iodide. At the same time the radioactivity in the plasma was substantially lower after iodide had been given than after methylthiouracil. The urine output of radioactive iodine was increased by both drugs.

It is suggested that high plasma-iodide levels, besides blocking the organic binding of I^{131} in the gland, an action similar to that of methylthiouracil, also slow down the release from the gland of preformed radioactive thyroid hormone. This probably indicates a real reduction in hormone output from the gland, though a complete interpretation of the results is not possible without a knowledge of the specific activities of the iodine compounds present in the cycle.

We are greatly indebted to Prof. E. J. Wayne for permission to undertake these studies on patients under his care, and for his interest and criticism. We also wish to thank Dr. Joyce Burke, Dr. A. G. Macgregor, and Dr. D. R. Wood, for their help, and Miss L. Fearn, Miss L. Mann, Mr. E. Salvin, Mr. D. Gow, and Mr. L. Leeming for technical assistance.

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EFFECT OF INDUCED VASCULAR HYPOTENSION ON THE LIVER

ALTERATIONS IN APPEARANCE AND CONSISTENCE

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The technique of controlled vascular hypotension in surgery is fashionable, and has the sanction of the following argument. The level of the systemic arterial blood-pressure is immaterial, provided that adequate capillary circulation exists; this is ensured when the pressure at the arteriolar end of the capillary exceeds the sum of the venous pressure and the colloid osmotic pressure of the plasma, a total of about 32 mm. of Hg in normal man (Landis 1930). Arterial pressures in excess of 32 mm. are expended solely in overcoming the peripheral arteriolar resistance, which stands guard, as it were, between the heart's excess and the capillary bed. It follows that if the arteriolar resistance is removed, a systolic pressure a little in excess of 32 mm. will suffice for tissue requirements (Griffiths and Gillies 1948).

It is agreed by all that such a procedure reduces the margin of safety. There is no reserve of pressure to increase the rate of capillary flow in response to anoxæmia, and a brief anoxic episode, well borne by a normotensive patient, will not be tolerated in the presence of profound hypotension. But it is granted, grudgingly perhaps, that although the bounds of physiological rectitude are approached by this technique, they are not exceeded where primary capillaries receiving arterial blood are considered.

THE BLOOD-SUPPLY OF THE LIVER

The liver is in different case, and a consideration o anatomy and physiology of its blood-supply will
show that a higher critical level of hypotensi
expected for the liver than for other tissues;
this level and 32 mm., the local circulati
deficient in the liver, in spite of adequate
circulation elsewhere.

Hepatic sinusoids receive blood from two s
hepatic artery and the portal vein, both of
capable of wide functional variation to suit
of quiet digestion or violent stress. Eithe
capable of supporting hepatic function in the
the other (Seneviratne 1949), as in the case
fistula (McIndoe 1928), or after excision of the
(Child et al. 1952) or ligation of the hepatic
portal hypertension in Laennec's cirrhosis
et al. 1949, Reinhoff 1951, Gray 1951). No
hepatic artery supplies up to 20% of the to
inflow at a constant high oxygen-tension (95%
(Blalock and Mason 1936), but the quantit
by this route is variable, and decreases du
lation of the sympathetic nerves in the hep
(Burton-Opitz 1912).

The liver sinusoids are a primary set of cap
the hepatic-artery blood, but a secondary s
laries for the portal blood. The oxygen c
made by the portal blood depends upon the
through the primary capillary net in the mu
brane of the intestinal tract and upon the oxy
there. Barclay and Bentley (1949) and Ba
(1951) have shown that during sympathetic s
arteriovenous channels open in the submucos
the stomach, the capillary net is by-passed, and
venous blood becomes arterial in character
oxygen saturation of 91% instead of 74%. Th
sympathetic stimulation, responsibility for t
supply to the liver is shifted from the meag
artery to the stout portal vein, by way of art
channels in the submucosa. It might be sup
the reverse would occur in the presence of sy
paralysis. Arteriovenous channels in the
remain closed, and blood would take the lo
through the mucosal capillaries, arriving at the
relatively deoxygenated state. The hepatic arte
be dilated, and contributing its maximum (i.e
to the hepatic inflow.

Under conditions of sympathetic paralysis
blood-pressure it is possible to imagine a point
the blood-flow is so slow that a high degree of
desaturation occurs in the intestinal capillaries,
oxygen tension of the blood in the portal vein
as low as that of the blood in the hepatic vein (M
1937). The liver will then depend upon the
artery for its entire oxygen supply. If the flow
the hepatic artery should be inadequate for t
needs of the liver, local tissue anoxia will occu

Shorr et al. (1945, 1948) have shown th
depressor material (V.D.M.), a substance that h
identified with ferritin, a protein linked wi
(Granick 1951), is formed in the liver under
conditions, and that it is inactivated by its
origin under aerobic conditions. It might be
that the anoxic level at which reversal of the
hepatic V.D.M. mechanism took place would be
by a simultaneous local vasodilatation in the liv
If sufficiently intense, this vasodilatation might
the colour and size of the liver to such an extent
detected by the naked eye. Such changes ha
observed in animals; hepatic engorgement an
soidal dilatation were found in rabbits, guineap
rats exposed to low oxygen-tensions for long
(Campbell 1927, 1928).

STUDY OF HEPATIC CHANGES

Observations were therefore made on the mac
appearance of the livers of 17 patients durin

operations under conditions of controlled otension to find out whether any gross to be seen at low blood-pressures. Patients or liver disease were excluded from the erential epidural block—i.e., sympathetic , but not motor, block—was induced by method under thiopentone and nitrous oxide/ sthesia, and the upper level of analgesia was the second thoracic segment or higher. The were delivered through a large-bore endo- in the proportions of 1 part oxygen to 2 s oxide at a high-rate of flow throughout the The blood-pressure was allowed to fall to its l during the early stages of the operation in (Bromage 1951), but if the systolic pressure 40 mm. it was corrected with a small dose of etamine (' Methedrine ') or *l*-noradrenaline. was inspected for colour and teneness of the l the surgeon was asked to palpate the organ ote its degree of flaccidity or turgidity. A uantity of vasopressor drug was then given ously—either 5–7 mg. of methedrine, or 50–200 oradrenaline as a continuous infusion at the rate g. per minute. After the systolic pressure had 70 mm. or higher, the liver was again inspected pated. The cases in this series were distributed five surgeons, whose lack of bias was encouraged ping them in ignorance of the purpose of the ation for as long as possible.

RESULTS

patients there was no detectable change in the ance or consistence of the liver after raising the ressure from low to normal levels.

he remaining 14 patients there were definite s. With a systolic pressure of 60 mm. or less, the ppeared darker than normal; the rich-brown darkened and developed a slaty shade of grey. raising the blood-pressure for some minutes, the r brown of the normal liver returned; the ce in colour was rather like that between plain lk chocolate. Sometimes a marbled-pink network be made out on the surface of the liver as each lobule became edged round with pink.

χ^2 test may be applied to the results for the two mous variables of blood-pressure and liver colour. pplying Yates's correction for continuity (Fisher and 943), $\chi^2_c = 20{\cdot}5$, n = 1. The chance of arriving at this or χ^2 on a basis of "no correlation" would be less ne chance in a thousand similar trials. Therefore the tion of colour change in the liver and falls of systolic ressure to 50–60 mm. is highly significant.

tence

consistence of the liver was changed in 11 patients; other 6 no change was felt. With systolic pressures en 45 and 60 mm., the surgeons described the livers ling either normal to the touch or definitely and rubbery. When the consistence changed at pressures, a liver that had been described as normal feel flabbier, and one that had been turgid would to a normal consistence. In some cases fine les appeared in the peritoneum on the anterior e of the liver, like those in the peritoneal coat of terus after cæsarean section—a sure indication he underlying organ has decreased in bulk. In 3 6 patients in whom noradrenaline was used as the r agent, the blood-pressure was allowed to fall a d time and in each case swelling and darkening of ver recurred. In these patients, by careful adjust- of the noradrenaline drip, it was possible to main- he systolic pressure at a steady level between 60 0 mm. for some time. So long as the pressure ned even slightly above 60 mm. the liver retained its normal appearance, but a fall to 50 mm. was sufficient to change the colour and consistence.

CHANGES IN APPEARANCE AND CONSISTENCE OF THE LIVER IN RESPONSE TO ALTERATIONS OF BLOOD-PRESSURE

Case	Age (yr.)	Resting blood-pressure (mm.Hg)	Low blood-pressure		Pressor drug	Raised blood-pressure	
			Blood-pressure (mm.Hg)	Liver appearance		Blood-pressure (mm.Hg)	Appearance of liver
1	37	125/80	50/30	D, S	m	100/70	L, S
2	27	120/80	55/35	D, T	m	110/80	L, S
3	56	190/100	60/40	D, T	m	120/80	L, S
4	69	120/70	58/28	D, S	m	102/55	L, S
5	62	125/70	60/40	L, S	m	110/75	L, S
6	48	130/70	45/30	D, T	m	78/58	L, S
7	69	170/105	60/40	D, S	m	70/45	L, S
8	67	140/85	35/?	D, S	m	75/45	D, S
9	57	165/90	55/35	L, S	none	80/60	L, S
10	66	145/90	45/30	D, T	n-a	100/80	L, S
11	61	150/90	55/40	D, T	n-a	80/60	L, S
12	34	120/75	58/40	D, T	n-a	120/90	L, S
13	63	120/80	50/?	D, T	m	70/?	L, S
14	63	160/85	58/40	D, T	n-a	120/85	L, S
15	65	170/85	55/35	D, T	n-a	120/80	L, S
16	39	140/80	55/?	D, T	m	105/70	L, S
17	51	120/80	45/30	D, T	n-a	75/55	L, S

D = dark; T = turgid; L = light; S = soft;
m = *d*-methylamphetamine (' Methedrine ');
n-a = *l*-noradrenaline.

Applying the χ^2 test to the degree of correlation between low blood-pressure and change of consistence, $\chi^2 = 13{\cdot}43$. With one degree of freedom, $p = .<0{\cdot}001$. Therefore the association is highly significant.

The results are summarised in the table. The normal liver is described as "light" and "soft," and the abnormal organ, manifestly the seat of local anoxic vasodilatation, as "dark" and "turgid."

DISCUSSION

It is unlikely that the turgor and darkening of the liver, seen when the systolic pressure was below 60 mm. was caused by anything other than local V.D.M. release in response to local tissue hypoxia. Contraction of a sphincter in the hepatic veins has been invoked as an explanation of increased intrahepatic pressures, but no such muscular sphincter has been demonstrated in man, despite assumptions that a hepatic "sluice mechanism" exists (Katz and Rodbard 1939). Moreover, the action of this hypothetical sphincter was supposed to account for changes caused by sympathetic stimulation—not sympathetic paralysis. Although no measurements of cardiac output were made in this series, a watch was kept for adequate capillary filling in other tissues. No great changes were found in the arteriolar-capillary refill-times in the skin, and it would be difficult to explain the obvious local hepatic changes by a fall in cardiac output and generalised vasodilatation.

A vasopressor drug such as methedrine or noradrenaline may counteract hepatic anoxia under these conditions by its generalised vasopressor effect and by raising the perfusion pressure through the liver, or by reopening arteriovenous channels in the intestinal wall thus increasing the oxygen tension in the portal vein. The first possibility is the more probable; for Bearn et al. (1951) have shown that, while splanchnic vascular resistance is decreased by adrenaline, it is slightly increased by noradrenaline. As noradrenaline was used in 5 patients whose livers changed quite definitely from dark and turgid to light and soft, it seems that here at least arteriovenous anastomoses played no part in improving the oxygenation of the liver, and that recovery was produced entirely by the increased perfusion pressure.

The critical level at which liver changes took place was surprisingly constant in this series, for the resting blood-pressures varied between 120/75 and 190/100. It is possible that with a larger series, and with quantitative methods of measuring transhepatic blood flow, a higher critical blood-pressure might be found in hypertensive patients. The critical threshold would be further raised by anything tending to increase local hepatic anoxia, such as anoxæmic anoxia from any cause, or existing hepatic disease (Kaufman et al. 1950). Conversely the threshold would be lowered by factors increasing hepatic oxygenation (Frank et al. 1946, Delorme 1951). It follows that controlled vascular hypotension should be used with extreme caution, if at all, in any patient with diminished hepatic function; when it is used, a clear airway and adequate oxygenation should be guaranteed throughout.

It may be argued that, despite this demonstration of local hepatic anoxia at systolic pressures below 60 mm., many patients have been kept at lower levels for a long time during controlled vascular hypotension, and have suffered no apparent harm: *experientia docet.* That is so, but it is possible that these patients have suffered occult liver damage from the temporary hepatic hypoxia (Delorme 1951), and that they will fall victims to hepatic disease more readily in the course of time. Watch should be kept for the delayed onset of hepatic disease in patients who have been submitted to prolonged vascular hypotension. In the meantime, 60 mm. should be regarded as the lowest permissible limit for the systolic pressure in hypotensive techniques, until a lower figure is proved safe.

SUMMARY

The vascular hypotension induced by sympathetic block may produce local hypoxia in the liver before other tissues are affected. This hypoxia may cause vasodepressor material to be released in the liver, producing local vasodilatation.

Observation of 17 livers during laparotomy under high epidural spinal block supported this suggestion. In 14 patients the liver appeared cyanosed at systolic pressures between 45 and 60 mm. of Hg, although tissues elsewhere were well oxygenated. In 11 the liver became turgid and rubbery to the touch at systolic pressures between 45 and 60 mm. These changes were reversed when the blood-pressure was raised by methedrine or noradrenaline.

Occult liver damage may result from this temporary hypoxia, and the systolic pressure should not be allowed to fall below 60 mm. which was found to be the critical figure for the obvious changes in this series.

I wish to thank the following surgeons for their patience and help in the observation of hepatic changes at operation: Mr. D. A. Langhorne, Mr. D. G. Martin, Mr. R. Brook, Mr. B. L. Williams, and Mr. W. S. Chapman. My thanks are also due to Mr. Nigel Cridland for his statistical advice.

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EFFECT OF HYPOTENSION-PRO
DRUGS ON THE RENAL CIRCUL

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Paton and Zaimis (1949) showed that in animals pentamethonium has a blocking act nomic ganglia, similar to that of tetraethy (T.E.A.) salts but of greater intensity an (Paton and Zaimis 1948a and b). In man T.E. a moderate fall in blood-pressure, acco tachycardia and increased blood-flow through and feet (Lyons et al. 1947). Arnold and (1949), who compared the clinical effects chloride and pentamethonium iodide (C5) in hypertensive persons, found C5 to be consid potent and to have a more prolonged action i blood-pressure and in increasing peripheral They observed postural hypotension occu $1^1/_2$ hours after its injection. These findings firmed by Burt and Graham (1950), who rapid and long-continued increase in blood-flo temperature in the lower limbs after the inj

The effective renal blood-flow is the amou in cubic centimetres per minute that circulat the functional renal tissue, measured by the or *p*-aminohippurate (P.A.H.) clearance (Gol Chasis 1944). In view of its reduction in hy and of the increasing use of C5 and other compounds in the treatment of hypertensi decided to study the effect of C5 on the renal in normal and hypertensive people. Later, the results obtained with C5, the effects o hypotensive agent—hydrazinophthalazine hyd ('prep. 5968,' Ciba), were also investigated.

Lyons et al. (1947) have shown that the effe blood-flow, as determined by the P.A.H. cleara significantly changed after the injection of T.E. normal or hypertensive people unless there is a lowering of the blood-pressure; yet Aas an (1949) reported a reduction in effective renal and glomerular filtration-rate in normal per the intravenous injection of T.E.A. bromide significant fall in the blood-pressure. It was to renal vasoconstriction.

TECHNIQUE

The renal circulation was investigated by mination of inulin and P.A.H. clearances in n hypertensive subjects.

Clearances were tested by the method of Smith et and inulin and P.A.H. were estimated by the described by Dick and Davies (1949). Urine wa through an indwelling catheter, and the bladder w out with sterile water and air at the end of each period.

TABLE I—RENAL CLEARANCES IN NORMAL PE

—	Range
In a group of 3 persons:	
Glomerular filtration-rate (ml. per min.)	122–134
Effective renal plasma-flow (ml. per min.)	646–706
Effective renal blood-flow (ml. per min.)	1218–1418
Filtration fraction	0·18–0·20
Renal resistance (absolute units) ..	5315–7[illegible]14
In a group of 14 persons:*	
Glomerular filtration-rate (ml. per min.)	119–174
Effective renal plasma-flow (ml. per min.)	540–817
Effective renal blood-flow (ml. per min.)	981–1483
Filtration fraction	0·18–0·30

* Normal values established by Davies (1951).

$$\text{Filtration fraction} = \frac{\text{Glomerular filtration-rate}}{\text{Effective renal plasma-flow}}$$

periods lasted 10–20 minutes. In all the observa- ontrol clearance periods were estimated before the njected, and at least two subsequently. All the ns were made with the person lying in bed at an out 30°.

in clearance was assumed to represent the glo- ration-rate, and that of P.A.H. the effective renal . The effective renal blood-flow was calculated fective renal plasma-flow and venous hæmatocrit. arance figure cited represents the mean of two clearance periods. The periods after the injection d from those available during the greatest hypo- onse, usually immediately after the injection of what later after the injection of prep. 5968 owing d action.

od-pressure was measured at short intervals after injection of the hypotension-producing e mean arterial blood-pressure was calculated stolic pressure plus one-third of the pulse

l resistance was calculated from the formula

$$R_k = \frac{Pm}{E.R.B.F.} \times 1332$$

ssed in absolute units as dynes cm.$^{-5}$ sec. al. 1944) where R_k = renal resistance, Pm = rial pressure, and E.R.B.F. = effective renal (ml. per sec.). The mean pressure is converted per sq. cm. by the factor of 1332.

EFFECT OF C5 ON RENAL CIRCULATION IN NORMAL PEOPLE

nd f C5	G.F.R. (ml. per min.)	Change in G.F.R. (%)	E.R.B.F. (ml. per min.)	Change in E.R.B.F. (%)	Arterial blood-pressure (mm. Hg)	Mean arterial blood-pressure (mm. Hg)	Change in mean blood-pressure (%)	R.R.	Change in R.R. (%)
re 50 .V.	134 126	−6	1418 1114	−21	145/80 130/85	102 100	−2	5755 7145	+24
ro 35 I.V.	131 96	−27	1282 1069	−17	115/70 105/65	85 78	−8	5315 5832	+10

G.F.R., Glomerular filtration-rate.
E.R.B.F., Effective renal blood-flow.
R.R., Renal resistance.

RESULTS

nge of values for renal clearances and their in seventeen normal persons are shown in

C5 on Renal Circulation in Normal Subjects

I shows the results in two normal volunteers. l-pressure did not fall to subnormal levels in them, but in both there was a considerable fall ve renal blood-flow after injection of C5. ar filtration-rate was reduced in one case but o significant change in the other. The renal , calculated as shown above, increased in both

C5 on Renal Circulation in Patients with Benign Hypertension

gn essential hypertension a change in the renal n develops before any impairment of renal func- parent (Goldring and Chasis 1944). The early consist of a reduction in renal blood-flow with nce of a relatively normal glomerular filtration- e filtration fraction is increased. The increase esistance which occurs is thought to be produced iction of the efferent glomerular arterioles and Chasis 1944).

TABLE III—EFFECT OF C5 ON RENAL CIRCULATION IN PEOPLE WITH ESSENTIAL HYPERTENSION

Case no.	Dose and route of C5	G.F.R. (ml. per min.)	Change in G.F.R. (%)	E.R.B.F. (ml. per min.)	Change in E.R.B.F. (%)	Arterial blood-pressure (mm. Hg)	Mean arterial blood-pressure (mm. Hg)	Change in mean blood-pressure (%)	R.R.	Change in R.R. (%)
3	Before After 75 mg., I.V.	59 28	−52	572 288	−49	240/125 140/90	163 107	−35	22,854 29,692	+30
4	Before After 50 mg., I.V.	102 53	−48	500 255	−49	235/130 130/95	165 107	−36	26,479 33,145	+25
8	Before After 20 mg. subcut.	116 97	−16	801 573	−28	215/120 180/120	152 140	−8	15,222 19,629	+28

Table III shows the renal clearance in three patients with benign essential hypertension. The range of glomerular filtration-rate before injection of C5 was 59–116 ml. per minute, and of effective renal blood-flow 500–801 ml. per minute. The renal resistance varied from 15,222 to 26,479 absolute units in the three subjects.

In case 8 the hypotensive response was small. In spite of this there was a considerable fall in effective renal blood-flow. The glomerular filtration-rate was reduced to a lesser extent, and renal resistance was increased.

In the other two patients a considerable fall in blood-pressure, but not to subnormal levels, was obtained. This was accompanied by a relatively greater fall in renal blood-flow and glomerular filtration-rate, and the renal resistance was increased.

Effect of C5 on Renal Circulation in People with Malignant Hypertension

Changes in the renal circulation in patients with malignant hypertension are greater than in those with essential hypertension. There is considerable reduction both in glomerular filtration-rate and in effective renal blood-flow. The renal resistance is greatly increased.

Table IV shows the results of four observations in three people with malignant hypertension accompanied by papillœdema, retinal hæmorrhages, and exudates. They all showed gross impairment of renal function. The range of glomerular filtration-rate before injection of C5 was 29–68 ml. per minute, and of renal blood-flow 177–588 ml. per minute. The renal resistance was 26,096–77,700 absolute units.

TABLE IV—EFFECT OF C5 ON RENAL CIRCULATION IN PEOPLE WITH MALIGNANT HYPERTENSION

Case no.	Dose and route of C5	G.F.R. (ml. per min.)	Change in G.F.R. (%)	E.R.B.F. (ml. per min.)	Change in E.R.B.F. (%)	Arterial blood-pressure (mm. Hg)	Mean arterial blood-pressure (mm. Hg)	Change in mean blood-pressure (%)	R.R.	Change in R.R. (%)
5	Before After 50 mg., I.V.	29 17	−41	302 212	−30	190/145 150/120	160 130	−19	42,624 49,474	+14
	Before After 100 mg., I.M.	37 31	−16	340 226	−34	230/160 180/150	183 160	−13	42,764 53,452	+25
6	Before After 10 mg., I.V.	32 22	−31	177 123	−30	245/140 210/125	175 153	−13	77,700 97,045	+25
7	Before After 15 mg., subcut.	68 42	−38	588 474	−19	255/160 200/130	192 153	−20	26,096 25,796	−1

TABLE V—EFFECT OF HYDRAZINOPHTHALAZINE HYDROCHLORIDE (CIBA 5968) *ON RENAL CIRCULATION IN PEOPLE WITH* ESSENTIAL OR MALIGNANT HYPERTENSION

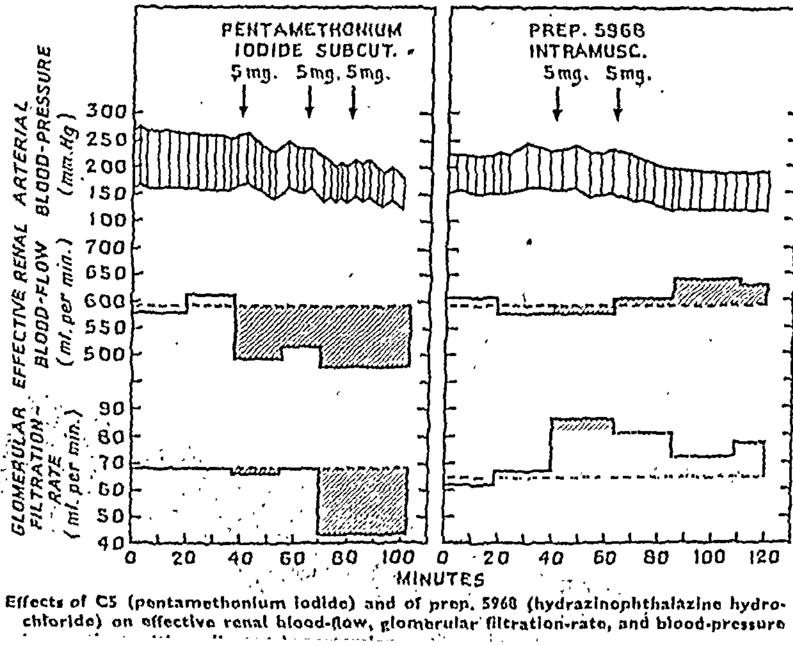
Type of hypertension	Case no.	Dose and route of Ciba 5968	G.F.R. (ml. per min.)	Change in G.F.R. (%)	E.R.B.F. (ml. per min.)	Change in E.R.B.F. (%)	Arterial blood-pressure (mm. Hg)	Mean arterial blood-pressure (mm. Hg)	Change in mean blood-pressure (%)	R.R.	Change in R.R. (%)
Essential	9	Before	78		739		170/120	137		14,836	
		After 5 mg., I.M.	71	−9	1294	+75	160/110	127	−7	7,831	−47
,,	13	Before	54		460		200/130	153		26,467	
		After 7 mg., I.M.	73	+35	1150	+150	195/125	148	−3	10,267	−61
Malignant	5	Before	19		102		235/170	192		150,437	
		After 15 mg., I.M.	21	+11	152	+49	160/110	127	−32	67,665	−55
,,	6	Before	23		113		250/135	173		121,282	
		After 20 mg., I.M.	20	−13	131	+16	210/105	140	−19	84,763	−30
,,	7	Before	66		576		230/160	183		25,391	
		After 10 mg., I.M.	74	+12	645	+12	200/120	147	−20	18,130	−29

A moderate reduction in blood-pressure was obtained with C5 in each patient and this was accompanied by a fall in both effective renal blood-flow and glomerular filtration-rate. Renal resistance was increased in all except one subject in whom there was no significant change.

Results Obtained with Hydrazinophthalazine Hydrochloride

Hydrazinophthalazine hydrochloride (*prep. 5968*) is known to produce renal hyperaemia in man (Reubi 1950) and in dogs (Gross et al. 1950). Table v shows the effect of intramuscular injection of prep. 5968 in five hypertensive subjects, three of whom (cases 5, 6, and 7) had malignant hypertension. In the two people with benign essential hypertension the reduction of the blood-pressure was insignificant; and, although the doses of prep. 5968 were small, there was a considerable increase in effective renal blood-flow. The glomerular filtration-rate was increased in one case and reduced slightly in the other.

In the three patients with malignant hypertension, the reduction in blood-pressure was comparable with that obtained with C5, but in contradistinction the renal blood-flow was increased in each case. Change in the glomerular filtration-rate was inconstant, there being an increase in two cases and a reduction in the third. In all subjects receiving prep. 5968 there was a diminution in renal resistance.



Effects of C5 (pentamethonium iodide) and of prep. 5968 (hydrazinophthalazine hydrochloride) on effective renal blood-flow, glomerular filtration-rate, and blood-pressure

DISCUSSION

The accompanying figure compares the effect of C5 and prep. 5968 on the blood-pressure, effective renal blood-flow, and glomerular filtration-rate in a patient with malignant hypertension. Although the fall in blood-pressure was similar on the two occasions, the figure shows the striking contrast in the changes in the renal circulation after the drugs. The fall in effective renal blood-flow after C5 shown in the figure is representative of the change in the other subjects investigated. The rise in effective renal blood-flow after prep. 5968 in this case was small, but renal resistance diminished. The ability to produce this latter change seems to be a desirable property of drugs used in the treatment of hypertension. Thus, although there is a considerable increase in blood-flow through the limbs after injection of C5 (Arnold and Rosenheim 1949, Burt and Graham 1950), the results of the present investigation show that the visceral blood-flow is not necessarily affected in the same way. Davies (1952) has shown that cardiac output may be increased, decreased, or remain unchanged after C5, the response varying in different people; but, when there was a steep fall in blood-pressure the cardiac output fell. In both normal and hypertensive subjects the effective renal blood-flow was reduced after C5, and renal resistance was increased. The increase in renal resistance indicates that renal vasoconstriction accompanies the redistribution of blood induced by the drug. This effect of C5 on the renal circulation differs from that produced by surgi [illegible] after which the renal [illegible] cantly altered, even when the blood-pressure is reduced (Talbott et al. 1943, Foà et al. 1943).

Changes in the renal circulation analogous to those [illegible] been described [illegible] tensive and normal people (Crosley et al. 1950) and after 5-imidazoline hydrochloride ('Priscoline') in normal adults and dogs (Young et al. 1950). Both drugs increase the peripheral blood-flow through the limbs, and probably renal vasoconstriction occurred which reduced the effective renal blood-flow.

Reduction in renal blood-flow is known to follow syncope or fright and administration of adrenaline (Smith 1943). The potentiation by T.E.A. of the pressor responses to epinephrine and norepinephrine in cats has been described by St. Clair and Stone (1951), and Paton (1951) recorded adrenaline-like effects after tetraethylammonium bromide and hexamethonium. Grob and Harvey (1950) have shown that drenaline antagonises the effects of C5 on skin-temperature and blood-pressure. Possibly, therefore, adrenaline r a similar substance is responsible for the changes bserved in the renal circulation after the injection of C5.

The foregoing observations are of an acute nature and o not represent the changes in the renal circulation ccuring throughout the day in patients undergoing reatment. In one patient with malignant hypertension nd severely impaired renal function an actual increase in ffective renal blood-flow was observed after an initial ll. This took place after a very small intravenous dose f C5. But a consistent increase in effective renal blood-ow and a reduction in renal resistance were observed fter prep. 5968, thus indicating that hypotension is not n itself responsible for the renal ischæmia following the dministration of the methonium compounds.

SUMMARY

The effect of pentamethonium iodide on the renal circulation has been investigated in normal volunteers and n patients with benign essential and malignant hypertension. The glomerular filtration-rate and effective enal blood-flow are reduced by this drug. The effective enal blood-flow is reduced even when the fall in blood-ressure is small, and the reduction is greater than can e accounted for solely by a lowering of the blood-ressure. Renal resistance is increased, owing to renal asoconstriction.

In hypertensive patients the effective renal blood-flow s increased by administration of prep. 5968, and the lood-pressure is reduced. Change in glomerular filtration-rate is inconstant, and renal resistance is diminished. This seems to be a more desirable effect in the treatment of hypertension.

My thanks are due to Prof. C. H. Stuart-Harris for his constant help and advice in the preparation of this paper and for the opportunity to study his patients, and to Dr. C. E. Davies for constructive criticism. My thanks are also due to Ciba Laboratories Ltd., who supplied the prep. 5968.

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". . . Writing, if not a lost art, seems at times to be a losing one. If editors have any function (and I would not disagree entirely with those who doubt it) it is that of trying to persuade authors that there is no good writing, only good rewriting—that what is worth setting down at all can be done twice as well in half the number of words—only it takes twice as long to do it. Original writing, like tapping a maple tree, is tedious business, but the really slow work, and the hard sugar, come in the boiling down of the sap."—JOSEPH GARLAND, Editor of the *New England Journal of Medicine*, *New Engl. J. Med.* 1952, 246, 801.

TREATMENT OF RHEUMATOID ARTHRITIS WITH BUTAZOLIDINE

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This paper records the effects of a new drug, butazolidine, on 81 patients with rheumatoid arthritis.

INTRODUCTION

The comparative efficacy of amidopyrine in relieving pain in rheumatoid arthritis and other "rheumatic" conditions has been commented upon since its introduction in 1884. Many workers, notably on the Continent, have described its apparent success in relieving rheumatic pain where salicylates, phenacetin, and other analgesics have failed.

The introduction of an injectable form of amidopyrine ('Irgapyrin') was followed by reports of the considerable relief from pain that it gave during acute exacerbations of rheumatoid arthritis. The use of irgapyrin in the clinic at Glasgow Royal Infirmary corroborated these observations, but it was thought that the relief obtained from this preparation was out of all proportion to the amount of amidopyrine given, and it was found that oral administration of amidopyrine, in doses sufficient to produce a similar blood concentration, did not give comparable symptomatic relief. Moreover, after daily injections of irgapyrin, many of the joint swellings were somewhat reduced—a benefit not conferred by oral amidopyrine.

The solvent used for the amidopyrine in irgapyrin is a pyrazolidine derivative, 1 : 2-diphenyl-3 : 5-dioxo-4-*n*-butylpyrazolidine (G 13871 or butazolidine). The pharmacology of this substance has already been investigated by Wilhelmi (1949), who showed that in laboratory animals it acted as a mild analgesic, a moderately powerful antihistaminic, an antiphlogistic, and an antipyretic. Pulver (1950) found that, although there is a close structural relationship between butazolidine and amidopyrine, their behaviour in the animal body is different; amidopyrine is rapidly converted into inactive decomposition products, while butazolidine is only slowly broken down and excreted.

So far as can be ascertained, the analgesic properties of butazolidine alone have not been investigated, and, since its toxicity has been shown to be low, it was decided to give this drug to a series of patients in the acute phase of rheumatoid arthritis.

METHOD AND RESULTS

All the patients selected for treatment fulfilled the following diagnostic criteria for rheumatoid arthritis: (1) acceptable clinical history and picture; (2) polyarthritis; (3) radiological confirmation, or lack of evidence of other joint disease; (4) normal blood-uric-acid level; (5) negative Wassermann and Kahn reactions; (6) negative Widal reaction for abortus fever; (7) negative gonococcal complement-fixation test; and (8) raised erythrocyte-sedimentation rate (E.S.R.) and reduced plasma viscosity. They were all suffering from acute exacerbations at the time of treatment.

The following subjective and objective tests of improvement were used:

Subjective

(1) Pain and tenderness.
(2) Performance:
  Dynamometer readings for power of grip.
  Range of movement voluntarily performed with affected joints.
  Time taken for performance of standard exercises.
(3) Well-being.

Objective

(1) Joint measurements.
(2) E.S.R. and plasma viscosity.
(3) Appearance of joints.

TABLE I—RESULTS AFTER 10 DAYS' TREATMENT

Treatment	No. of cases	Symptomatic		Performance		Objective	
		Improvement	Relapse	Improvement	Relapse	Improvement	Relapse
Butazolidine	41	40 *(97·6%)*	0	40 *(97·6%)*	0	10 *(24·4%)*	0
Saline	40	9 *(22·5%)*	1 *(2·5%)*	8 *(20%)*	0	0	0

The patients were given either daily intramuscular injections of 1·0 g. of butazolidine as a 20% solution, or injections of sterile normal saline. In each case treatment was given for ten days. Treatment was then changed without the patients' knowledge; those previously having butazolidine were given sterile saline and vice versa.

The interphalangeal joints were measured by the 'Wheatsheaf' ring method (Hart and Clark 1951), and the larger joints by ringing them with indelible ink and applying a tape-measure round the ring. It follows that the assessment of improvement in joint swelling was easy in the fingers and very difficult in the larger joints. As has been indicated elsewhere (Currie and Will 1950), variations of up to 0·5 cm. may arise from experimental error, and therefore any changes of less than 0·5 cm. were not regarded as significant. The cases were assessed before treatment, after ten days' treatment, and at the end of twenty days' treatment.

Tables I–III show the results in 81 patients.

DISCUSSION

The difficulties of assessing improvement in rheumatoid arthritis are well known. Efforts were made to "control" this clinical trial of butazolidine by ensuring that patients did not know when they were receiving butazolidine and when saline. The injections of butazolidine usually caused local pain, and care was taken to inject enough saline, when this was being given, to give at least some discomfort at the site of injection.

TABLE III—EFFECT OF TREATMENT ON E.S.R. AND JOINT SWELLING WHERE THESE WERE AFFECTED

Treatment	No. of cases showing								
	Reduction in E.S.R.			Reduction in swelling of large joints			Reduction in total ring count for all 10 fingers		
	1–10 mm. per hr.	11–20 mm. per hr.	Over 20 mm. per hr.	Slight	Moderate	Marked	5–10 sizes	11–15 sizes	Over 15 sizes
Butazolidine..	3 *(7·3%)*	7 *(17·1%)*	0	0	4 *(9·7%)*	6 *(14·6%)*	1	3	1
Butazolidine followed by saline	2 *(4·9%)*	5 *(12·2%)*	0	4 *(9·7%)*	3 *(7·3%)*	0	3	1	0
Saline followed by butazolidine	6 *(15%)*	4 *(10%)*	2 *(5%)*	0	7 *(17·5%)*	7 *(17·5%)*	2	5	1

Of the 81 patients treated with butazolidine, 77 said that their symptoms were relieved—i.e., that their pain was less and that their joints moved more easily. Only 24, however, showed measurable evidence of improvement. All the patients who showed objective signs of improvement also reported subjective improvement. The importance of recognising the subjective nature of performance tests seems to be well shown in the tables. Generally, when a patient feels better he performs better. The number of patients showing objective improvement during this short test seems significantly high; for, while some 30% of patients suffering from rheumatoid arthritis will show spontaneous remission or temporary arrest of the disease over a period of some months, it is difficult to believe that 30% would do so within the three weeks of this trial. Of these 24 patients wit objective improvement, 4 have remained both objectivel and subjectively better (for sixteen, fourteen, eleven, or eight weeks respectively), 11 relapsed within three „ and 9 within twenty weeks.

These limited trials suggest that butazolidine doe produce a marked degree of symptomatic relief i acute exacerbations of rheumatoid arthritis. Moreove the drug seems to have some antirheumatic propert which can reduce periarticular swelling, tenderness, an œdema.

During the administration of the drug, no electrolyt shift was observed in any patient nor was there an evidence of fluid retention or diuresis. The eosinophi count was unaffected, and, in 5 patients whose 17 keto steroid excretion was measured, no significant chang was noted. These investigations were made becaus the benefit given by any drug in rheumatoid arthritis i often suggested to be connected with cortisone or adreno corticotropic hormone activity, but this does not seem t be the case here. Wilhelmi (1951, 1952), however, note a big fall in the eosinophil-count after giving the drug t rats, and he believed that adrenocortical stimulation ma follow the use of butazolidine.

TABLE II—RESULTS AFTER 20 DAYS' TREATMENT

Treatment	No. of cases	Symptomatic		Performance		Objective	
		Improvement	Relapse	Improvement	Relapse	Improvement	Relapse
Butazolidine followed by saline	41	34 *(82·9%)*	6 *(14·6%)*	32 *(78%)*	5 *(12·2%)*	7 *(17·1%)*	0
Saline followed by butazolidine	40	37 *(92·5%)*	0	37 *(92·5%)*	0	14 *(35%)*	0

The drug cannot be just an analgesic, because tha would hardly explain a fall in E.S.R. and a reduction i the joint swelling. Further, when test-doses were give in cases of cephalgia, neuralgia, postoperative pain, pai from trauma, &c., the drug compared poorly with ful doses of aspirin. I have no hesitation in claiming, however, that, as an anodyne in cases of rheumatoid arthritis, butazolidine is quite exceptionally effective.

My thanks are due to Dr. J. W. Macfarlane for placing bed at my disposal while carrying out these trials, and to Pharma ceutical Laboratories Geigy Ltd. for their help and for supplie of butazolidine.

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BENEMID IN THE TREATMENT OF STREPTOCOCCAL ENDOCARDITIS

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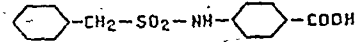
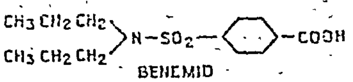
IN a small proportion of cases of subacute bacterial endocarditis the causal organism is highly resistant to penicillin; usually it is a non-hæmolytic *Streptococcus fæcalis* of Lancefield's group D (Robbins and Tompsett 1951). Various antibiotics have been recommended for these resistant cases, but hitherto none has been completely satisfactory. Aureomycin and chloramphenicol have been disappointing; but some patients have been cured with streptomycin, alone or in combination with penicillin (Hunter 1947, Cates et al. 1951), and others have responded to high blood-penicillin levels achieved with the aid of caronamide (Boger et al. 1947, Stuart-Harris et al. 1949).

We report here a case of *Strep. fæcalis* endocarditis treated successfully with large doses of penicillin together with 'Benemid,' a new compound introduced by Boger et al. (1950). Benemid (Sharp & Dohme) is p-(di-n-propylsulphamyl) benzoic acid, and, like caronamide, it temporarily blocks excretion by the renal tubules of such substances as penicillin, p-aminosalicylic acid, and phenolsulphonephthalein. The dose suggested is 0·5 g. six-hourly (2 g. daily), which is much less than the caronamide needed for a similar effect (18–24 g. daily). From the data published benemid seems to have fewer side-effects than caronamide; in particular, there is less nausea and vomiting (Boger and Crosson 1950, Boger et al. 1950). Benemid was first used in this country by Walker and Hunter (1951). The chemical formulæ of the two substances are shown below:



CARONAMIDE



BENEMID

CASE-RECORD

A R.A.F. fighter-pilot, aged 30, was in perfect health until December, 1949, when he suddenly complained of slurring of speech, which rapidly cleared up. This was followed by malaise, pyrexia, and various aches and pains. In February, 1950, he was diagnosed as having rheumatic fever, and he was treated at home with salicylates for two months. In April, 1950, he was admitted to another hospital, where subacute bacterial endocarditis was diagnosed (positive blood-culture), and he was treated with large doses of penicillin and streptomycin, both separately and together (for details see table I). He made an apparent recovery and was discharged in August, 1950.

On admission to St. George's Hospital in September, 1950, he was pyrexial, and there was a loud rough systolic murmur at the apex. A fading Osler's node was present on the left palm. The spleen was not palpable, no red cells were found in the urine, and there was no clubbing of the fingers. Blood-cultures were persistently positive, and *Strep. fæcalis* (group D) was grown from each of them.

TABLE I—DETAILED SUMMARY OF TREATMENT AND FINDINGS

Dates	No. of days	Drug	Dosage		Blood-cultures	Clinical findings
			Daily	Total		
1950 April 17–June 6	51	Penicillin	4–8 mega units	308 mega units	May 6 : sterile	Feeling very well, apyrexial
June 7–June 24	18	Streptomycin	2 g.	34 g.	June 22 : positive	Normal pulse-rate
,, 25–Aug. 6	43	Penicillin	10 mega units	430 mega units	July 5 : sterile	..
July 1–July 31	31	Streptomycin	3 g.	93 g.	,, 12 : sterile	Relapse after 2 weeks without treatment
					From Sept. 10 to 14 : positive	12 cultures were made; 11 were positive and grew *Strep. fæcalis* group D
Sept. 15–Nov. 17	64	Aureomycin	6 g.	384 g.	Oct. 7 : positive	Feeling very well, except for nausea during last two weeks of aureomycin course; apyrexial; normal pulse-rate
Nov. 18–Dec. 1	14	Penicillin (six-hourly)	20 mega units	280 mega units	..	..
1951					Jan. 12 : positive	Relapse after 3 weeks without treatment
Jan. 17–March 7	50	Aureomycin and chloramphenicol (six-hourly)	2 g. āā	100 g. āā	..	Feeling well, apyrexial; normal pulse-rate
March 8–April 10	Patient taking drugs on alternate weeks only as out-patient	Aureomycin and chloramphenicol	2 g. āā	28 g. āā	..	..
					April 11 : positive	Relapse during 4th week and while not taking drugs
April 11–May 2	22	Aureomycin and chloramphenicol	2 g. āā	44 g. āā	April 25 : positive	Feeling very well, painful embolus in finger on April 16
May 3–June 27	56	Penicillin (six-hourly)	20 mega units	1120 mega units	May 17 : sterile	Feeling very well
		Streptomycin	2 g.	112 g.	June 31 : positive	Relapse 3 days after discontinuing therapy
July 5–10 ..	6	Sulphadiazine	(Usual course)	35 g.	July 5 : positive	General malaise, tachycardia, and pyrexia showed that bacteræmia was not controlled; fresh petechiæ regularly
July 11–25 ..	15	Terramycin	3 g.	45 g.	July 17 : positive	
July 26–30 ..	5	Aureomycin and chloramphenicol	2 g. āā	10 g. āā	..	Symptoms controlled, but petechiæ still appearing
Final course July 31–Sept. 27	59 3 56	Benemid six-hourly and penicillin three-hourly	4 g. 20 mega units } 32 mega units }	236 g. 1852 mega units	Aug. 11 : sterile	Feeling very well; petechiæ gone
					Oct. 1 : sterile ,, 2 : sterile ,, 4 : sterile ,, 6 : sterile	Well and working nine months later

TABLE II—HOURLY BLOOD-PENICILLIN LEVELS ACHIEVED WITH THE AID OF BENEMID

Treatment		Blood-penicillin level (units per ml.)			Remarks
Benemid (g.) six-hourly	Penicillin (mega units) three-hourly	1st hr.	2nd hr.	3rd hr.	
1	2½	64·0 25·6	16·0 12·8	16·0 12·8	Blood-urea level 28 mg. per 100 ml., no casts, no albumin
	4	128·0 ..	64·0 32·0	64·0 32·0	

Cardioscopy showed slight left-ventricular enlargement, with systolic expansion to the left auricle. Electrocardiography showed partial right bundle-branch block. The patient's general physical condition was surprisingly good in spite of his long illness, and he was not anæmic (Hb 91%).

Treatment.—Qualitative estimation of the sensitivity of the streptococcus to antibiotics showed that it was highly resistant to penicillin and streptomycin, but very sensitive to aureomycin and to chloramphenicol. The patient was accordingly treated with a large dose of aureomycin (6 g. daily in divided doses for sixty-four days); yet even in the middle of this course a blood-culture was positive. He was later treated with courses of penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, and sulphadiazine, either alone or in various combinations (table I); but the symptoms of bacteræmia were merely suppressed, and he promptly relapsed a few days after each course of treatment. In July, 1951, the streptococcus was found to resist the following drugs up to the following levels:

Penicillin	2·5 units per ml.
Streptomycin	25·0 μg. per ml.
Chloramphenicol	0·5 μg. per ml.
Aureomycin	0·125 μg. per ml.
Terramycin	1·0 μg. per ml.

Finally the patient was treated with penicillin 4 mega units three-hourly (32 mega units daily) and benemid 1 g. six-hourly (4 g. daily) for fifty-nine days. No toxic effects, apart from slight abdominal discomfort, were noted with this dosage of benemid, although it was twice as large as that used by Boger et al. (1950). During this treatment sufficient penicillin was excreted in the urine to reduce Benedict's reagent. The very high blood-penicillin levels achieved are shown in table II, which also shows that there was no evidence of renal damage.

Progress and Follow-up.—During treatment and subsequently, the patient remained apyrexial and blood-cultures were negative. He is now, nine months later, apparently perfectly fit and is working. His cardiac signs remain unchanged, but there is no functional impairment.

DISCUSSION

In this case the causal streptococcus was sensitive in vitro to aureomycin and chloramphenicol, but these antibiotics did not eradicate the infection. The streptococcus was relatively insensitive to penicillin, but the very high blood-penicillin levels achieved with the aid of benemid were sufficient to arrest the disease permanently. This observation is consistent with the view that penicillin is bactericidal, whereas the other antibiotics used are only bacteriostatic.

The scheme of treatment recommended by Cates et al. (1951), using penicillin and streptomycin together, has the disadvantage that large doses of streptomycin may damage the inner ear; and it seems that in combating micro-organisms with a high resistance to penicillin, the use of benemid to raise the blood-penicillin level may be the best course.

SUMMARY

A case of *Strep. fæcalis* endocarditis is described.

It did not respond to large and long-continued dosage with penicillin, streptomycin, aureomycin, and chloramphenicol.

Complete cure appears to have resulted from the high blood-penicillin levels achieved with the aid benemid.

Our thanks are due to Dr. Kenneth Robson, under care the patient was admitted, for permission to and to Dr. Stephen Elek for numerous bac examinations. We are indebted to Dr. William P. director of the medical division of Sharp & Dohme for supplies of benemid; and to Dr. M. M. Nagley, of Park Hospital, who gave us some of his own very limit supplies.

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HÆMATURIA FROM AN UNDETECTED URACHAL TUMOUR

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SURROUNDED by muscle and resting on the mucosa without penetrating it, the walnut-sized conoidal mass bled from time to time into the urachal canal which traversed it. Being a transitional-celled carcinoma, devoid of the usual goblet cells, it produced no "jelly" in the urine to betray its presence. The vesical outlet of the urachus, minute and concealed by a mucosal fold, eluded discovery during seven cystoscopies, and was revealed at the eighth only by the stalactite of blood-clot which depended from it. The diagnosis was delayed for five years. The extenuating circumstances of this humiliating lag may be judged from the following story.

CASE-REPORT

Mr. A was a robust man of 73. He owned two farms remote from Johannesburg, one on either side, and he secured his medical advice in instalments as he passed through the city from one to the other. His boyhood had been marred by two years of terminal hæmaturia from the prevailing bilharzia, but it was fifty years later that he again passed "pure blood." The attack was accompanied by frequency, urgency, and strangury. This he endured for four weeks on his Zeerust farm before coming to Johannesburg for advice and relief. The consultation took place on Oct. 29, 1945. The gross hæmorrhage had ceased, but the urine contained a heavy sediment of red and white cells and bacteria. A few days' treatment ameliorated the inflammation, and a satisfactory investigation was carried out; but it disclosed no abnormality in the urinary tract with the exception of an early trilobed hypertrophy of the prostate. It was concluded that the bleeding had been caused by an intense cystitis originating in a prostatitis or even in the rupture of a small abscess in the gland.

Twelve months passed without further incident, and a routine examination, including cystoscopy and pyelography, gave the same negative results. The prostate was causing no trouble and there was no residual urine at all. It was not until April, 1950, nearly five years after the original attack, that the bleeding began again. As before, there was an inflammatory element, but it was overshadowed by the hæmaturia, which was at times alarming though not sustained. Repeated cystoscopies failed to locate the bleeding, which was invariably in abeyance at the times of examination. Always the ureteric effluxes were clear, the urine drawn from each kidney free from blood, and the pyelograms, intravenous and retrograde, normal. In the fruitless search of the whole bladder mucosa, the vault received special attention; for the possibility of an invading urachal tumour was by no means overlooked.

In the intervening five years the prostate had not increased in size. It was no hindrance to diagnosis; for it did not revent catheters being passed into the ureters. This point is mentioned because it is sometimes necessary to do a prostatectomy to find the site of hæmorrhage in the upper urinary tract. Most urologists have learnt, often by the hard way, that even grossly hypertrophied prostates are, as a rule, incidental to, and not the cause of, massive hæmaturia. In this patient there was very little excuse for interfering with the gland. Operation was a counsel of despair, given when he demanded action. I had no real conviction that the prostate could cause the hæmorrhage; but, after all, no other abnormality could be found, and adenomatous prostates do bleed! Be that as it may, the operation was advised and carried out—an easy and uneventful enucleation. Pathologically the specimen was an adenoma with some round-cell infiltration but no malignancy. The route chosen was the suprapubic one, correct enough in ordinary circumstances but faulty in this case, because the incisions in the abdominal wall and bladder were transverse—according to my usual practice. Thus the vesical apex remained above the field, and the growth perched on it was by-passed. It was so mobile that the palpating finger, even through the open bladder, felt no thickening or resistance.

Wisdom after the event, and possibly more versatility before it, would have insisted that a longitudinal incision, while not prejudicial to the prostatectomy, was imperative for the discovery and removal of any lurking urachal growth.

Nemesis followed quickly on the heels of this hit-or-miss surgery. All seemed well. The urine remained clear after the first few postoperative days. Exactly two weeks after the operation, the grateful and happy patient said goodbye to the ward staff, went to his hotel, and started to bleed that very night! When he was readmitted the following morning, the urine was again clear and cystoscopy profitless. Six days later he was discharged once more only to undergo the same tantalising sequence of events. The next cystoscopy disclosed a clot of unknown origin lying in the bladder. After it was removed the irrigating fluid returned absolutely clear. The prostatic cavity was completely epithelialised. There was one new finding—a tiny patch of telangiectasis on the vault—but its significance was not appreciated. The diagnostic drama, with anxious patient and baffled surgeon, was, however, drawing towards its climax. It was clear that not even a logical guess could be made until the bleeding was actually seen. The patient waited in his hotel while arrangements were made for cystoscopy at any hour of the day or night. The moment bleeding began he must send the signal and immediately follow it in person, in office hours to the surgery, at other times to the nursing-home. These clear-the-line tactics succeeded. Thirteen days later, and six weeks after his prostatectomy, the call came through at 2.30 in the afternoon. At 3 o'clock, with the cytoscope in the bladder, I was watching the drops of blood falling from the lower end of a thin festoon of clot hanging from the vault just behind the telangiectatic patch. The latter, as it now appeared, was the herald of a malignant invasion on its way towards the vesical aspect of the mucosa. Strangely enough and for the first time, there was some tenderness on deep pressure behind the symphysis pubis. It was as if Nature, tired of concealment, was liberally giving up the carefully guarded secret. Next day I carried out my radical operation for urachal tumours (Begg 1931). This was Sept. 21, 1950. Section of the specimen showed no involvement of the vesical aspect of the mucosa.

Mr. A died suddenly of coronary disease in March, 1952, just eighteen months after the last operation. He was then 81. I examined him a few months before his death. There had been no bleeding. The urine was microscopically clear; bladder function was normal; and clinically and radiologically there was no evidence of metastases.

CONCLUSIONS

Some conclusions may be drawn from this story.

A urachal tumour may cause hæmaturia, even though there is no clinical or cystoscopic evidence of its presence. The blood passes down the terminal urachal canal which in a high proportion of normal people communicates with the bladder cavity.

Such a tumour can only be diagnosed if blood is seen to drip from the bladder vault. Only under exceptionally favourable conditions can bleeding be seen. If it is known that the blood comes from the bladder and not from the upper urinary tract, it may be permissible to make a small suprapubic incision to palpate the bladder apex.

Elderly men with gross hæmaturia often have adenomatous prostates. These are rarely the cause of the bleeding, but should it be decided that a prostatectomy is advisable, the operation should be done in such a way that the apex of the bladder is exposed and a urachal tumour may be discovered.

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Medical Societies

BRITISH TUBERCULOSIS ASSOCIATION

Isoniazid in Pulmonary Tuberculosis

Five or six years ago, as Dr. Andrew Morland reminded this association at its annual conference held at Cambridge last week, we had no drugs which touched the tubercle bacillus. Now we have some formidable ones, and each newcomer will have to be proved against the best performance of its forerunners. It was therefore natural that the first session, with Sir Geoffrey Todd, the president, in the chair, should be devoted to the results so far achieved with isonicotinic acid hydrazide—referred to variously as INAH, I.N.A.H., I.N.H., and isoniazid.

THE DRUG AND ITS PROPERTIES

Prof. Robert Cruickshank said that the antituberculous properties of isoniazid were discovered at about the same time by the experimental chemists of three firms, Roche, Squibb, and Bayer; and, since it is easy and cheap to make, a flood of preparations have now been released. The tubercle bacillus, in its waxy coat, multiplying relatively slowly, and almost certainly able to multiply within the macrophages, can live for years in the necrotic centre of the tubercle, protected by the fibrous wall; and it thus presents a special problem to pharmacology. As long ago as 1932 we were saying that we must consider what drugs would penetrate both the tubercle and the wall of the macrophage.

Recent methods have made it easier to study the action of drugs. The new medium, ‘Tween-albumen” allows the tubercle bacillus to grow easily and diffusely; Sir Howard Florey and his colleagues at Oxford have devised a beautiful technique by which a tubercle on a rabbit's ear can be watched minutely, and the effect of drugs directly observed; while in the same laboratory a technique has been devised by Dr. G. B. Mackeness for keeping macrophages alive in nutrient medium for three weeks, and studying the intracellular as well as the extracellular action of drugs on tubercle bacilli which the cells have ingested. This last method, Professor Cruickshank said, may make the use of animals unnecessary for drug studies on tuberculosis.

Isoniazid has proved to be highly specific, acting on acid-fast bacilli and otherwise only on some fungi. It is more effective against virulent tubercle bacilli than against those which are less virulent, and its action is not affected by resistance of the bacillus to streptomycin or *p*-aminosalicylic acid (P.A.S.). We do not know yet whether it is bactericidal; but this must be decided, for recent work on combined therapy shows that while two bactericidal drugs given together may reinforce each *other's action*, a bactericidal drug and a bacteriostatic drug may be antagonistic. Mackeness has shown that isoniazid is as active inside the phagocyte as outside, and acts in very low concentration. Streptomycin is less active inside than outside the cell; terramycin is equally active in both; while P.A.S. has almost no action inside the cell. Experimentally, isoniazid, when given early, has been effective in the treatment of tuberculosis in mice, guineapigs, and rabbits: but in these animals the disease relapsed when the drug was stopped. It has also proved effective in animals infected intracranially with tuberculosis. But it seems that almost any culture of virulent tubercle bacilli contains some naturally resistant strains, especially when grown for more than two weeks in a liquid medium; and the resistance of strains increases rapidly. We need to know whether the virulence of these mutants is the same as that of the parent strain, and how quickly they will revert to non-resistant strains when the drug is withdrawn.

Pharmacologically, isoniazid is almost perfect—easily prepared, stable, possible to autoclave, quickly absorbed (reaching a peak in the blood in $^{1}/_{2}$–1 hour), causing little intestinal disturbance, and readily diffusible, even into the cerebrospinal fluid. Some 45–70% is excreted in the urine in 24 hours, and a further percentage in the fæces and saliva. At least ten times the effective dose can be attained in the blood within an hour, and, since it stays at an effective level for 12 hours, two doses daily are sufficient. The level in the C.S.F. is as high as in the blood. Liver damage and some excitation of the central nervous system have been seen as toxic effects in animals.

EARLY CLINICAL EXPERIENCE

Dr. **Morland** discussed experience with isoniazid at the Seaview Hospital, New York, which he visited in April. This vast hospital of 12,000–15,000 beds receives mainly cases regarded as hopeless. A group of 44 patients with bilateral caseous disease of the pneumonic type were selected for treatment; all were febrile and going downhill, and all were resistant to streptomycin. They were treated with isoniazid only; their temperatures fell to normal, and there was an average gain of 19 lb. in weight among them over 15 weeks. Their appetites became ravenous, they lost their apathy and became euphoric, and the number of tubercle bacilli in their sputa was much reduced. But cavity closure was not common, and the erythrocyte-sedimentation rate (E.S.R.) was little affected. There was some insomnia, but no serious injuries such as liver damage. The isopropyl derivative of the drug gave much the same results as the acid hydrazide, but was a little more toxic. Dr. Morland was told that there was no evidence of drug-resistance at Seaview, but this is not the opinion of other American centres. The gain in weight stopped when patients reached their maximum normal weight. Chronic cases did not improve to the same extent as acute cases, and 2 patients became respiratory cripples because the lung parenchyma left to them was not sufficient to meet the demands of their increased energy. Dr. Morland pointed out that some gain in weight and improvement in well-being may always be expected when P.A.S. is stopped, because, good as it is, P.A.S. is no stimulant to appetite.

He has himself given isoniazid, in daily doses of 2–4 mg. per kg. body-weight, to 40–50 patients, and has seen no toxic effects, not even insomnia or nervousness. Some gained up to 2 st. in weight, others showed little change. It is not known whether or not the increased appetite is due to a specific action on the tubercle bacilli or to some other cause; but he has lately given the drug to a girl with anorexia nervosa with benefit to her weight and appetite. He has seen rapid healing of tuberculous ulceration of the larynx with isoniazid, and one case of a streptomycin-resistant ulcer of the tongue and larynx which healed in 2 weeks. He has also seen the drug check the downward course in 6 out of 7 advanced chronic cases; but how lasting, he asked, will this effect be? He thinks the drug *may* be as effective as streptomycin given with P.A.S., but he doubts it. On the other hand it is pleasant to take and it produces euphoria, which means much for the patient with deteriorating disease.

Dr. E. G. **Sita-Lumsden** has visited centres in o parts of the United States, as well as Seaview, confirmed that no serious toxic results have been there, though some patients have shown eu nervousness, twitching, and occasionally dryness of mouth, postural hypotension, fall in hæmoglobin centration, eosinophilia, and transient albuminuria. severe liver damage has been seen in man. Reports now coming in of delayed improvement, with [illegible] of cavities, after 5–6 months of treatment. The seems to have about the same activity in acute culosis as streptomycin, though it is less predictable its results. The more acute the disease, the more the response: fever may even terminate by crisis. acute pneumonic disease the cough is usually gone the end of the second week, and sputum decreases much that by the end of the third week it may be di to get any for testing. The clinical and sub changes, however, are much more immediate impressive than radiological changes, which are slo and less certain. Fluid levels in cavities may dry out, in 3 of Dr. Sita-Lumsden's patients fluid levels ap during treatment. He thinks isoniazid alone is prob not quite so good as streptomycin with P.A.S., isoniazid and streptomycin together will probably better. He has known isoniazid produce reco without relapse or meningitic spread, in 6 cases of a miliary tuberculosis. Resistant strains may develop rapidly, and probably 60–80% of patients will b resistant after 3 months; but resistance may soon lost, for artificially induced resistance in B.C.G. is quickly lost by back-mutation. It may thus be useful to give courses lasting 6–8 weeks. His experience with 65 cases has borne out these generalisations: the general pic of improved appetite, reduced sputum, and gain in weight was there, with some improvement, great or little, in the X-ray findings in nearly half the cases. He noted that while under treatment 7 patients had hæmoptysis for the first time. He concluded that isoniazid is no mere appetiser but a powerful drug of the same order as streptomycin given alone.

INVESTIGATIONS IN PROGRESS

Dr. **Marc Daniels** told the meeting that the largest coöperative clinical investigation ever undertaken by the Medical Research Council is now in progress on this drug. Some 38 hospitals in various regions of the United Kingdom, and half the chest services of the country, are taking part in it. The chest clinics are providing acute cases and the hospitals intermediate and chronic cases and studies are being made of streptomycin and P.A.S. (for comparison), isoniazid alone, and streptomycin combined with isoniazid. Results are being analysed as they come in, so that significant findings can be published at once.

Dr. C. W. **Bartley** reported a series of 67 cases treated, at the London Hospital, on isoniazid alone. At first 2–4 mg. per kg. body-weight was given, and later 5–7 mg. There was no toxicity worth talking about. In 1 patient, with tuberculous endometritis, there was constipation for 9 days, and 2 had albuminuria (but one of these already had nephritis and the other a tuberculous kidney). Several patients showed an immediate reaction in the form of a brisk febrile response, increased cough, and tightness of the chest, lasting a few days, but this was followed by fall of temperature to normal levels, and general improvement on the lines already described. Hæmoptysis was a fairly common complication, being seen in 13 cases. Several cases behaved memorably. Thus a cavity which had been full for 10 years emptied in 10 days; two tension cavities in a girl of 15 closed in a few weeks; an untreatable case with 11 years' history gained $1^{1}/_{2}$ st. and closed one cavity in 6 weeks, and showed much thinning of the wall of another. Dr.

Bartley thought isoniazid an extremely effective drug even by itself, but there was strong clinical evidence that resistant strains may emerge after 8–12 weeks.

Dr. **J. W. Craig** has treated with isoniazid 55 cases aged 45 and over, and 50 cases under 45. They had all been treated by other methods for more than 2 years. What struck him forcibly was the reduction, after 6 weeks, of the total weekly sputum of the group by 12 pints. Moreover 65 became sputum-negative. The gain in weight, he found, was much greater in the younger patients.

Dr. **E. K. Pritchard** reported a controlled trial at Guy's Hospital. All were advanced bilateral cases in which other methods had failed. After 4 weeks the examining physicians, who did not know which were the treated patients and which the controls, were able to discriminate between them on the clinical findings. The weight of the treated cases was up, their temperatures and their E.S.R.s were down, their appetites were increased, and their euphoria evident.

Prof. **Robert Knox**, whose department has undertaken the bacteriological side of the Guy's study, noted that there was a rapid drop in the sputum count in patients on isoniazid, followed by a slow rise. Resistance to the drug is developing so far in 3 patients. In vitro, combination with streptomycin seems to increase the effectiveness of isoniazid; and patients on both isoniazid and streptomycin are also being investigated bacteriologically. Referring to Professor Cruickshank's remarks on its ready diffusibility, Professor Knox drew attention to its low molecular weight.

Dr. **Peter Edwards** reported from his series moderate gains in weight, and a sputum conversion-rate of 69%, with no complications. He mentioned that 16 control cases given lactose also felt well and put on weight for 4 weeks; but after that their improvement ceased, whereas among patients on isoniazid it continued.

Dr. **Tanner**, visiting from Switzerland, said that in his 100 cases he is beginning, after 2 months, to find improvement in cases which earlier showed no change. Though cavities sometimes enlarged, the walls of them thinned during treatment with isoniazid, and thus allowed better access to other drugs. He has had 3 cases of hæmoptysis but no other serious complication.

ROYAL SOCIETY OF MEDICINE

Treatment of Anuria

The section of urology of the Royal Society of Medicine met on June 26 under the chairmanship of Mr. **A. H. Jacobs**, the section's president, to discuss the treatment of anuria.

Dr. **E. M. Darmady**'s opening remarks referred to the improved prognosis in the anurias since he last addressed the section four years ago. This he attributed to better understanding of the pathology and natural history of these conditions with consequent improvement in treatment. Referring particularly to the syndrome of acute tubular necrosis, he suggested that renal circulatory embarrassment was of paramount importance in ætiology and that eight hours was a critical time for the human kidney to remain severely ischæmic. Nephron dissections by Oliver and by his own group had shown that, whatever the ætiology of the tubular necrosis, there was a characteristic pathological lesion consisting of patchy epithelial degeneration and areas of basement-membrane disruption affecting the whole tubule. The natural history of the disease had been described by Bull and his colleagues. In the precipitating phase there was usually renal circulatory disturbance due to a wide variety of causes. This was succeeded by a period of anuria or severe oliguria, and this in turn by a period of diuresis characterised by excessive loss of water and electrolytes.

As regards treatment, he referred to the possible use in the onset phase of osmotic diuretics (e.g., intravenous sodium sulphate) where hæmoglobin or other nephrotoxic substances were being excreted, and to measures that might restore renal blood-flow (e.g., caudal anæsthesia in obstetric anurias or blood-transfusion in oligæmic shock). As regards management of the anuric phase, there had been a swing away from the use of dialysis methods in favour of conservative treatment. There was considerable difficulty in assessing the state of cellular and extracellular hydration of these patients, and such simple procedures as hæmatocrit readings could be misleading. Hamburger had recently championed the so-called "effective osmotic pressure" (determined by the freezing-point of the plasma with allowance for the osmotic pressure of urea which is freely diffusible), and this could be a useful guide to treatment. Simple methods of estimating total body water and extracellular water were urgently needed. In the phase of excessive diuresis standard solutions containing potassium should be readily available—e.g., 1·9% potassium lactate or 1·1% potassium chloride solutions.

Dr. **G. M. Bull** said that the experience of the Hammersmith group had been largely with anuria due to circulatory renal insufficiency (extrarenal uræmia) or to acute tubular necrosis. In a five-year period, 48 patients were seen who were classified in the first group and 47 in the second group. Less common causes of anuria were nephritis and malignant hypertension. Obstructive anurias would naturally be referred directly to surgical units; and in his medical unit, of 112 anuric subjects only 6 were so classified. The commonest cause of circulatory renal insufficiency was oligæmic shock, but it might occur in heart-failure. Renal vasoconstriction compensating for inadequacy of the general circulation led to renal dysfunction with increasing blood-urea levels. If the general circulation were not restored to normal within a critical time, which varied with the severity of the renal vasoconstriction, then renal damage —i.e., acute tubular necrosis—would result. In any uræmic patient, then, such extrarenal factors as dehydration and cardiac failure must be sought and corrected, whether they occurred alone or complicated a pre-existing renal lesion.

Having referred to previous publications by his group at Hammersmith relating to the disturbed physiology in acute tubular necrosis[1] and to the conservative management of such cases by careful water and electrolyte balance and protein-free, high-calorie diet,[2] Dr. Bull took up some special points in treatment. Anæmia was common in acute tubular necrosis, and the hæmoglobin concentration should be kept above 70% of normal by transfusion of packed red cells. Where feeding by intragastric drip was difficult because of vomiting, he advocated the passing of a 'Polythene' catheter into the superior vena cava and the infusion of 40% glucose solution containing 2500 units of heparin per litre. Such treatment could be maintained for at least two weeks. Dangerous hyperpotassæmia was not common in the well-managed cases, except where severe infection caused excessive tissue breakdown or where potassium was administered in therapeutic error. The routine use of potassium citrate for patients in urological wards was to be guarded against. Some centres considered a high serum-potassium level an absolute indication for some form of dialysis, but such treatment was too dangerous and complicated for routine use. As an emergency treatment glucose and insulin could be injected intravenously. This could be followed, if need be, by feeding cation-exchange resin in the sodium cycle—a measure which he had found more effective than intermittent peritoneal dialysis. In the early diuretic phase potassium

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1. Bull, G. M., Joekes, A. M., Lowe, K. G. *Clin. Sci.* 1950, 9, 379.
2. Bull, G. M., Joekes, A. M., Lowe, K. G. *Lancet*, 1949, ii, 229.

deficiency could readily occur and was best prevented by allowing a liberal intake of potassium (e.g., as fruit) about two days after diuresis had been frankly established. Infection was an important cause of death in anuria and hence penicillin should be given routinely. One dose was sufficient whilst the patient was anuric and unable to excrete the antibiotic. Similarly with the other antibiotics there was no need for continued dosage during anuria, and with some of them there was the risk of toxic effects. For example, an anuric patient could get 2 g. of aureomycin initially and then about 1 g. in divided doses until diuresis occurred.

Mr. Ashton Miller discussed surgical measures in the broad group of anurias. Renal decapsulation was unjustifiable as, in his experience, the capsule of the kidney was rarely tense in these conditions and the operation was only occasionally followed by diuresis. Such diuresis, from the natural history of the disease, was to be expected coincidentally in some cases. Renal decapsulation did not, by the way, lead to renal sympathectomy. He also advised against the use of renal sympathetic block in the established anurias. Turning to the obstructive anurias, Mr. Miller stated that ligation of a ureter led to short-lived loin pain and a non-functioning kidney that was capable of functioning again if the obstruction were relieved within fourteen days. The term "calculous anuria" should not be used for the terminal stages of bilateral calculous disease but for cases where both ureters or the ureter of a sole functioning kidney were obstructed. Obstruction was commonest in the upper third of the ureter and normally led to colic and a palpable tender kidney. Obstruction was rarely absolutely complete. Usually there was X-ray evidence of the site of obstruction. In puzzling cases old surgical practices of operating on the side where pain was last felt or where muscular rigidity persisted should not be forgotten.

In anuria it was always imperative to determine whether obstruction was present, and this usually involved ureteric catheterisation. Normally a rapid return of renal function occurred after the obstruction was released. When a calculus had been pushed back into the renal pelvis, operation should be deferred until the general condition had improved following diuresis. Where a calculus could not be dislodged and the catheter by-passed it, thus allowing drainage, then the catheter should be removed after twenty-four hours and open operation performed. "Reflex anuria" was a blunderbuss term that he did not favour, especially in the absence of any experimental evidence of renorenal shunt. It had been used loosely, for example, where a stone blocked one ureter and function had failed in the other kidney on account of severe dehydration or other circulatory disturbance. Sulphonamide obstructive anurias were still common, especially in febrile dehydrated patients. Sulphonamide crystals were rarely found, and more commonly there was only a brown deposit of epithelial cells and red blood-cells. In one patient removal of such debris was followed by diuresis, but the urine-flow fell off again and the secondary episode of anuria had all the characteristics of acute tubular necrosis. Recovery eventually followed with the use of the Hammersmith régime. He felt that there was no sharp division between sulphonamide obstructive anuria and sulphonamide tubular necrosis. Acute pyelonephritis occasionally led to ureteric obstruction from inflammatory products lodging in the lower end of the ureter even in the absence of treatment with sulphonamides. Obstruction from external pressure on the ureter might occur, for example, after gynæcological operations and was usually only seen by the urologist after a lapse of more than forty-eight hours. At this time pyelostomy was indicated as an emergency measure; later on, the lower end of the ureter could be exposed, and divided and reimplanted into the bladder. In pelvic carcinomas sudden anuria might occur, an drainage of the ureters seemed indicated only whe treatment of the carcinoma was possible.

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In summing up, Dr. Bull referred to 36 cases, collected between the three opening speakers, in which anuria due to acute tubular necrosis had not been influenced by renal sympathetic block.

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Dr. Mary Pickford described the release of antidiuretic hormone from the posterior pituitary following injections of acetylcholine, nicotine, morphine, and ferritin. Acetylcholine is rendered temporarily ineffective in this respect after application of di-isopropylfluorophosphonate (D.F.P.) to the supraoptic nuclei. Intracarotid injection of adrenaline before an antidiuretic dose of acetylcholine regularly annuls the action of the latter. Morphine is still effective in inhibiting a high rate of urine flow if applied directly to the supraoptic nerve-cells, whether or not the cholinesterase of the cells has been disorganised by D.F.P. It appears that the cells of the supraoptic nuclei, like others in the body, can be activated by different types of stimuli, some arriving by nervous pathways, some being directly chemical, and some being physical or physicochemical. Also like the cells of other tissues, when the supraoptic nerve-cells are rendered unresponsive to one type of stimulus they can still respond to another.

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Prof. H. B. van Dyke (New York) described work in which he and his colleagues[1] extracted a protein from the pars nervosa of the pituitary with the biological activities of both principles (antidiuretic pressor and oxytocic) in about the same ratio as they are found in the gland. Its molecular weight was about 30,000, and its biological activity was found to be low (1 unit = 61 μg.). Although considerable evidence has been obtained that oxytocic and antidiuretic activities are present in constant ratios and that the protein is homogeneous, the possibility of adsorption of highly active principles on to an inert protein molecule has not been excluded. The highly purified principles recently isolated by du Vigneaud and his co-workers[2] were discussed. These principles have been isolated in extremely active forms—1 unit of the oxytocic principle being contained in 1·25 μg., and 1 unit of the antidiuretic-vasopressor principle in 1·6 μg. The amino-acid content of these two principles has been investigated; tyrosine, cystine, aspartic acid, glutamic acid, glycine, and proline are common to both, whereas arginine and phenylalanine characterise the oxytocic principle and leucine and isoleucine characterise the antidiuretic-vasopressor principle. Using these principles, various workers have established that neither the contraction of the isolated rat uterus nor the ejection of milk by the lactating mammary gland is a specific test for the oxytocic principle, whereas the depressor response of the fowl's blood-pressure appears to meet this requirement provided that contamination by antidiuretic-vasopressor principle is not excessive. The extremely sensitive antidiuretic test in the dog proved specific for the antidiuretic-vasopressor principle. It is not yet possible to decide whether the neurohypophysis secretes a large molecule containing both oxytocic and antidiuretic-vasopressor principles, or smaller molecules of highly active principles. The separate secretion of the latter has more teleological attraction.

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MILK EJECTION

Mr. B. A. Cross described the evidence underlying the present concept of a milk-ejection reflex.[3] The act of suckling stimulates a nervous reflex excitation of the posterior pituitary gland, and the secretion from this gland causes contraction of some element in the mammary gland and thus a positive ejection of milk from the mother to the young. Recent work, using du Vigneaud's highly active oxytocic and antidiuretic extracts, indicates that the posterior pituitary principle underlying milk ejection is the oxytocic principle, and not a mixture of the two as had been previously suggested. Mr. Cross also discussed unpublished work in which it was found that previous administration of adrenaline, or stimulation of the posterior region of the hypothalamus with resultant sympathetic excitation, will inhibit the milk-ejection reflex. Since the same procedures inhibit the milk-ejection effect of posterior pituitary extract it is likely that the effect of adrenaline is, at least in part, on the mammary gland itself.

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Dr. A. G. Lewis produced evidence that after 18 hours' dehydration a normal person had posterior pituitary hormone in the circulation with an antidiuretic activity equal to approximately 20 milli-units 'Pitressin.' It seems unlikely that the 5 milli-units per ml. of antidiuretic substance which has been detected by rat assay of human serum has any physiological action. Direct assay in man has shown that human serum contains less than 0·1 milli-unit per ml. after 12 hours' dehydration. Emotional stimuli, intravenous infusion of acetylcholine, hypertonic saline, nicotine, or morphine, anæsthesia and surgical operations, and syncope may all produce large releases of the antidiuretic hormone in man.

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Dr. J. E. Gates described the results of investigation, in collaboration with Dr. O. Garrod, on fifteen patients with diabetes insipidus. Pitressin tests separate the rare pitressin-resistant cases. Water deprivation gives variable results. Hickey and Hare's test with hypertonic saline may be nullified by an osmotic diuresis. Nicotine intravenously causes little or no antidiuresis when given in doses large enough to cause antidiuresis in normal persons; larger doses usually cause some antidiuresis. The effect of nicotine in clinical diabetes insipidus supports the belief that nicotine stimulates the secretion of the antidiuretic hormone. The response to large doses suggests that the lesion of the supraopticohypophysial system is often not complete.

Reviews of Books

Psychiatry in General Practice

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Dr. and Mrs. Watts have written an original and stimulating book showing, with many illustrative cases, how the generally accepted principles and techniques of psychiatry have been applied to the problems of a busy general practice in a mining district of Leicestershire. Dr. C. A. H. Watts appears to have had the advantage of learning and practising psychiatric methods in the war-time school of the South African Medical Corps, perhaps thus escaping the formidable task of devising them ab initio in the surroundings of an established practice; but this book shows clearly that, with a sufficiency of knowledge and the will and patience to use it, a general practitioner can make of psychiatry the kind of specialty another may make of obstetrics or pædiatrics.

The authors divide psychotherapy into three grades. Major psychotherapy, like major surgery, is for the specialist; elementary first-aid psychotherapy is an inescapable part of every doctor's task; while the intermediate field should belong to the general practitioner but too often goes uncultivated from real or supposed lack of time, from lack of knowledge or imagination, or from plain dislike. The book explores this intermediate field, section by section, showing the problems which commonly present themselves, the guise in which they appear, and how their solution may be attempted. The unsuccessful or half-successful case is not omitted, and the limitations of psychotherapy are clearly indicated; the authors do not for a moment pretend that it can relieve a practice of every troublesome psychopath or neuropath, but they do maintain that to tackle emotional problems on their own ground and not merely to treat their physical symptoms will in the end save time, and will restore many patients, if not to full health, at least to working capacity. Preventive psychotherapy, especially in childhood and before marriage, is fully considered; and there are interesting reflections on mental hospitals and on the limited usefulness of voluntary admission. The book ends with a reasoned plea for mental wings in general hospitals—for the diagnosis and treatment, as distinct from the segregation and maintenance, of the mentally sick—and for a multiplication of general-practitioner psychiatrists.

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Renal Function

Transactions of the Second Conference. Editor: STANLEY E. BRADLEY, department of medicine, College of Physicians and Surgeons, Columbia University. New York: Josiah Macy, Jr., Foundation. 1951. Pp. 178. $3.00.

GONE are the days when a conference on renal function discusses, in simple language, such topics as glomerular filtration or tubular reabsorption, or even devotes its time to a review of clearance techniques. Investigation of renal activity during the past years has shown how intimately the endocrine glands are concerned in its control, and in this record of the second Josiah Macy conference, held in October, 1950, we find discussions on antidiuretic factors, on the influence of the adrenal cortex on water metabolism, on sodium excretion, and on the action of A.C.T.H. and cortisone on renal function in man. Much that is reported has been already published, much is new and as yet unproven, part is still hypothesis. A review of active work is of course the purpose of such conferences and it is valuable to have the discussion, as well as the main papers, recorded.

Das Phäochromozytom

Professor H. SACK, Chefarzt der inneren Klinik, Städtischen Krankenanstalten, Krefeld. Stuttgart: Thieme. 1951. Pp. 93. D.M. 11.70.

THIS is a short but thorough account of our present knowledge of the adrenaline and noradrenaline secreting tumours of the adrenal cortex. Professor Sack has drawn both on his own experience and on the growing literature of the subject. Starting with a historical survey, he discusses the clinical features, the physiopathology, and the various pharmacological methods used in the diagnosis of this rare but important tumour. He has given us a valuable and timely review, supplemented by a full bibliography.

Photography of Patients

H. LOU GIBSON, F.B.P.A., A.P.S.A., medical division, Eastman Kodak Company, Rochester, New York. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 118. 40*s.*

CLINICIANS who are amateur photographers will find parts of this book of great assistance in making records of their patients. The emphasis is on the practical, and there is a good section on methods of adapting standard small cameras for carrying out close-up work quickly and easily. The illustrations are good and well reproduced, but two of the prints have been transposed on p. 102. Most of the materials mentioned in the table are not to be had in this country, but in many cases it would not be difficult to adapt our own materials. It is a pity that so much of this monograph has been taken up with the basic principles of photography; this information is more cheaply available in a dozen standard textbooks.

Educability of Cerebral Palsied Children

M. I. DUNSDON, M.A., F.B.PS.S. Publication no. 4 of the National Foundation for Educational Research in England and Wales. London: Newnes Educational Publishing Company. 1952. Pp. 163. £1 1*s.*

IN this book are reported the results of a three-year investigation into the educability of children with cerebral palsy. The difficulty of assessing intelligence in a severely handicapped child is discussed, and the problems presented to the teacher by physical handicaps (including defects of special sense and speech difficulties) and by deficiencies in intelligence, temperament, and social adjustment are considered. Data on the frequency and extent of the various handicaps, and correlation of these with competence as assessed in various ways, are given in tabular form. No statistical analysis is attempted, and the conclusions drawn are sometimes of doubtful validity.

The incidence of cerebral palsy in England and Wales is calculated from replies by 101 local education authorities to a questionary sent out by the British Council for the Welfare of Spastics, but most of the other information presented is based on individual assessments of "abilities, aptitudes and attainments" made in most instances by the author. The majority of cases had been referred for admission to a special cerebral-palsy school. Such cases are often referred because they present special problems, and hence, as pointed out by the author, they do not constitute a fair sample for the calculation of general incidences. The proportions of these cases included in the tables is not always stated.

In making a direct attack on the question of educability—an inquiry into the educational progress actually achieved by cerebral palsied children—the author was unfortunate. "Rapid turnover of children for various reasons, frequent staff changes, necessary changes in routines due to general re-organisation, and interruptions due to illness among children or staff, all militated against the carrying out of planned experiments." Few will doubt that some of these factors must have influenced the rate of educational progress achieved, and there is some evidence in the text that this rate was lower than the best possible. Yet the author accepts the results as of general application; her plan for the educational care of cerebral palsied children in England and Wales is based largely on them.

It may be said that in this book the difficulties to be encountered by any teacher who has to deal with cerebral palsy are well set out, but that little contribution is made to overcoming them.

Use of Tracer Elements in Biology (London: Heinemann. 1951. Pp. 57. 3*s.* 6*d.*).—This little book by Mr. W. G. Overend, PH.D., of Birmingham, begins by explaining very briefly how radioactive isotopes of usually stable elements are formed. The use of suitable radioactive (and sometimes of stable) isotopes of carbon, nitrogen, hydrogen, oxygen, sulphur, and phosphorus in biology is described and illustrated at some length and mention is made of some others like iron and iodine. There is a very short account of the use of tracers in medicine. The language is clear and only absolutely essential technical formulæ are used. The book can be confidently recommended to those who want to grasp, in outline, the facts behind the use of tracers and who are defeated by the larger volumes.

British Encyclopædia of Medical Practice (2nd ed. London: Butterworth Medical Publications. 1952. Vol. 10. Pp. 678. £3 5*s.*). *Cumulative Supplement*, 1952 (Pp. 126. £1 5*s.*). *Medical Progress*, 1952 (Pp. 319. £1 12*s.* 6*d.*).—The editor-in-chief, Lord Horder, and his contributors are within sight of the finishing line. They run on as strongly as ever in the 10th stage of their marathon which takes them from pituitary-gland diseases (by Dr. H. Gardiner-Hill) to retina diseases (by Mr. R. C. Davenport). They have set a cracking pace all along; it is barely 20 months since we reviewed the first volume of the 2nd edition, and now a final spurt will carry them across the line before this Olympic year is out. The *Cumulative Supplement* contains material that has been substantiated since the publication of the main volumes, and *Medical Progress* covers by critical survey and abstract the advances of the last year or so.

Textbook of Surgical Treatment (4th ed. Edinburgh: E. & S. Livingstone. 1952. Pp. 744. 45*s.*).—Under Prof. C. F. W. Illingworth's editorship this book maintains its popularity north of the Tweed, and its 22 contributors well reflect Scottish surgical practice. The new edition has been extensively revised and new sections on congenital heart conditions and hypertensive states have been added. In general the senior student will find what he wants, but a few minor criticisms may be made. Sulphanilamide, instead of its less toxic derivatives, is used for septic conditions and is recommended for local use, though experience has shown how ineffective it is in wounds. The newer antibiotics streptomycin, aureomycin, and chloramphenicol are not mentioned. Some surgeons would dispute the omission of urethrotomy as a treatment for stricture. No account is given of complete cystectomy, on the ground that it is too advanced for this book; yet the complex procedures required to remedy the tetrad of Fallot are fully described and well illustrated. In the instructions for removing the rectum by the abdomino-perineal method no warning of the proximity of the left ureter is given. Resection of the rectum with restoration of continuity of the bowel finds no place. From the account of amputation of the rectum for prolapse it would be fair to deduce that this was a successful solution of the difficulty, which it is not. Yet who could compile a book covering so great an area of knowledge without leaving some points open to criticism? Professor Illingworth, in fact, has left surprisingly few.

THE LANCET

LONDON: SATURDAY, JULY 5, 1952

Complications of Controlled Hypotension

In many eyes the practice of deliberately inducing hypotension to lessen bleeding during operations has become a mark of modernity and progress. Hitherto, reports have mostly been enthusiastic, though last year we suggested that caution was needed.[1] Our impression now is that hypotension is often induced for insufficient reasons, with too little regard for the patients' physical state, and even with little check on the blood-pressure during operation. Tooth extractions and the smaller orthopædic operations are taken by some to be suitable for hypotension, as are laryngectomy in feeble carcinomatous patients and prostatectomy in the semi-uræmic. The result is that at meetings of anæsthetists round the country instances are recounted, by word of mouth, of death and near-death. Of the known deaths, some have taken place on the table, others after a few hours without recovery from the anæsthetic, and still others somewhat inexplicably after two or three days. So widespread is the feeling that controlled hypotension is less safe than some surgeons and anæsthetists believe, that the Section of Anesthesiology of the Yale University School of Medicine has circularised British anæsthetists asking for anonymous reports of accidents with the method. As the circular puts it:

> "Certain fatal and non-fatal complications resulting from the use of the technique have been much more common than was previously supposed, but very little has been published concerning these disasters due to the very normal fear on the part of the involved surgeons and anesthetists of the possibility of the institution of medico-legal action."

Evidence which may explain some of the disasters is now coming to light. **McQueen**[2] studied the glomerular filtration-rate, renal plasma-flow, and urine-flow in volunteers who received 100 mg. of hexamethonium in the proper posture, and he found a sharp fall in the filtration-rate and in the urine-flow. He points out that since hexamethonium is excreted by the kidneys, a gross fall of blood-pressure is likely to delay its excretion and prolong its action. In our present issue Dr. **Mackinnon** records similar findings: he has found that pentamethonium reduces both the glomerular filtration-rate and the effective renal blood-flow. As might be expected, hypotension has a disagreeable effect on the liver. Dr. **Bromage**, whose paper we also publish this week, describes macroscopic observations on the liver in 17 patients with hypotension during anæsthesia, and says that in 14 there were changes clearly indicating hypoxia. When the systolic pressure was between 45 and 60 mm. Hg the liver appeared cyanosed and was turgid and rubbery; but it quickly became pink and of normal consistence when the pressure was raised with 'Methedrine.' Dr. **Bromage** emphasises that these changes take place before much else seems wrong with the patient; and thus occult liver damage may be more likely than general inspection indicates.

These reports are probably the first of many in similar strain. They underline the need for carefully selecting cases in which the blood-pressure is to be deliberately lowered: without good reason none but the robust should be subjected to this procedure. Where hypotension is proposed, the surgeon must ask himself whether the lessening of capillary oozing during the operation is so important that it really compensates for the possibility of grave interference with some vital body process. Anæsthetists, too, will clearly see the need for moderation in the use of controlled hypotension, and for careful supervision during and after the operation. Some of those most favourable to the method will nevertheless agree with Dr. **Bromage** that the blood-pressure should never be allowed to fall below 60 mm. Hg.

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[1] Annotation, *Lancet*, 1951, ii, 161.

[2] McQueen, E. G. *Med. J. Aust.* 1952, i, 769.

Clot Retraction

The 18th-century doctors who used bleeding in everyday therapy naturally observed the clotting of blood and remarked on the fact that the clot retracted and expressed serum. **Charles Thackrah** of Leeds, is best known for having given the first systematic account of industrial medicine in his book *The effects of arts, trades and professions and of civic states and habits of living, on health and longevity, with suggestions for the removal of many of the agents which produce disease and shorten the duration of life.* But he also wrote a book on blood, in which he noted that the average proportion of serum squeezed out from normal clots was 42%. This early estimate was accurate, and **Thackrah** also remarked that temperature variations influenced the result. Since then there have been many attempts to measure clot retraction, and almost as many explanations of its mechanism—a multiplicity partly due to the singular reluctance of workers in this small corner of hæmatology to consult previous reports. Perhaps this is because the problem has specially interested the "gadgeteer"—an individualistic type. Now, however, Dr. O. E. **Budtz-Olsen**[1] has put us in his debt by collecting and collating the known information, providing a good method of estimation, and propounding a reasonable explanation.

The retraction of the clot of blood formed after shedding is measured by the ratio between the volume of the serum expressed and the original volume of the blood; this ratio is usually given as a percentage. The retraction is influenced by many factors, including temperature, gravity, the size, shape, and surface of the vessel used to collect the blood, and even the material the container is made of. **Budtz-Olsen** avoids most of these difficulties by suspending the blood in a mixture of liquid paraffin and trichlorethylene adjusted to the specific gravity of the blood. A known volume of blood withdrawn from a vein is ejected into some of this fluid contained in a tall vessel; the blood forms a globule which remains stationary, suspended in the liquid. When it clots and the clot begins to retract and squeeze out serum, the serum rises to the surface and the remaining clot and enmeshed red cells fall downwards; the serum can be pipetted off and measured.

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[1] Budtz-Olsen, O. E. Clot Retraction. Oxford: Blackwell Scientific Publications. 1951. Pp. 149. 25s.

By this method Budtz-Olsen studied once again the influence of various factors, such as temperature, and the presence of red and white blood-cells in the expressed serum; and he found that the blood-platelets are the most important factor. When the other clotting factors of blood are normal, clot retraction depends directly on the number of platelets present. Fibrinogen is also important, and clots retract better when *less* fibrinogen is present. Consequently when blood is diluted, clot retraction, as is well known, remains more or less unaltered because the lowered platelet-count diminishes retraction and the lower fibrinogen content increases retraction, and these two effects tend to balance. The fibrin formed in the clot acts mechanically by holding serum in the clot and giving rise to a network that becomes denser, and therefore harder to pull together, the higher the fibrin concentration. Such an explanation assumes that fibrin plays only a passive part in clot retraction; Budtz-Olsen shows that this is so, and that the platelets are the active retractile agents.

When platelets are shed they are "activated" so that they will cause clot retraction; and experiments show that the activator is produced when prothrombin is converted to thrombin, though it is not thrombin itself. Activated platelets swell up and coalesce, and in the process they pull the fibrin network with them. The process is more easily followed in birds' blood, where the thrombocytes in shed blood can be seen to swell and throw out long processes which join with processes from other platelets; then these processes retract, drawing the two cells together until they fuse. Electron-microscope pictures of human blood have shown these processes very clearly.[2] Budtz-Olsen points out that in crabs, which have no fibrinogen in their blood, this so-called "viscous metamorphosis" of the amœbocytes or spindle-cells in the blood is the sole method of forming a network clot for hæmostasis, and the network of coalesced amœbocytes becomes firm by contraction. The lobster has some fibrinogen, but the amœbocyte clot forms first and the fibrin clot is added later. In birds there are specialised thrombocytes; while in mammals there are still more specialised platelets and the fibrin clot forms at the same time as the platelet changes occur, so the clot retracts steadily. Budtz-Olsen suggests that in mammals clot retraction is now a "phylogenetic relic"—a vestigial process that still remains although mammals (and birds) have now developed more efficient methods of hæmostasis. The blood-platelets of the mammal still undergo "viscous metamorphosis" and cause retraction of the fibrin clot; but they now have other functions—they release thromboplastin activator to initiate the clotting process, and they form masses that plug breaks in small vessels. If this hypothesis is correct, we should not expect to find that defective clot retraction causes ineffective hæmostasis. Clinical experience shows that this is so, unless the clot retraction is defective as in hæmorrhagic syndromes caused by low platelet-counts.

All this Dr. Budtz-Olsen presents, with full experimental details, in an astonishingly readable little monograph. The physician and the clinical pathologist can study it with detached appreciation; for, since clot retraction is a mere relic of our evolutionary history, there is no need to remember a list of conditions in which it should be estimated. The clinical pathologist has not to organise yet another test; nor need any research-worker fear that he will be asked if he has carried out "Budtz-Olsen's test for clot retraction." Nowadays investigations in hæmatology rarely have so happy a conclusion.

Recoverable Psychosis in the Old

Now that we are turning a considering eye on the ills of old people, many conditions which we have been accustomed to regard as terminal or irremediable are proving to be not so serious after all. Even mental disorders in old age, as Dr. Martin Roth and Dr. J. D. Morrissey[1] point out, do not really present the gloomy picture suggested by the rising rates of admission of these patients to mental hospitals. They quote the finding of R. E. L. Faris and H. W. Dunham, in 1939, that the number of admissions of the old to mental hospital varies with their degree of social security; and they think that the difference between the vast rise in admission-rates in the United States and the relatively smaller rise in Great Britain may well be due to differences in the social and economic status of the old in the two countries. They particularly emphasise that those admitted do not form a homogeneous group: some will deteriorate, certainly, and end their lives in senile dementia; but a large proportion will recover, and above all will respond to modern methods of treatment if these are used. This conclusion was reached from a study of 150 patients over sixty admitted to Graylingwell Hospital during 1948, and followed up until the end of March, 1951, either in hospital, or by letter, or by a visit from a psychiatric social worker. They judged that affective psychosis—usually depression—accounted for 81 (54%) of the cases, and senile psychosis for only 36 (24%). For the rest, 7 were diagnosed as cases of arteriosclerotic psychosis, 12 as schizophrenia, and 14 as confusion (quite apart from those cases in which confusional symptoms complicated some other disorder).

The follow-up studies showed that six months after admission 46 (more than half) of the 81 cases of affective psychosis were out of hospital, and only 5 had died. Of the 36 patients with senile psychosis only 5 had been discharged, and 19 had died. By the end of the study, some two to three years later, 43 of the affective patients had maintained their recovery, 7 had recovered and relapsed after discharge, 8 were ill in hospital, 19 (a quarter) had died, and 4 were untraced. Thus a substantial proportion were finding life worth living. Of the 36 with senile psychoses, 32 (nearly 90%) were dead, 3 were deteriorating inpatients, and 1 was untraced. These observations demonstrate the very real importance of distinguishing between the two types of psychosis, especially since patients with affective depression respond well to electroconvulsive therapy (E.C.T.). The conclusion that affective disorder and senile dementia are distinct is further supported by Roth and Morrisey's findings with a battery of tests on 84 patients over sixty admitted consecutively to Graylingwell.[2] The mean score of the affective patients was eight or nine times as good as that of the senile psychotics.

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[2] See leading article, *Lancet*, 1950, i, 1076.

[1] *J. ment. Sci.* January, 1952, p. 66.

Among the features of depression at this time of life, apathy is common in long-standing cases. In the present series hypochondriacal and paranoid symptoms were more often found than in younger age-groups, and if prominent were an unfavourable sign. Neurotic symptoms, beginning for the first time, and suddenly, in old age often seemed to be a symptom of affective disorder and responded quickly to treatment. Of the 12 patients in the series who made a clear-cut attempt at suicide, all were cases of depression. Confusion, which sometimes leads to difficulty in the diagnosis during the acute phase, was present in only 3 cases of affective disorder, but was noted at the outset in 28 of the 36 patients with senile psychosis; and 18 of these were dead in six months. In the 12 cases of schizophrenia in this series the disorder had started after the patients had reached sixty; paraphrenic delusions were prominent, in a setting of well-preserved intellect and personality. The 7 cases of arteriosclerotic psychosis showed a fluctuating course with cerebrovascular symptoms, a patchy deterioration of personality, and relatively good insight.

The main task is to winnow out cases of affective disorder soon after admission, for failure to diagnose them may prove disastrous for the patients. "Depressive illness in the aged," as ROTH and MORRISSEY point out, "takes a terrible toll in death from exhaustion, pneumonia and other intercurrent infections"; and death after months or years in hospital, preceded by some physical decline and mental confusion, does not mean that the patient must have had a senile psychosis after all. It is easy to make mistakes at the start; for an apathetic, retarded, wasted, dirty, neglected patient readily gives the impression of suffering from a long-established cerebral degeneration rather than a curable disorder. The clue to the diagnosis is often to be found in a detailed and carefully taken history; but the patient may not be able to give such a history, and if he lives alone neither may anybody else. Fortunately, in the great majority of cases positive affective symptoms make the diagnosis possible; and depression is, in any case, less likely to be due to an organic disorder of the brain.

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[2] *Proc. R. Soc. Med.* 1952, 45, 369.

Annotations

CONFERENCE ON REMUNERATION

IT is now clear that the Working Party's report[1] on the future distribution of the central pool of remuneration is, in general, acceptable to doctors up and down the country. The Conference of Local Medical Committees that was held in London on June 26 was the culmination of a series of local constituency meetings called all over the country by members of the local medical committees. The Working Party must have been gratified to learn how acceptable their suggestions have proved. A surprisingly large number of local medical committees—some forty in all—sent in reports that they could accept all the recommendations. Other committees asked for clarification of certain sections and for assurances that the new distribution would not fail in its objective of bringing about "a relative improvement in the position of those practitioners least favourably placed under the present plan of distribution." In particular it was feared by some members of the Conference that practitioners who practised in areas where the practice size was often small and static, who had lists of 750 or less, and whose present income was augmented by a fixed annual payment, might find themselves no better off, or perhaps even worse off. This, it was suggested, might be avoided if a different range of 1000 patients (e.g., 251–1250) were chosen for the capitation load. The conference as a whole was satisfied that the load could most fairly be placed at the level of 501–1500 suggested by the Working Party, but accepted a motion from Cornwall that "provision be made for review of the success or otherwise of the new method of distribution with a view to further modification as found necessary in the light of experience." To this was added a rider, at the suggestion of Dr. S. Wand,

> "That if, when the new scheme of distribution has been endorsed by both parties, it is found in the light of experience that certain groups of practitioners who under the terms of reference of the Working Party might have expected to have benefited have, in fact, not done so, it be left to the Working Party provisionally to allocate an appropriate proportion of the final settlement monies for the purpose of remedying any obvious defects in the distribution scheme, such allocation to be subject to confirmation by the next Conference before it becomes a permanent feature of the scheme."

In the course of the discussions it was announced that in conversations at Somerset House an understanding had been reached that the income-tax assessable on the retrospective monies under the Danckwerts award would be "spread over the periods over which they are taken as having accrued." Where a doctor arranges himself to make a retrospective payment to an assistant it will be possible for him to charge this as part of his expenses for that particular year when his own retrospective receipts are assessed for tax. If a doctor has died before Parliament has eventually sanctioned the retrospective award, any monies that will accrue to his widow from the award will not be subject to payment of estate duties.

The Working Party's report has still to come before Parliament for approval; and the statement by the Parliamentary Labour Party, which we reproduce on p. 46, suggests that some of its terms will be keenly debated.

RADIOGRAPHY FOR THE ACUTE ABDOMEN

THE art of accurate diagnosis in acute abdominal disorders comes only with long experience. Nothing can replace the long apprenticeship in emergency surgery that is a feature of British surgical training. Of the ancillary aids to diagnosis, most are disappointing and some even misleading. To be sure it is helpful to know if there is pus in the urine; but many patients with pyuria have acute appendicitis. The white-cell count, as performed by the occasional leucocytologist in the hospital side-room, may be so inaccurate as to be almost valueless. What of the plain radiograph of the abdomen? On the whole, in the experience of most surgeons it is not of much help. In perforation of a hollow viscus air will be seen under the diaphragm if the picture is taken with the patient upright; but this is as a rule evident from the clinical examination. Opacities in the region of the gall-bladder and kidneys are likely to be misleading unless their appearance is very characteristic. Moreover, to depend on blurring of the renal and psoas shadows and on scoliosis for the diagnosis of a perinephric abscess is like photographing the sun to see if it is shining.

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[1] See *Lancet*, 1952, i, 1147, 1155.

In intestinal obstruction, however, the plain film of the abdomen might be more extensively studied than it is at present, not so much for diagnosis (for this is usually obvious and nothing much is gained by seeing fluid levels on an X-ray film) as for localisation of the level of obstruction.

McLanahan et al.[1] have again drawn attention to the different gas pattern given by the different levels of the bowel. The transverse striations of the jejunum, the smooth loops of the ileum, and the segmented appearance of the colon are all characteristic. In high small-bowel obstructions only jejunal gas is visible; in ileal or right colonic obstruction there is jejunal and ileal gas and the descending colon is empty; in left-colon obstructions the gas shadows are present in the cæcum and transverse and descending colon, and little gas is present in the jejunum though ileal loops may be evident. The appearance of two enormous loops of bowel crossing the abdomen obliquely from the lower left to the upper right quadrant is pathognomonic of sigmoid volvulus. These radiographic signs are well known. Possibly, however, further study of the radiographic aspects of intestinal obstruction might bring still others to light.

SYRINGE-TRANSMITTED TUBERCULOSIS

It is well known that an imperfectly sterilised syringe or needle may convey infection from one patient to another; and, like other organisms, the tubercle bacillus may profit by some flaw in aseptic technique.

In 1946, Ebrill and Elek[2] treated a tuberculous abscess in a boy's thigh at the site where penicillin had been given by intramuscular drip, and came to the conclusion that tubercle bacilli had gained access either to the penicillin powder, to the diluted solution, or to the drip apparatus. Debré et al.[3] have reported 95 cases, 37 from the literature and 58 personal observations, of such primary tuberculosis. Of these, 78 had had penicillin injections; the remainder had received various substances, including physiological saline solution, soluble camphor, extract of artichoke leaves, various vaccines, salts of testosterone, vitamin C, and, paradoxically, streptomycin. There were 9 deaths, all in infants; 5 from generalised tuberculosis, 3 from intercurrent infections, and 1 from an unknown cause. The majority of infections occurred in chain epidemics. The abscess usually appeared within a fortnight of a subcutaneous or intramuscular injection (never after an intradermal one), and contained many tubercle bacilli (100 or more per microscope field) when the pus was examined within a month of infection. In all their own cases the organism was of the human type. A fistula developed and the regional lymph-glands were involved. The tuberculin reaction became positive after the usual ante-allergic period. Suppuration usually continued for a long time, to be followed by permanent recovery with a retracted scar. Complications included caseous abdominal glands (which tended to resolve), splenomegaly, hepatomegaly, discrete pleural effusions, nodular erythema, phlyctenular conjunctivitis, and spina ventosa. Treatment of the primary lesions with streptomycin did not give decisive results, but surgical drainage was effective.

Accidental inoculation of tubercle bacilli into the cellular tissue of children has results very similar to those obtained in guineapigs—nodules at the site of inoculation, adenitis, and fistula formation. The subcutaneous nodule appears at the end of the ante-allergic period, and successive guineapig inoculations during this period each produce a nodule evolving in the same way. But in children generalised tuberculosis is exceptional, while in the guineapig it is the rule.

Two explanations have been suggested for tuberculous abscesses in man: firstly, that infection is hæmatogenous and a hæmatoma at the injection site provides a focus for infection from a transient tuberculous bacteræmia; and, secondly, that the bacillus is introduced from without, either in the substance injected or from a contaminated syringe or needle.

Three cases have been recorded which support the hæmatogenous theory. In one a tuberculous abscess developed at the site of intramuscular injections of procaine.[4] Subsequent X-ray examination of the chest revealed pulmonary tuberculosis from which there possibly had been a hæmatogenous spread. In another a boy received an injection of penicillin into the buttock, and, two weeks later, injections into both thighs.[5] After a further three weeks a tuberculous abscess developed in the left thigh, followed by one in the right buttock. Later on, a spina ventosa was found in the right index finger. In the third case a child with pulmonary tuberculosis received a blow over the right supraorbital margin, where a tuberculous abscess later developed.[5]

But even if this mechanism was really responsible, it must be exceptional, for it has not been described after therapeutic injections in patients known to be tuberculous. Ebrill and Elek[2] could find no other tuberculous focus in their patient; and in the first 3 patients of Debré's series the tuberculin reaction was initially negative and became positive only after weeks or months.

It is most unlikely that the drug itself is infected, because so many different products have been involved and infections have occurred in several countries and seldom singly. The evidence that the infection is transmitted by the syringe is overwhelming. When a syringe is not disinfected between injections, tubercle bacilli may easily pass from patient to patient.

This mechanism was demonstrated by Debré and his colleagues[3] when they watched nurses giving penicillin injections. The penicillin in the bottle was dissolved in 20 ml. of physiological saline solution. A 2 ml. syringe filled with air was then fitted to the needle, air was introduced, and 2 ml. of penicillin withdrawn. The nurse then injected the solution into the indurated site of a previous injection in a child. At that moment the authors intervened. They emptied the syringe and filled it with saline solution, which then appeared slightly turbid. When it was injected into a guineapig an abscess containing tubercle bacilli formed at the point of inoculation 22 days later, and there was other evidence of tuberculosis. The implication is that the indurated area was a tuberculous focus. This procedure was repeated three times and on two occasions positive results were obtained. After an injection had been given to another child solid particles were seen floating in the syringe, and one of them contained tubercle bacilli.

Hughes[6] has demonstrated the reflux of tissue fluid into a syringe after an intramuscular injection, and this accounts for the presence of tuberculous material in the syringe after an injection into an infected focus.

There is therefore very strong evidence that the tubercle bacillus can enter the syringe during an injection. In other instances the syringe probably becomes accidentally contaminated during manipulations. The syringe and needle are the sources of danger, and they should be properly disinfected after every injection. Debré et al. found that boiling for 2–5 minutes usually destroyed all tubercle bacilli, but the time required was longer in the presence of oil, pus, or blood. Immersion in alcohol was useless. Fleming and Ogilvie[7] suggested that the risk of transmitting infection by syringes could be overcome by dipping the needle into liquid paraffin at 130°C for 10 seconds without removing the needle from the syringe. Boiling water was also effective, but the paraffin was preferable because it did not rust or blunt the needles. But this method has not, as far as we know,

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1. McLanahan, S., Watt, C. H. jun., Green, J. S. *Ann. Surg.* 1952, 135, 586.
2. Ebrill, D., Elek, S. D. *Lancet*, 1946, ii, 379.
3. Debré, R., Lamy, M., Koupernik, C., Costil, L., Coutel, Y. *Ann. Méd.* 1951, 52, 433.
4. Hounslow, A. G. *Lancet*, 1949, i, 709.
5. Debré, R., Brissaud, E., Canlorbe, P. *Arch. franç. Pédiat.* 1951, 8, 49.
6. Hughes, R. R. *Brit. med. J.* 1946, ii, 685.
7. Fleming, A., Ogilvie, A. C. *Ibid*, 1951, i, 543.

been proved lethal to the tubercle bacillus, though it quickly and easily disposed of *Staphylococcus aureus*. Fleming and Ogilvie also concluded that reflux into the syringe did not take place if pressure was maintained on the piston until the needle was withdrawn; but if more than one injection was given from a single filling of the syringe, the contents might be contaminated.

RED CELLS IN ANIMALS

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All these figures show that the red-cell count is inversely proportional to cell volume. Wintrobe points out that this means that the amount of hæmoglobin available for the transport of oxygen is remarkably constant, though the size of the "packet" varies, and that evolutionary progress has favoured the smaller packets because they present, in sum, a greatly enlarged surface through which exchanges of gases and electrolytes can proceed more efficiently. Hartridge[2] showed that the red cell in the form of a biconcave disc has the most efficient shape for rapid gaseous exchange.

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Holman therefore set out to investigate the relation between the red-cell count, the packed-cell volume, and the mean cell volume in cows, sheep, goats, and horses. His results, based on a large number of observations, show quite clearly that there is a negative correlation between the red-cell count and the red-cell size (as shown by the mean cell volume) in all these animals. In other words, animals with counts *above* the average have corpuscles *below* average size, and vice versa. Individual cases did not keep strictly to this rule; for instance, in goats the lowest red-cell count recorded was 8·8 million per c.mm. and the highest 19·9 million, while the corresponding mean cell volumes were 23 c.µ and 16 c.µ. The smallest of all the mean cell volumes was 15 c.µ and the corresponding red-cell count was 18·9 million per c.mm. The greatest volume of 30 c.µ occurred in a goat with a count of 12·6 million.

Holman takes these observations as a warning against judging the state of the blood in farm animals by the red-cell count alone—a method that was abandoned long ago in examining human blood. He also points out that this variation must be taken into account when diagnosing macrocytic anæmia. But apart from these practical consequences, it is interesting to speculate why this variation, which, as we have seen, is a general feature in the animal world, is so striking among our domestic animals. Present-day domestic animals have a very complicated parentage; it may be worth seeing whether ancestry has any bearing on the size and number of red cells and on the relation between the two.

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FROM time to time some particularly notable piece of medical research receives the full light of publicity, but in the main the work goes forward in relative obscurity. For every published investigation there are many preliminary and tentative, yet none the less vital, experiments which are known only to a few. The latest unobtrusive annual report from the Lister Institute of Preventive Medicine gives some inkling of the volume of work that is being done in just one research centre. True enough, there is an impressive list of scientific papers published from the laboratories of the institute in recent months, but it tells only a part of the story.

In the few pages they have allowed themselves, the governing body can do no more than mention the latest work. Among these allusions, often tantalisingly brief, we read that Dr. D. McClean, Mr. L. Vallet, and Dr. L. H. Collier are investigating the antigenicity of vaccinia virus that has been irradiated with ultraviolet light. Both vaccine lymph and purified elementary-body suspensions have been irradiated and completely inactivated so far as can be judged by tests on the rabbit's skin and on the embryonated egg. Rabbits immunised with these preparations are less susceptible to vaccination than normal rabbits, and they develop more virus-neutralising antibody. Further experiments are necessary to ensure that this apparent antigenic activity is not caused by small doses of living virus that have survived irradiation. If these results are confirmed and extended, preliminary immunisation with irradiated virus may provide a basal immunity that will modify the reaction to subsequent vaccination with living virus, and thus reduce its risks, particularly in primary vaccination in later life. Dr. W. d'A. Maycock and Miss L. L. Lorenz are studying the fate of dextran after intravenous injection, and a method has been developed for estimating dextran in urine and in aqueous tissue extracts. Most of the dextran which can be recovered from the tissues has been found in the liver, bone-marrow, lymph-glands, and spleen. It has also been observed that dextran is still excreted in the urine of the rabbit long after it can be detected serologically in the plasma. Sir Alan Drury, F.R.S., director of the institute, and Miss M. E. Blewett have been examining the various plasma-protein fractions for substances of biological interest. One fraction constricts the guineapig's intestine and also constricts perfused mammalian blood-vessels. Attempts are being made to discover the source of this substance. It is hoped that these observations may help to explain some of the effects of serum that have been known for many years but are as yet imperfectly understood. These

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[1] Wintrobe, M. M. Clinical Hematology. London, 1951; p. 998.
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[4] Rusoff, L. L., Piercy, P. L. *J. Dairy Sci.* 1946, 29, 526.

In intestinal obstruction, however, the plain film of the abdomen might be more extensively studied than it is at present, not so much for diagnosis (for this is usually obvious and nothing much is gained by seeing fluid levels on an X-ray film) as for localisation of the level of obstruction.

McLanahan et al.[1] have again drawn attention to the different gas pattern given by the different levels of the bowel. The transverse striations of the jejunum, the smooth loops of the ileum, and the segmented appearance of the colon are all characteristic. In high small-bowel obstructions only jejunal gas is visible; in ileal or right colonic obstruction there is jejunal and ileal gas and the descending colon is empty; in left-colon obstructions the gas shadows are present in the cæcum and transverse and descending colon, and little gas is present in the jejunum though ileal loops may be evident. The appearance of two enormous loops of bowel crossing the abdomen obliquely from the lower left to the upper right quadrant is pathognomonic of sigmoid volvulus. These radiographic signs are well known. Possibly, however, further study of the radiographic aspects of intestinal obstruction might bring still others to light.

SYRINGE-TRANSMITTED TUBERCULOSIS

It is well known that an imperfectly sterilised syringe or needle may convey infection from one patient to another; and, like other organisms, the tubercle bacillus may profit by some flaw in aseptic technique.

In 1946, Ebrill and Elek [2] treated a tuberculous abscess in a boy's thigh at the site where penicillin had been given by intramuscular drip, and came to the conclusion that tubercle bacilli had gained access either to the penicillin powder, to the diluted solution, or to the drip apparatus. Debré et al.[3] have reported 95 cases, 37 from the literature and 58 personal observations, of such primary tuberculosis. Of these, 78 had had penicillin injections; the remainder had received various substances, including physiological saline solution, soluble camphor, extract of artichoke leaves, various vaccines, salts of testosterone, vitamin C, and, paradoxically, streptomycin. There were 9 deaths, all in infants; 5 from generalised tuberculosis, 3 from intercurrent infections, and 1 from an unknown cause. The majority of infections occurred in chain epidemics. The abscess usually appeared within a fortnight of a subcutaneous or intramuscular injection (never after an intradermal one), and contained many tubercle bacilli (100 or more per microscope field) when the pus was examined within a month of infection. In all their own cases the organism was of the human type. A fistula developed and the regional lymph-glands were involved. The tuberculin reaction became positive after the usual ante-allergic period. Suppuration usually continued for a long time, to be followed by permanent recovery with a retracted scar. Complications included caseous abdominal glands (which tended to resolve), splenomegaly, hepatomegaly, discrete pleural effusions, nodular erythema, phlyctenular conjunctivitis, and spina ventosa. Treatment of the primary lesions with streptomycin did not give decisive results, but surgical drainage was effective.

Accidental inoculation of tubercle bacilli into the cellular tissue of children has results very similar to those obtained in guineapigs—nodules at the site of inoculation, adenitis, and fistula formation. The subcutaneous nodule appears at the end of the ante-allergic period, and successive guineapig inoculations during this period each produce a nodule evolving in the same way. But in children generalised tuberculosis is exceptional, while in the guineapig it is the rule.

Two explanations have been suggested for tuberculous abscesses in man: firstly, that infection is hæmatogenous and a hæmatoma at the injection site provides a focus for infection from a transient tuberculous bacteræmia; and, secondly, that the bacillus is introduced from without, either in the substance injected or from a contaminated syringe or needle.

Three cases have been recorded which support the hæmatogenous theory. In one a tuberculous abscess developed at the site of intramuscular injections of procaine.[4] Subsequent X-ray examination of the chest revealed pulmonary tuberculosis from which there possibly had been a hæmatogenous spread. In another a boy received an injection of penicillin into the buttock, and, two weeks later, injections into both thighs.[3] After a further three weeks a tuberculous abscess developed in the left thigh, followed by one in the right buttock. Later on, a spina ventosa was found in the right index finger. In the third case a child with pulmonary tuberculosis received a blow over the right supraorbital margin, where a tuberculous abscess later developed.[5]

But even if this mechanism was really responsible, it must be exceptional, for it has not been described after therapeutic injections in patients known to be tuberculous. Ebrill and Elek [2] could find no other tuberculous focus in their patient; and in the first 3 patients of Debré's series the tuberculin reaction was initially negative and became positive only after weeks or months.

It is most unlikely that the drug itself is infected, because so many different products have been involved and infections have occurred in several countries and seldom singly. The evidence that the infection is transmitted by the syringe is overwhelming. When a syringe is not disinfected between injections, tubercle bacilli may easily pass from patient to patient.

This mechanism was demonstrated by Debré and his colleagues [3] when they watched nurses giving penicillin injections. The penicillin in the bottle was dissolved in 20 ml. of physiological saline solution. A 2 ml. syringe filled with air was then fitted to the needle, air was introduced, and 2 ml. of penicillin withdrawn. The nurse then injected the solution into the indurated site of a previous injection in a child. At that moment the authors intervened. They emptied the syringe and filled it with saline solution, which then appeared slightly turbid. When it was injected into a guineapig an abscess containing tubercle bacilli formed at the point of inoculation 22 days later, and there was other evidence of tuberculosis. The implication is that the indurated area was a tuberculous focus. This procedure was repeated three times and on two occasions positive results were obtained. After an injection had been given to another child solid particles were seen floating in the syringe, and one of them contained tubercle bacilli.

Hughes [6] has demonstrated the reflux of tissue fluid into a syringe after an intramuscular injection, and this accounts for the presence of tuberculous material in the syringe after an injection into an infected focus.

There is therefore very strong evidence that the tubercle bacillus can enter the syringe during an injection. In other instances the syringe probably becomes accidentally contaminated during manipulations. The syringe and needle are the sources of danger, and they should be properly disinfected after every injection. Debré et al. found that boiling for 2–5 minutes usually destroyed all tubercle bacilli, but the time required was longer in the presence of oil, pus, or blood. Immersion in alcohol was useless. Fleming and Ogilvie [7] suggested that the risk of transmitting infection by syringes could be overcome by dipping the needle into liquid paraffin at 130°C for 10 seconds without removing the needle from the syringe. Boiling water was also effective, but the paraffin was preferable because it did not rust or blunt the needles. But this method has not, as far as we know,

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1. McLanahan, S., Watt, C. H. jun., Green, J. S. *Ann. Surg.* 1952, 135, 586.
2. Ebrill, D., Elek, S. D. *Lancet*, 1946, ii, 379.
3. Debré, R., Lamy, M., Koupernik, C., Costil, L., Coutel, Y. *Ann. Méd.* 1951, 52, 433.
4. Hounslow, A. G. *Lancet*, 1949, i, 709.
5. Debré, R., Brissaud, E., Canlorbe, P. *Arch. franç. Pédiat.* 1951, 8, 49.
6. Hughes, R. R. *Brit. med. J.* 1946, ii, 685.
7. Fleming, A., Ogilvie, A. C. *Ibid*, 1951, i, 543.

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are only three of the many ways in which the institute continues as one of the foremost solvers of the biological jigsaw puzzle, many of whose perplexing pieces it has helped to put together in the past.

Much regret will be felt at the news that Sir Alan Drury is retiring, at the end of September, from the post of director which he has held since 1943. Despite all difficulties, his period of office has seen considerable developments at the institute, and his quiet wisdom and experience have been of great service both at the Lister itself and in the counsels of medical research.

ATMOSPHERIC CARCINOGENS

CHEMICAL compounds now known to be carcinogenic are numbered in hundreds; but so far only three—arsenic, benzpyrene, and radioactive substances—have been detected in notable quantities in atmospheric dust. These atmospheric carcinogens are discussed in the latest issue of the *British Journal of Cancer* [1–3] and in the report for 1951 of the British Empire Cancer Campaign.[4]

It has been found [1] that the arsenic content of the air in winter is twice that in summer; which suggests that the domestic combustion of coal is the chief source. The quantity of arsenic is, however, comparatively small; on the average the air breathed in a year by one person contains 0·5 mg., which is what might be found in 100 cigarettes. Waller [2] describes the estimation of benzpyrene in the smoke from eight different towns in England. As with arsenic, the concentration rises sharply in winter, and the mean annual value increases with the size of the town. Again the domestic fire appears to be the principal source. Benzpyrene has also been detected in the exhaust from internal-combustion engines, but in small amounts. It has not been found in cigarette smoke, but there seem to be considerable technical difficulties in detecting its presence there. Though it is now virtually certain that cigarette smoke is commonly carcinogenic, the fact remains that, judging by death certificates, the ratio of urban to rural cancer incidence in this country is of the order of two or three to one.[5] Much further information is needed before the part possibly played by benzpyrene can be assessed; it would be helpful to obtain data for lung cancer in localities where little coal is combusted, where the population does not smoke, where there are no exhaust fumes, and where there is nevertheless a good standard of hygiene and nutrition by present-day standards. Systematic elimination of these various factors should certainly yield interesting information.

Radioactivity in air dust [3] proved much the same in the heart of London, at Chiswick, at Rothamsted (a semi-rural district 30 miles from London), and in Manchester. Fluctuations in the activity at each site are attributed to varying weather conditions, the rate being higher when the ground is dry and the air still. The radioactivity in a cellar and in an air-raid shelter in London was remarkably high—up to 120 times as great as in the open air above the shelter. The floor dust was inactive, suggesting that the radioactive material is adsorbed on particles so small as to sink very slowly to floor level and that it has too short a life to accumulate on the floor. The very high activity in the shelter is ascribed to the lack of ventilation, which allows the radioactivity from the large wall area to accumulate in the suspended dust particles in the air. The highest value recorded in the shelter was, however, only one-eighth of the official tolerance dose. For comparison, the activity in the Joachimstaal mines is stated to be thirty times the tolerance dose. It is scarcely surprising, therefore, that in the past more than half the miners died of lung cancer.[6]

Whether atmospheric or dietetic carcinogens, the end-result of infective processes, or genetic changes are important factors in the rise of lung cancer has still to be decided. New carcinogens are being brought to light; for example, among workers in the chromate industry lung cancer is 16–80 times as common as in the general population, although chromate dust does not produce the disease in animals. Possibly carcinogens in trace amounts may reinforce each other's potency. Summation effects of this kind have already been described in clinical conditions (for instance, in xeroderma pigmentosum involving the human epidermis, where the two factors are a genetic one and sunlight) and in experimental carcinogenesis (for instance, dibenzanthracene-endosuccinate and X rays; methylcholanthrene, the Bittner virus, and a genetic factor; and dibenzanthracene and œstrone).

RETIREMENT OF DR. J. A. GLOVER

THE retirement of Dr. J. Alison Glover this week from the Ministry of Health, after $32^1/_2$ years' unbroken service with that Ministry and the Board of Education, marks the end of an epoch. The last of fourteen medical officers appointed by Dr. Addison just after the creation of the Ministry of Health, Dr. Glover is a direct link with an older age. His father, James Grey Glover, was a friend of Lord Lister and Sir John Simon, and as ethical adviser to THE LANCET exerted a wide influence over the policy of this journal for 37 years. Dr. Glover himself, as a dresser to Sir Henry Howse, carried out his dressings under a carbolic spray. He served with the infantry in the C.I.V. in 1900 and in the R.A.M.C. throughout the first world war, joining the Ministry of Health in 1920. From 1934 to 1941 he was senior medical officer at the Board of Education, and after his official retirement he re-joined the Ministry of Health to edit the annual reports of its Chief Medical Officer—"On the State of the Public Health"—and the Ministry's section of the *Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service.* As we recorded at the time, he received last year the Jenner medal of the Royal Society of Medicine, of which he is an honorary fellow.

At a small private ceremony at the Ministry of Health last week Dr. Glover was presented with an 18th-century corner cupboard as a token of the affection in which he is held by all his colleagues.

ORTHOPÆDISTS MEET

THE first joint meeting of all the orthopædic associations of the English-speaking world opened in London last Monday in the presence of Queen Elizabeth the Queen Mother, who presented jewels of office to the presidents of visiting associations: Dr. Fremont Chandler (U.S.A.), Dr. R. Graham Huckell (Canada), Mr. Esmond West (Australia), Mr. Alexander Gillies (New Zealand), and Mr. G. du Toit (South Africa). Sir Reginald Watson-Jones, president of the British Orthopædic Association, read a telegram from the Queen, expressing her thanks for a message of good wishes. The scientific meetings were continuing for five days.

Welcoming delegates at a luncheon given by the Royal College of Surgeons after the inaugural ceremony, Sir Cecil Wakeley, P.R.C.S., remarked that the college is playing an ever-increasing part in postgraduate education and has instituted a joint committee for postgraduate orthopædic training, under the chairmanship of Sir Reginald Watson-Jones.

SIR PERCIVAL HORTON-SMITH HARTLEY, consulting physician to St. Bartholomew's Hospital, died in London on June 30, at the age of 84.

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1. Goulden, F., Kennaway, E. L., Urquhart, M. E. *Brit. J. Cancer,* 1952, 6, 1.
2. Waller, R. E. *Ibid,* p. 8.
3. Dawson, K. B. *Ibid,* p. 22.
4. British Empire Ca [illegible] ninth annual report, covering the y [illegible] by the Campaign, 11, Grosvenor Cr [illegible]
5. Kennaway, E. L., [illegible] *Cancer,* 1947, 1, 260.
6. Peller, S. *Human Biology,* 1939, 11, 130.

Points of View

A PHILOSOPHY OF HOSPITAL ADMINISTRATION*

STEPHEN TAYLOR
B.Sc., M.D. Lond., M.R.C.P.

ADMINISTRATION is simply an enabling process; it enables other people to get on with their jobs. This is no cause for shame, for the same is true of politics and all aspects of higher direction and government. In a completely wise society, we should be able to chop out these processes as unnecessary overheads. But in the imperfect world in which we live, the science and art of administration is forced into a key position by the technical complexities of society and the intellectual simplicity and emotional entanglements of the people who compose it.

Administration is a product of the large social group, which in turn is a product of technical and scientific advance and work-specialisation. The easy way of exploiting the marvels of factory production is to produce great concentrations of population. A dispersed factory population is possible, but men only learn its social and strategic value by bitter experience. Administration and the large social group march hand in hand. So we find administrators operating in large social groups of all kinds, at the hub of the megalopolis itself, and in each of the groups which compose it: in the factory, at the town hall, on the building site, in the newspaper office, at the pithead, in the film studio, at the traffic control point, in the government office, and, of course, in the hospital.

In each of these places unique work is being done. Sometimes by an engineer, a builder, or a surgeon; sometimes by a writer or creative artist, or some technical expert. This unique work is often both satisfying and exciting; for it is the field of creative craft and experimental advance. By comparison, administration is often tedious, repetitive, and dull. Indeed, the best justification for paying the administrator highly, compared with the technical expert, is that his work is so much more laborious, and so much less stimulating and satisfying. Nevertheless, the social value of administration in a modern society cannot be far behind the technical processes, for without administration there can be no large-scale technical activity.

COMMON FACTORS OF ADMINISTRATION

Wherever administration is needed, its basic technique is much the same, though administrators in each field are often concerned to prove that their particular job is unique. Usually this turns out to mean no more than the need for a smattering of technical knowledge, easily and swiftly acquired by an intelligent administrator from another field. I have tried to pick out the common factors in the administrative process.

Probably the most important are the multitude of *personal problems* and difficulties which arise in all large groups, and which it is the administrator's duty to disentangle and smooth out. These irritations may arise from genuine injustice or fabricated ill will; or they may be generated spontaneously by unhappy psychopaths, a proportion of whom must be carried in every group. Whatever their origin, it is easy to overrate their importance. The young administrator is at first overwhelmed and depressed by the volume and strength of the emotions with which he finds himself surrounded; but as he grows in wisdom and stature, so he learns to let them wash around him like a tide, secure in the knowledge that before many hours have passed the tide will have gone out again. The two great prophylactics in this field of human relations are selection and morale maintenance.

The next common factor in administration is the planning of *group structure* in its relation to function. Bound up with this is the level at which different types of decision ought to be taken. The bigger an organisation, the more complicated does its administration tend to become. Where peripheral units do a precisely similar routine job, tight central control is practicable—e.g., in Post Offices and National Insurance offices. But the more diverse local functions become, and the more varied the human needs which the service has to meet, the more paralysing is tight control from the centre. Not only is it paralysing, but it is also enormously wasteful. By detailed instruction central control attempts to make each peripheral unit capable of dealing with every eventuality. In practice, each peripheral unit has to deal with comparatively few of the possible eventualities, and these are best dealt with by a ready wit rather than a vast clutter of instructions and circulars. It is, I think, reasonable to lay down centrally very broad divisions of functions; it is convenient, also, to deal centrally with minimum wage and salary-rates, and conditions of service; but nothing more. Here, then, the keys to successful administration are broad central planning, coupled with almost complete peripheral autonomy.

Next come a group of common factors concerned with the *material facets* of any large organisation. There are premises, supplies, stores, rates and taxes, insurance, health of staff, and much else. I am by no means convinced that it is always necessary to subdivide functions here and to specialise excessively. Certainly the higher administrator should have had some "in the field" experience of all these activities, but in so far as they are professions in their own right I am in favour of calling in the expert, whether he be a surveyor, an income-tax consultant, or an industrial medical expert.

Imposed over all these varied activities is the controlling factor of *finance*. The bread-and-butter finance of the payment of wages, salaries, and bills, of records and balances, need not detain us. Our only concern is that it should be efficiently done, and that as few people as possible should have to spend their time in this necessary but sterile occupation. Finance, in its broader sense, is both a tool and a measuring instrument. It is a tool which will work miracles if it is applied at the right time and place. The art of buying, for quality as well as price, is one of the key actions in successful administration. Money wisely spent is what controls the environment in which we work. And we must always know how much we intend to spend on current consumption and maintenance, and how much on capital development. As a measuring instrument, financial analysis can show us precisely how we are deploying our forces, how much on each department, how much on each service cutting across departments, and how much on the overheads of administration. Costs must then be related to achievement, and so true cost can be determined. When this has been done, notional budgets are possible, against which to assess requirements and by means of which to devise equitable block grants.

In a hospital, measurement of achievement is not easy. What appears good at first sight may in fact be anything but good. A high rate of cure may be due to good work; but it may also be due to the admission of many mild cases and the rejection of severe cases. Two vital elements in estimating the achievement of a hospital are (1) the size of the community served, and (2) the overall recovery-rates in that community. Suppose the bed-costs of a hospital are high; that does not necessarily mean that the hospital is inefficient: it may be that it has a speedy turnover, and is successfully caring for many more patients than a cheaper and quieter hospital. Similarly, a high death-rate in a hospital does not necessarily mean bad work, for often a low death-rate in one hospital means a high death-rate somewhere else.

The hospital administrator, like the educational administrator and the county education officer, has two populations to deal with. There are the permanent "servers" (the nurses and doctors, or the school-are only three of the many ways in which the institute continues as one of the foremost solvers of the biological jigsaw puzzle, many of whose perplexing pieces it has helped to put together in the past.

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* An address given to a weekend school of the Sheffield regional branch of the Institute of Hospital Administrators on April 19.

Much regret will be felt at the news that Sir Alan Drury is retiring, at the end of September, from the post of director which he has held since 1943. Despite all difficulties, his period of office has seen considerable developments at the institute, and his quiet wisdom and experience have been of great service both at the Lister itself and in the counsels of medical research.

ATMOSPHERIC CARCINOGENS

CHEMICAL compounds now known to be carcinogenic are numbered in hundreds; but so far only three—arsenic, benzpyrene, and radioactive substances—have been detected in notable quantities in atmospheric dust. These atmospheric carcinogens are discussed in the latest issue of the *British Journal of Cancer* [1–3] and in the report for 1951 of the British Empire Cancer Campaign.[4]

It has been found [1] that the arsenic content of the air in winter is twice that in summer; which suggests that the domestic combustion of coal is the chief source. The quantity of arsenic is, however, comparatively small; on the average the air breathed in a year by one person contains 0·5 mg., which is what might be found in 100 cigarettes. Waller [2] describes the estimation of benzpyrene in the smoke from eight different towns in England. As with arsenic, the concentration rises sharply in winter, and the mean annual value increases with the size of the town. Again the domestic fire appears to be the principal source. Benzpyrene has also been detected in the exhaust from internal-combustion engines, but in small amounts. It has not been found in cigarette smoke, but there seem to be considerable technical difficulties in detecting its presence there. Though it is now virtually certain that cigarette smoke is commonly carcinogenic, the fact remains that, judging by death certificates, the ratio of urban to rural cancer incidence in this country is of the order of two or three to one.[5] Much further information is needed before the part possibly played by benzpyrene can be assessed; it would be helpful to obtain data for lung cancer in localities where little coal is combusted, where the population does not smoke, where there are no exhaust fumes, and where there is nevertheless a good standard of hygiene and nutrition by present-day standards. Systematic elimination of these various factors should certainly yield interesting information.

Radioactivity in air dust [3] proved much the same in the heart of London, at Chiswick, at Rothamsted (a semi-rural district 30 miles from London), and in Manchester. Fluctuations in the activity at each site are attributed to varying weather conditions, the rate being higher when the ground is dry and the air still. The radioactivity in a cellar and in an air-raid shelter in London was remarkably high—up to 120 times as great as in the open air above the shelter. The floor dust was inactive, suggesting that the radioactive material is adsorbed on particles so small as to sink very slowly to floor level and that it has too short a life to accumulate on the floor. The very high activity in the shelter is ascribed to the lack of ventilation, which allows the radioactivity from the large wall area to accumulate in the suspended dust particles in the air. The highest value recorded in the shelter was, however, only one-eighth of the official tolerance dose. For comparison, the activity in the Joachimstaal mines is stated to be thirty times the tolerance dose. It is scarcely surprising, therefore, that in the past more than half the miners died of lung cancer.[6]

Whether atmospheric or dietetic carcinogens, the end-result of infective processes, or genetic changes are important factors in the rise of lung cancer has still to be decided. New carcinogens are being brought to light; for example, among workers in the chromate industry lung cancer is 16–80 times as common as in the general population, although chromate dust does not produce the disease in animals. Possibly carcinogens in trace amounts may reinforce each other's potency. Summation effects of this kind have already been described in clinical conditions (for instance, in xeroderma pigmentosum involving the human epidermis, where the two factors are a genetic one and sunlight) and in experimental carcinogenesis (for instance, dibenzanthracene endosuccinate and X rays; methylcholanthrene, the Bittner virus, and a genetic factor; and dibenzanthracene and œstrone).

RETIREMENT OF DR. J. A. GLOVER

THE retirement of Dr. J. Alison Glover this week from the Ministry of Health, after 32½ years' unbroken service with that Ministry and the Board of Education, marks the end of an epoch. The last of fourteen medical officers appointed by Dr. Addison just after the creation of the Ministry of Health, Dr. Glover is a direct link with an older age. His father, James Grey Glover, was a friend of Lord Lister and Sir John Simon, and as ethical adviser to THE LANCET exerted a wide influence over the policy of this journal for 37 years. Dr. Glover himself, as a dresser to Sir Henry Howse, carried out his dressings under a carbolic spray. He served with the infantry in the C.I.V. in 1900 and in the R.A.M.C. throughout the first world war, joining the Ministry of Health in 1920. From 1934 to 1941 he was senior medical officer at the Board of Education, and after his official retirement he re-joined the Ministry of Health to edit the annual reports of its Chief Medical Officer—"On the State of the Public Health"—and the Ministry's section of the *Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service*. As we recorded at the time, he received last year the Jenner medal of the Royal Society of Medicine, of which he is an honorary fellow.

At a small private ceremony at the Ministry of Health last week Dr. Glover was presented with an 18th-century corner cupboard as a token of the affection in which he is held by all his colleagues.

ORTHOPÆDISTS MEET

THE first joint meeting of all the orthopædic associations of the English-speaking world opened in London last Monday in the presence of Queen Elizabeth the Queen Mother, who presented jewels of office to the presidents of visiting associations: Dr. Fremont Chandler (U.S.A.), Dr. R. Graham Huckell (Canada), Mr. Esmond West (Australia), Mr. Alexander Gillies (New Zealand), and Mr. G. du Toit (South Africa). Sir Reginald Watson-Jones, president of the British Orthopædic Association, read a telegram from the Queen, expressing her thanks for a message of good wishes. The scientific meetings were continuing for five days.

Welcoming delegates at a luncheon given by the Royal College of Surgeons after the inaugural ceremony, Sir Cecil Wakeley, P.R.C.S., remarked that the college is playing an ever-increasing part in postgraduate education and has instituted a joint committee for postgraduate orthopædic training, under the chairmanship of Sir Reginald Watson-Jones.

Sir PERCIVAL HORTON-SMITH HARTLEY, consulting physician to St. Bartholomew's Hospital, died in London on June 30, at the age of 84.

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1. Goulden, F., Kennaway, E. L., Urquhart, M. E. *Brit. J. Cancer*, 1952, 6, 1.
2. Waller, R. E. *Ibid*, p. 8.
3. Dawson, K. B. *Ibid*, p. 22.
4. British Empire Cancer Campaign: Twenty-ninth annual report, covering the year 1951. Published by the Campaign, 11, Grosvenor Crescent, London, S.W.1.
5. Kennaway, E. L., Kennaway, N. M. *Brit. J. Cancer*, 1947, 1, 260.
6. Peller, S. *Human Biology*, 1939, 11, 130.

Points of View

A PHILOSOPHY OF HOSPITAL ADMINISTRATION*

STEPHEN TAYLOR
B.Sc., M.D. Lond., M.R.C.P.

ADMINISTRATION is simply an enabling process; it enables other people to get on with their jobs. This is no cause for shame, for the same is true of politics and all aspects of higher direction and government. In a completely wise society, we should be able to chop out these processes as unnecessary overheads. But in the imperfect world in which we live, the science and art of administration is forced into a key position by the technical complexities of society and the intellectual simplicity and emotional entanglements of the people who compose it.

Administration is a product of the large social group, which in turn is a product of technical and scientific advance and work-specialisation. The easy way of exploiting the marvels of factory production is to produce great concentrations of population. A dispersed factory population is possible, but men only learn its social and strategic value by bitter experience. Administration and the large social group march hand in hand. So we find administrators operating in large social groups of all kinds, at the hub of the megalopolis itself, and in each of the groups which compose it: in the factory, at the town hall, on the building site, in the newspaper office, at the pithead, in the film studio, at the traffic control point, in the government office, and, of course, in the hospital.

In each of these places unique work is being done. Sometimes by an engineer, a builder, or a surgeon; sometimes by a writer or creative artist, or some technical expert. This unique work is often both satisfying and exciting; for it is the field of creative craft and experimental advance. By comparison, administration is often tedious, repetitive, and dull. Indeed, the best justification for paying the administrator highly, compared with the technical expert, is that his work is so much more laborious, and so much less stimulating and satisfying. Nevertheless, the social value of administration in a modern society cannot be far behind the technical processes, for without administration there can be no large-scale technical activity.

COMMON FACTORS OF ADMINISTRATION

Wherever administration is needed, its basic technique is much the same, though administrators in each field are often concerned to prove that their particular job is unique. Usually this turns out to mean no more than the need for a smattering of technical knowledge, easily and swiftly acquired by an intelligent administrator from another field. I have tried to pick out the common factors in the administrative process.

Probably the most important are the multitude of *personal problems* and difficulties which arise in all large groups, and which it is the administrator's duty to disentangle and smooth out. These irritations may arise from genuine injustice or fabricated ill will; or they may be generated spontaneously by unhappy psychopaths, a proportion of whom must be carried in every group. Whatever their origin, it is easy to overrate their importance. The young administrator is at first overwhelmed and depressed by the volume and strength of the emotions with which he finds himself surrounded; but as he grows in wisdom and stature, so he learns to let them wash around him like a tide, secure in the knowledge that before many hours have passed the tide will have gone out again. The two great prophylactics in this field of human relations are selection and morale maintenance.

The next common factor in administration is the planning of *group structure* in its relation to function. Bound up with this is the level at which different types of decision ought to be taken. The bigger an organisation, the more complicated does its administration tend to become. Where peripheral units do a precisely similar routine job, tight central control is practicable—e.g., in Post Offices and National Insurance offices. But the more diverse local functions become, and the more varied the human needs which the service has to meet, the more paralysing is tight control from the centre. Not only is it paralysing, but it is also enormously wasteful. By detailed instruction central control attempts to make each peripheral unit capable of dealing with every eventuality. In practice, each peripheral unit has to deal with comparatively few of the possible eventualities, and these are best dealt with by a ready wit rather than a vast clutter of instructions and circulars. It is, I think, reasonable to lay down centrally very broad divisions of functions; it is convenient, also, to deal centrally with minimum wage and salary-rates, and conditions of service; but nothing more. Here, then, the keys to successful administration are broad central planning, coupled with almost complete peripheral autonomy.

Next come a group of common factors concerned with the *material facets* of any large organisation. There are premises, supplies, stores, rates and taxes, insurance, health of staff, and much else. I am by no means convinced that it is always necessary to subdivide functions here and to specialise excessively. Certainly the higher administrator should have had some "in the field" experience of all these activities, but in so far as they are professions in their own right I am in favour of calling in the expert, whether he be a surveyor, an income-tax consultant, or an industrial medical expert.

Imposed over all these varied activities is the controlling factor of *finance*. The bread-and-butter finance of the payment of wages, salaries, and bills, of records and balances, need not detain us. Our only concern is that it should be efficiently done, and that as few people as possible should have to spend their time in this necessary but sterile occupation. Finance, in its broader sense, is both a tool and a measuring instrument. It is a tool which will work miracles if it is applied at the right time and place. The art of buying, for quality as well as price, is one of the key actions in successful administration. Money wisely spent is what controls the environment in which we work. And we must always know how much we intend to spend on current consumption and maintenance, and how much on capital development. As a measuring instrument, financial analysis can show us precisely how we are deploying our forces, how much on each department, how much on each service cutting across departments, and how much on the overheads of administration. Costs must then be related to achievement, and so true cost can be determined. When this has been done, notional budgets are possible, against which to assess requirements and by means of which to devise equitable block grants.

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The hospital administrator, like the educational administrator and the county education officer, has two populations to deal with. There are the permanent "servers" (the nurses and doctors, or the school-teachers) and the transitory "served" (the patients or the school-children). The manufacturer, the building contractor, and the Civil Servant also have this second population; but their consumers are not concentrated under a common roof.

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Indeed, the only peculiarities I can discover in hospital administration spring from its relation with illness and the emotions which illness arouses, and its relation with the *most affluent and powerful of all professions* in modern society—the medical profession. In a sense, the hospital administrator is less a master in his own house then any other administrator; though more and more the technicians in other walks of life are giving the administrator a run for his money.

ADMINISTRATIVE VICES AND VIRTUES

My own attitude to administrators depends on the behaviour of the last with whom I have had dealings. Their range is extraordinary, from the bottom of the barrel of humanity to the top. The great administrator is a great creative artist; because his medium is the lives of other people, the outline of the picture he is painting may be a little obscured, but *it can live as truly as any* other work of art. The good administrator is less spectacular but he is of vital importance to society; he may mould less, but sometimes this may be a powerful virtue. The bad administrator varies from being a nuisance to a menace; while the evil administrator is a creator of frustration, hatred, and malice, a person more pernicious than the *criminal operating against property* or even life, because he is beyond the arm of the law. The two extremes are rare, but these potentialities for good or evil are within most of us.

Administration carries a special mental occupational risk, for it is concerned with power. It is quite untrue to say that all power corrupts; but it is true that many people are more easily corrupted by power than anything else. All who practise administration must keep watch against this subtle corruption.

The first symptom is "important-itis." It is often seen in some young clerk or executive, a promising worker who is rewarded by promotion; one catches him shouting at a nurse, giving orders to a sister old enough to be his mother, or by his rudeness reducing the patient's wife to tears. Closely linked with this type of bumptiousness is the overcompensated second-rater who hides his defects in blustering self-importance.

One of the diagnostic features of the administrator who is too small for his job is the inflated team which he creates, immediately responsible to himself. He fails to realise that true administrative virtue is measured by the smallness, rather than the largeness, of the staff needed for any job.

The last two vices of administrators I shall mention are the top and bottom ends of the same curve of normal distribution. We all know the over-administrator who is continually poking and prying into the work of subordinates and technical colleagues. Over-administration is a fault to which many good administrators are prone; unhappily, experience often proves it to be necessary as a spur and stimulus to those administered. The alternative, the other side of the penny as it were, is administrative laziness, which is perhaps the greater failing. As it so often turns out, true administrative wisdom is to be found in the happy medium.

True humility I would put as the first and cardinal virtue of the administrator. By this I mean neither sloppy tolerance nor feeble discipline, but rather the realisation of the basic unimportance of the process of administration, and the basic equality of all of us in the last ethical analysis. True humility leaves no room for snobbishness, pomposity, a false sense of values, and magnification of the trivial. Above all, it puts the patient at the centre of the picture. The only excuse for the existence of doctors and nurses is the existence of the patient, and the hospital administrator exists only to enable doctors and nurses to care for the patient.

As a corrective to administrative *pride*, I like to imagine a congress of administrators meeting aboard a luxury liner. A great storm arises and the liner is wrecked on a desert island. None but the administrators survive. Imagine the consternation. There is real work to be *done!* The recording of minutes, the taking of decisions, the delegation of functions, will no longer suffice. He who will not work with his hands neither will he eat. Imagine the fresh evaluation of society which would follow. The key men would now be the amateur gardeners, farmers, and first-aiders. The one occupation for which there would be no call would be administration.

Yet there are some administrators, both outside and inside official service, who by their inherent excellence would rise like cream to the top of any society. Such men and women would shine no less in the search for food, clothes, and shelter on a desert island than they do in our complex civilisation. On the whole, I think they are more often found in private than in public enterprise, *though this is less true than it was.*

Such people are the creative adventurers of our society. It is they who make things happen. It is their magic touch which builds the social and economic units of our society, whether such units are factories, shops, housing estates, schools, colleges, or even hospitals.

ADVENTURERS AND MAINTAINERS

The creative adventurer must possess three things: first, the intellectual capacity for creation; second, the driving force, the *élan vital*, without which nothing happens; third, the spirit of adventure, the love of battle and the fight for its own sake, the thrill of taking the risk and the nice calculation of the risk taken.

The *capacity for creation* is a complex of mental facets. Analytical intellectual activity may be a positive disadvantage; barristers are seldom builders, and it is a criticism of the higher Civil Service that it relies too much on analytical capacity and too little on creative ability. At first sight these creators may seem to lack basic intelligence. But this may be no more than an expression of their lack of interest in spheres of life which they have dismissed as unimportant or outside their field of activity. Sometimes their contempt for intellectual activity is an expression of their age of school-leaving. Many a creator regards school activities as boring and divorced from reality.

The *æsthetics* of social and economic creation are *practised intuitively rather than explicitly.* Many of the physical defects of our society may be traced to the lack of social taste in the age in which the creative adventurer rose to maturity. The builder must have his vision, but that vision will be determined by the society in which he lives. For it will always be capable of interpretation in terms of everyday reality. It will, however, be no static vision; it will evolve in the light of experience and change with its changing environment. The satisfaction of this æsthetic urge comes in the building rather than in the final product. Once the edifice is made, this type of creative artist will slip away to try his hand in a different field.

The creative adventurer is a man of both *speech* and *action*. He is seldom to be found in his office, and indeed, the best administrator is often *the least* office-bound; clerical work should be delegated to clerks, and not undertaken by the administrator. The volubility of the creative adventurer may make it difficult to distinguish him from his disreputable first-cousin, the huckster on his market stall, the confidence trickster, the windbag and the humbug, who sometimes manages to foist himself on the unsuspecting selection committee. The simplest test to distinguish the true from the false, the solid building from the empty façade, is to see if the talker is equally prepared to listen and learn.

The *driving force* of the creative adventurer is often phasic in its manifestations. Though there must be a measure of perseverance, the creative act is essentially rhythmic and mercurial. The energy output cannot be maintained all the time, and there must be periods of quiet build-up when nothing much happens. Then a threshold is reached and he is off once more. He bangs into his environment; his aim is to give better than he gets, to mould rather than to be moulded.

The *spirit of adventure* expresses itself most clearly in a readiness to take risks and delight in so doing. He has an attitude of sturdy independence to authority, a regard for the law based on the spirit rather than the letter, and no great thought for the morrow in terms of present security. It is the exact opposite of respectability, of playing for safety, of "pension-itis," and all the other signs of a desire to gain security in a changing world and sell one's soul for a mess of rather dull pottage.

That, then, is a picture of one type of great administrator. In a sense it is both incomplete and over-complete, for no-one will fit precisely into the pattern. There are, however, other pictures of administrative excellence. There are the maintainers, the great exponents of the holding action, who "keep right on to the end of the road" at a slower and less hectic pace. They are less likely to create, but are more likely to hold fast to what is good. They, too, must be intelligent, with an even temper, patience, and humour. They must be able to pick out the essential from the inessential; indeed one of the secrets of good administration is to eliminate everything extraneous or unimportant from any problem or situation.

HUMAN PROBLEMS OF ADMINISTRATION

In many human situations administrative action can convert unhappiness into happiness. It is a good principle always to stretch a point in favour of the individual, and in particular in favour of the freedom of the individual. The petty tyrant is the great author of the unnecessary negative.

But most human problems in administration are far less tangible. They are, in the main, the products of unsatisfied emotion. By this I do not mean cattiness or waspishness, though this does occur, but rather unused emotion in people of both sexes, people in whom part of the trouble is that they are underworked.

There are simple remedies for this. It is as well always to aim at being slightly understaffed, so that everyone always has plenty of real work to do. If by overtime it is possible to avoid the employment of more staff, then overtime is socially desirable, provided it does not mean skimping work during real time, and provided it is not pushed so far as to produce inefficiency through fatigue.

The other great remedy is to build up and maintain staff morale. Everyone should feel that his or her job is really worth while, and that the hospital as a whole is moving steadily forward in service. The citizens of any community should have faith in their hospitals and feel proud of them. They will do so precisely in proportion to the pride which the hospital workers feel in themselves and their work. Once good morale has been built up, staff recruitment becomes comparatively easy. Personal smartness of the staff is important; the hospital or institution which issues its porters with uniforms which cannot look well is making a shortsighted economy. Slovenliness in porters and servants, and rude offhandedness in clerks and officials, should be jumped on at once. If they are allowed to pass, they become infectious and the whole tone of the place is lowered. But coupled with justifiable pride must be an ultimate humility; for it is from humility that all humanity stems. Indeed, the nice balance of pride and humility is the basis of good morale.

The administrator who despises staff negotiating machinery is foolishly shortsighted. Often negotiations are piffling in themselves; in fact, they are then acting as an emotional safety-valve. They are also a training in occupational democracy, and sometimes they may even be of real value in righting genuine wrongs. Their final use is as a means of dealing with the complaining psychopath, a curse inside any organisation. Once the complaints of the psychopath get into the official machine there is every hope of their being able to travel up and down for years without harming anyone.

ADMINISTRATORS AND DOCTORS

Perhaps the greatest difficulty which faces the hospital administrator is his relationship with the doctors. It is a subtle and difficult one. The medical man who decides to become a hospital administrator is, in this country at any rate, in a worse position than the layman. Other doctors tend to regard his decision as one dictated by lack of clinical skill, and they will dispute his administrative decisions simply because they resent the possibility that they may be based on medical knowledge. On the whole, therefore, I am in favour of the lay administrator; but it may sometimes happen that a medical man proves himself to be supremely competent in administration, and our system should be sufficiently flexible to make use of such exceptions to any general rule.

One of the great advances brought by the National Health Service has been the abolition of medical hierarchy in hospital as it was seen in most local-authority hospitals, and as it is still seen in some Service hospitals. The substitution of a number of parallel teams, units, or firms gives to the senior doctors complete clinical autonomy, without which, in my view, good medicine cannot be practised. The new liberty and equality take getting used to. The fraternity needed is not always forthcoming, and the need does sometimes arise for a measure of discipline, to correct either laziness or clinical failings on the medical side. I have no doubt that such discipline can only be a self-discipline applied by the medical profession itself.

The question is, how should it be applied? What is the best technique? The medical staff committee is a useful device, but only sometimes will its chairman feel that he has the necessary authority to administer a correction to his colleagues. Where his personality is such that he is able to do this, I have no doubt that he is the right ally for the lay administrator.

The Americans seem to have adopted a good system, whereby the chief of each department is known as a "chief of service." These chiefs of service form a medical board, and one of them is elected its president. The board meets weekly to perform an audit of service in the hospital, and any medical failures are investigated before the board and, if need be, correction is administered. The medical board is the police machine for the medical side of the hospital, and it looks as though it works effectively. It would be an interesting experiment to see such boards tried in a few English hospitals; save on the rarest occasions, it is not part of the job of the medical committee to investigate the failings of medical staff, yet healthy self-criticism inside each hospital might do a lot of good.

I am quite sure it is wrong to try to establish any other kind of supervising machinery for the doctors. Good medicine demands the occasional taking of risks, and those risks must be taken in the interest of the patient without regard to possible subsequent lay criticism. The doctor who is always looking over his shoulder at some other authority is certain to be a bad doctor.

If administrators are varied in their personalities, so too are the doctors. And doctors, like administrators, are subject to special occupational risks. Doctors may be brusque and rude at times; above all they may exhibit contempt for lay authorities. This is entirely healthy. Their job is to serve their patients, and not toady to committees or officialdom. The doctor who successfully squirms his way into the good graces of the lay authorities teachers) and the transitory "served" (the patients or the school-children). The manufacturer, the building contractor, and the Civil Servant also have this second population; but their consumers are not concentrated under a common roof.

Indeed, the only peculiarities I can discover in hospital administration spring from its relation with illness and the emotions which illness arouses, and its relation with the most affluent and powerful of all professions in modern society—the medical profession. In a sense, the hospital administrator is less a master in his own house then any other administrator; though more and more the technicians in other walks of life are giving the administrator a run for his money.

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My own attitude to administrators depends on the behaviour of the last with whom I have had dealings. Their range is extraordinary, from the bottom of the barrel of humanity to the top. The great administrator is a great creative artist; because his medium is the lives of other people, the outline of the picture he is painting may be a little obscured, but it can live as truly as any other work of art. The good administrator is less spectacular but he is of vital importance to society; he may mould less, but sometimes this may be a powerful virtue. The bad administrator varies from being a nuisance to a menace; while the evil administrator is a creator of frustration, hatred, and malice, a person more pernicious than the criminal operating against property or even life, because he is beyond the arm of the law. The two extremes are rare, but these potentialities for good or evil are within most of us.

Administration carries a special mental occupational risk, for it is concerned with power. It is quite untrue to say that all power corrupts; but it is true that many people are more easily corrupted by power than anything else. All who practise administration must keep watch against this subtle corruption.

The first symptom is "important-itis." It is often seen in some young clerk or executive, a promising worker who is rewarded by promotion; one catches him shouting at a nurse, giving orders to a sister old enough to be his mother, or by his rudeness reducing the patient's wife to tears. Closely linked with this type of bumptiousness is the overcompensated second-rater who hides his defects in blustering self-importance.

One of the diagnostic features of the administrator who is too small for his job is the inflated team which he creates, immediately responsible to himself. He fails to realise that true administrative virtue is measured by the smallness, rather than the largeness, of the staff needed for any job.

The last two vices of administrators I shall mention are the top and bottom ends of the same curve of normal distribution. We all know the over-administrator who is continually poking and prying into the work of subordinates and technical colleagues. Over-administration is a fault to which many good administrators are prone; unhappily, experience often proves it to be necessary as a spur and stimulus to those administered. The alternative, the other side of the penny as it were, is administrative laziness, which is perhaps the greater failing. As it so often turns out, true administrative wisdom is to be found in the happy medium.

True humility I would put as the first and cardinal virtue of the administrator. By this I mean neither sloppy tolerance nor feeble discipline, but rather the realisation of the basic unimportance of the process of administration, and the basic equality of all of us in the last ethical analysis. True humility leaves no room for snobbishness, pomposity, a false sense of values, and magnification of the trivial. Above all, it puts the patient at the centre of the picture. The only excuse for the existence of doctors and nurses is the existence of the patient, and the hospital administrator exists only to enable doctors and nurses to care for the patient.

As a corrective to administrative pride, I like to imagine a congress of administrators meeting aboard a luxury liner. A great storm arises and the liner is wrecked on a desert island. None but the administrators survive. Imagine the consternation. There is real work to be done! The recording of minutes, the taking of decisions, the delegation of functions, will no longer suffice. He who will not work with his hands neither will he eat. Imagine the fresh evaluation of society which would follow. The key men would now be the amateur gardeners, farmers, and first-aiders. The one occupation for which there would be no call would be administration.

Yet there are some administrators, both outside and inside official service, who by their inherent excellence would rise like cream to the top of any society. Such men and women would shine no less in the search for food, clothes, and shelter on a desert island than they do in our complex civilisation. On the whole, I think they are more often found in private than in public enterprise, though this is less true than it was.

Such people are the creative adventurers of our society. It is they who make things happen. It is their magic touch which builds the social and economic units of our society, whether such units are factories, shops, housing estates, schools, colleges, or even hospitals.

ADVENTURERS AND MAINTAINERS

The creative adventurer must possess three things: first, the intellectual capacity for creation; second, the driving force, the *élan vital*, without which nothing happens; third, the spirit of adventure, the love of battle and the fight for its own sake, the thrill of taking the risk and the nice calculation of the risk taken.

The *capacity for creation* is a complex of mental facets. Analytical intellectual activity may be a positive disadvantage; barristers are seldom builders, and it is a criticism of the higher Civil Service that it relies too much on analytical capacity and too little on creative ability. At first sight these creators may seem to lack basic intelligence. But this may be no more than an expression of their lack of interest in spheres of life which they have dismissed as unimportant or outside their field of activity. Sometimes their contempt for intellectual activity is an expression of their age of school-leaving. Many a creator regards school activities as boring and divorced from reality.

The *æsthetics* of social and economic creation are practised intuitively rather than explicitly. Many of the physical defects of our society may be traced to the lack of social taste in the age in which the creative adventurer rose to maturity. The builder must have his vision, but that vision will be determined by the society in which he lives. For it will always be capable of interpretation in terms of everyday reality. It will, however, be no static vision; it will evolve in the light of experience and change with its changing environment. The satisfaction of this æsthetic urge comes in the building rather than in the final product. Once the edifice is made, this type of creative artist will slip away to try his hand in a different field.

The creative adventurer is a man of both *speech* and *action*. He is seldom to be found in his office, and indeed, the best administrator is often the least office-bound; clerical work should be delegated to clerks, and not undertaken by the administrator. The volubility of the creative adventurer may make it difficult to distinguish him from his disreputable first-cousin, the huckster on his market stall, the confidence trickster, the windbag and the humbug, who sometimes manages to foist himself on the unsuspecting selection committee. The simplest test to distinguish the true from the false, the solid building from the empty façade, is to see if the talker is equally prepared to listen and learn.

The *driving force* of the creative adventurer is often phasic in its manifestations. Though there must be a measure of perseverance, the creative act is essentially rhythmic and mercurial. The energy output cannot be maintained all the time, and there must be periods of quiet build-up when nothing much happens. Then a threshold is reached and he is off once more. He bangs into his environment; his aim is to give better than he gets, to mould rather than to be moulded.

The *spirit of adventure* expresses itself most clearly in a readiness to take risks and delight in so doing. He has an attitude of sturdy independence to authority, a regard for the law based on the spirit rather than the letter, and no great thought for the morrow in terms of present security. It is the exact opposite of respectability, of playing for safety, of "pension-itis," and all the other signs of a desire to gain security in a changing world and sell one's soul for a mess of rather dull pottage.

That, then, is a picture of one type of great administrator. In a sense it is both incomplete and over-complete, for no-one will fit precisely into the pattern. There are, however, other pictures of administrative excellence. There are the maintainers, the great exponents of the holding action, who "keep right on to the end of the road" at a slower and less hectic pace. They are less likely to create, but are more likely to hold fast to what is good. They, too, must be intelligent, with an even temper, patience, and humour. They must be able to pick out the essential from the inessential; indeed one of the secrets of good administration is to eliminate everything extraneous or unimportant from any problem or situation.

HUMAN PROBLEMS OF ADMINISTRATION

In many human situations administrative action can convert unhappiness into happiness. It is a good principle always to stretch a point in favour of the individual, and in particular in favour of the freedom of the individual. The petty tyrant is the great author of the unnecessary negative.

But most human problems in administration are far less tangible. They are, in the main, the products of unsatisfied emotion. By this I do not mean cattiness or waspishness, though this does occur, but rather unused emotion in people of both sexes, people in whom part of the trouble is that they are underworked.

There are simple remedies for this. It is as well always to aim at being slightly understaffed, so that everyone always has plenty of real work to do. If by overtime it is possible to avoid the employment of more staff, then overtime is socially desirable, provided it does not mean skimping work during real time, and provided it is not pushed so far as to produce inefficiency through fatigue.

The other great remedy is to build up and maintain staff morale. Everyone should feel that his or her job is really worth while, and that the hospital as a whole is moving steadily forward in service. The citizens of any community should have faith in their hospitals and feel proud of them. They will do so precisely in proportion to the pride which the hospital workers feel in themselves and their work. Once good morale has been built up, staff recruitment becomes comparatively easy. Personal smartness of the staff is important; the hospital or institution which issues its porters with uniforms which cannot look well is making a shortsighted economy. Slovenliness in porters and servants, and rude offhandedness in clerks and officials, should be jumped on at once. If they are allowed to pass, they become infectious and the whole tone of the place is lowered. But coupled with justifiable pride must be an ultimate humility; for it is from humility that all humanity stems. Indeed, the nice balance of pride and humility is the basis of good morale.

The administrator who despises staff negotiating machinery is foolishly shortsighted. Often negotiations are piffling in themselves; in fact, they are then acting as an emotional safety-valve. They are also a training in occupational democracy, and sometimes they may even be of real value in righting genuine wrongs. Their final use is as a means of dealing with the complaining psychopath; a curse inside any organisation. Once the complaints of the psychopath get into the official machine there is every hope of their being able to travel up and down for years without harming anyone.

ADMINISTRATORS AND DOCTORS

Perhaps the greatest difficulty which faces the hospital administrator is his relationship with the doctors. It is a subtle and difficult one. The medical man who decides to become a hospital administrator is, in this country at any rate, in a worse position than the layman. Other doctors tend to regard his decision as one dictated by lack of clinical skill, and they will dispute his administrative decisions simply because they resent the possibility that they may be based on medical knowledge. On the whole, therefore, I am in favour of the lay administrator; but it may sometimes happen that a medical man proves himself to be supremely competent in administration, and our system should be sufficiently flexible to make use of such exceptions to any general rule.

One of the great advances brought by the National Health Service has been the abolition of medical hierarchy in hospital as it was seen in most local-authority hospitals, and as it is still seen in some Service hospitals. The substitution of a number of parallel teams, units, or firms gives to the senior doctors complete clinical autonomy, without which, in my view, good medicine cannot be practised. The new liberty and equality take getting used to. The fraternity needed is not always forthcoming, and the need does sometimes arise for a measure of discipline, to correct either laziness or clinical failings on the medical side. I have no doubt that such discipline can only be a self-discipline applied by the medical profession itself.

The question is, how should it be applied? What is the best technique? The medical staff committee is a useful device, but only sometimes will its chairman feel that he has the necessary authority to administer a correction to his colleagues. Where his personality is such that he is able to do this, I have no doubt that he is the right ally for the lay administrator.

The Americans seem to have adopted a good system, whereby the chief of each department is known as a "chief of service." These chiefs of service form a medical board, and one of them is elected its president. The board meets weekly to perform an audit of service in the hospital, and any medical failures are investigated before the board and, if need be, correction is administered. The medical board is the police machine for the medical side of the hospital, and it looks as though it works effectively. It would be an interesting experiment to see such boards tried in a few English hospitals; save on the rarest occasions, it is not part of the job of the medical committee to investigate the failings of medical staff, yet healthy self-criticism inside each hospital might do a lot of good.

I am quite sure it is wrong to try to establish any other kind of supervising machinery for the doctors. Good medicine demands the occasional taking of risks, and those risks must be taken in the interest of the patient without regard to possible subsequent lay criticism. The doctor who is always looking over his shoulder at some other authority is certain to be a bad doctor.

If administrators are varied in their personalities, so too are the doctors. And doctors, like administrators, are subject to special occupational risks. Doctors may be brusque and rude at times; above all they may exhibit contempt for lay authorities. This is entirely healthy. Their job is to serve their patients, and not toady to committees or officialdom. The doctor who successfully squirms his way into the good graces of the lay authorities may be a poor servant of his patients. Long may the doctors continue to knock about all who are set in authority!

There are, however, other aspects of medical behaviour where improvement is eminently desirable. It might be expected that medicine would be a profession which broadened the mind; in fact, it often has the reverse effect. Partly this is due to the situation in which a doctor sees his patients; they want his help, and self-interest dictates deference and honesty. But partly it is due to the *high remuneration which doctors have commanded* for many years; even at the outset of their careers this is now the rule. This places them in a different position from the rest of society, where such high earnings are exceptional. Yet doctors tend to take their high cash rewards as a matter of course. So you will sometimes find that they regard themselves as a privileged community. High cash rewards certainly produce isolation. But privilege is to be earned and won by service, and each generation of doctors must earn and win it anew.

The way our doctors behave is, in part, determined by the way we treat them. The social contract of medicine is not a one-sided affair, and if we as patients accept rudeness, brusqueness, inadequate explanations of our troubles, and low standards of waiting-room accommodation, then we have only ourselves to blame if these continue.

Having criticised my own profession, perhaps I may be allowed to add that similar failings may be seen in administrators. Moreover, it is the job of the administrator to cope with such failings, whereas in medicine they are quite secondary to the performance of the job itself, the science and art of healing.

CENTRE AND PERIPHERY

One of the great jobs of this half-century is to establish the right relations between the centre and the periphery. We have to work out the right level at which policy decisions are to be made, and the right level at which to translate them into action.

In the administrative creation of a national service, there are two phases. The first is a process of centralisation, when the greatly varying local units are integrated and welded into potentially efficient local groups, and gross local defects are ironed out. The second process is one of decentralisation, when power is shed at the centre, so that only a broad planning function remains. There is no doubt that Parliament designed the National Health Service wisely in this respect; indeed the first circular of all (R.H.B./1) sets out a reasonable relation between the Ministry, the boards, and the management committees. The muddle which has followed is due to the activities of a small group of Civil Servants who are bogged down by their inexperience of practical work in hospitals or any other peripheral administration. The flood of circulars which they have produced proves this. *Mistakes are occurring continuously at the periphery*—and always will do so in any large service. A small proportion of these fortuitously reach the centre. They are there studied and analysed, and detailed administrative steps are worked out in vacuo for the prevention of similar errors. The result is a circular which bears only on the past. For in future it will be other and different errors, or similar errors in new circumstances, which will cause trouble.

The battle of the periphery against the centre will not be won until regional boards receive block grants, to spend as they will, subject only to the broadest general directions (including, however, minimum wage-rates and conditions). When regional boards have won their battle, it is every bit as important that they, in their turn, should give the fullest autonomy with block grants to management committees. Of course, the work of management committees *must be watched, and stimulated* from time to time. But it is the duty of the region again to lay down principles of work, leaving the details of execution to the periphery. Indeed devolution should be the rule down to the humblest employee. But it carries with it the necessity that everyone, *all the way down the scale*, should both feel responsible and be responsible for doing the job. And if devolution is to be combined with effective work, the *higher authority must be prepared* from time to time to pounce upon the lower, and to be pounced upon from above in turn. Such pouncings must become steadily rarer as one goes up the scale, or they will make nonsense of devolution.

To create a feeble administrative and executive body, give it 30 or more members, representing as many different interests, and no power over its own finances. With any luck, no action at all will result. Private enterprise has learned by bitter experience that the proper size for an executive committee of directors is from 5 to 7. I look forward, in the not too distant future, to regional boards and hospital management committees of this size,[1] with every decision definitive, no subcommittees, and the members paid a small directorial fee for their work. It is sometimes said that the payment of such fees makes the directors less willing to resign as a method of coercing the centre. I do not think this is so, since it is very rare to find unpaid nominated committee members who are ready to resign on specific issues. In any case, the threat of resignation is a poor weapon, save in exceptional circumstances.

The small board or committee not only simplifies administration, but keeps the administrator much more on his toes. In the multi-committee system the slacker can assist in the process of getting nothing done, by feeding potential decisions into committees, where they run up and down the line for months. With the single definitive committee, this is impossible.

SIZE OF COMMUNITIES

Another great job for this half-century is to find out the right size for different social groups. This is part of what I call "social architecture." There are certain basic material considerations, where the physical and the social scientist and the economist can make precise statements at the outset. In hospitals these include, for example, the turnover of cases of any *particular* kind necessary for the development of medical and nursing skills. Some material considerations, such as those of supply, are of secondary or even tertiary importance compared with human considerations. My personal internal experience is limited to some five former voluntary hospitals, three former municipal hospitals, and one Service hospital. I am fairly sure that too big a hospital of any kind is a mistake; here I include mental hospitals, mental-deficiency institutions, and chronic-sick hospitals. I put 600 beds *in one institution* as the maximum, and I am not sure that this is not too many; but I may be wrong.

It seems to me that the ultimate strength of any society is determined by the size of its peripheral units. If they become too big, there is a point at which spontaneous disruption takes place. If, on the other hand, they become too small, they lack the technical skills which follow from specialisation. Our job is to find the happy optimum, which may well be different for different types of community. Sometimes there will be a clash between the technical and the human considerations. Such clashes can almost always be resolved by getting the full facts on both sides. The more *detailed* the data, the more easily does the decision make itself. There is, however, often the need for an act of creative ingenuity in the solution of such difficulties; and in the final analysis, human considerations must always win.

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[1] Taylor, S. *Lancet*, 1951, ii, 725.

GROWTH, REGRESSION, AND PROGRESS

Every society and community has its dynamic. Some folk think they can make the world stand still, but it is only they who remain motionless; around them there will always be advance or regression. In Canada, if one leaves a farm for a year or so, a forest of conifers springs up and engulfs all. One can only beat Nature by keeping at it. In administration it is the same thing. You can only beat the laziness, the sloth, the selfishness, and the sluttishness which is in all of us, by keeping at it. In small-scale private enterprise, if one lets things drift, the firm goes bust. In large-scale enterprise, public or private, it is possible to ride on the machine for years; but slowly the oil and petrol will be exhausted, the bearings will be worn, and one day you or someone else will find you are riding on a wreck.

It is the job of the administrator to make things tick, and to take command of the dynamic processes of a hospital. In any institution, there will be points of growth and points of regression, responses to increased or decreased need. Existing interests will fight the regression, for no-one likes to see his own department withering away. Yet a new discovery—for example, the new methods of treating venereal disease—may greatly reduce the needs, and facilities must be reduced correspondingly. Similarly, conservatism may struggle against desirable growth.

On the other hand, there are the people who want to empire-build for personal reasons. It is a high administrative skill to be able to distinguish the good man faced with a genuine need for expansion, from those who desire to build for the sake of self-importance.

It is vital never to confuse buildings with progress—a common fault with lay committees. I know of no more dreary sight than the empty hydrotherapy and physiotherapy rooms which decorate so many mental hospitals. Time and again the great work of medicine has been done in humble environments. Addison, Hodgkin, and Bright worked at Guy's in buildings which were old in their day. Yet they built a clinical tradition without equal. It was with home-made apparatus that the atom was first split at Cambridge, and the possibility of radioactive isotopes established. Whenever I see marble magnificence in hospital architecture, and excessive polish and tidiness, I at once suspect that I am looking at something second-rate. After all, the hospital is a noble institution, but it is an over-head on society, as indeed, is the whole of curative medicine. We must remember that and keep our activities and our demands in proportion.

In all administration the act of creation is one of great excitement. It should be a source of additional satisfaction when it is achieved with the smallest possible outlay of money, materials, and man-power. I venture to commend the little health centre which has been built by the Harlow Development Corporation, as an example of what can be done without great expenditure of capital.[2] In all new buildings be on guard against the grandiose. We must build efficiently and with beauty, but the grandiose is seldom either efficient or beautiful. I think it is unwise for any public authority to employ more than a very small nucleus of staff architects: the great bulk of its building should be entrusted to outside firms. Architecture is a creative art, and as a rule it flourishes best in an environment of freedom and risk. Stereotyped dullness in public architecture is usually associated with the salaried architect, though the converse is not necessarily true.

The creative act is not necessarily expensive. It need not be so, and, when the health service is fully deployed, creative acts will often save money. At this particular point in the growth of the health service, when big capital developments are impossible, it is vitally important that all administrators should be trying out new ideas. It does not matter how small the scale of these experiments; it is the spirit of experiment, of improvisation, of adventure, that is important. The psychiatric day hospital is one experiment which commends itself to me as a possible means of saving hospital beds. The Mothers' and Babies' Hospital at Newcastle upon Tyne seems another useful experiment. The experiments which have been carried out in the field of geriatrics since the Appointed Day are most exciting. Less happy, I feel, are some efforts at creating rehabilitation centres, where one has a suspicion that industrial neurotics may be holidaying, rather than recovering.

I commend also the process of marsupialisation—or opening up to the outside what is at present inside. As applied to hospitals this means open access for general practitioners to pathology and X-ray departments, and pushing the specialist services out to the periphery. I have in mind a small laboratory in charge of a technician, or a small gymnasium in charge of a masseuse, serving perhaps fifteen or twenty general practitioners in an outlying area.

Do not be put off by the growls of the vested interests in your hospitals. There is no need to wait until health centres are built for we can create an atmosphere of coöperation not by creating new committees, but by coöperating in our daily work. Above all, do not wait for the Ministry of Health cumbrously to formulate its mind. Get moving with your own experiments and innovations, for it is at the periphery, where patient and service and doctor meet, that the real work is done. It is at the periphery that the real opportunities for advance now exist.

A POSTSCRIPT ON TRADITION

Every institution has its pattern of behaviour; if the institution survives for several generations, the pattern crystallises into a tradition. A tradition of snobbery, of rigidity, of self-satisfaction can be stultifying in the extreme. On the other hand, a tradition of open-mindedness, of adaptability, of humanity, and of energetic achievement can be a constant stimulus to better performance. In Britain we are fortunate in having a number of institutions, in greatly differing fields of endeavour, with traditions of superlative performance. Whatever the initial motives may have been, with the passage of time, the superlative performance becomes an end in itself. Though standards may fluctuate at times, at their worst these institutions are still among the world's best. Among such institutions and their products I number certain ancient schools, colleges and hospitals, the Royal Navy, the *Times* and the *Manchester Guardian*, in more specialised fields *Nature* and the *Lancet*, the productions of our two older university presses, the branded Scotch whiskys, the Bristol sherries, and Stilton and Wensleydale cheeses. To these continuing superlatively excellent human achievements our modern age makes its select additions. The Rolls Royce motor-car, the de Havilland aeroplane, and the B.B.C. are worthy of admission to our Pantheon. I hope that one day our National Health Service, and in particular our hospital service, may have proved itself as a member of this select band.

The essence of such achievement is unvarying quality of service. All who come to us should receive the best that mankind anywhere has to offer. This does not mean frills or luxury, but skilled, dutiful, and courteous service, free from all red tape and restriction, so given that there is no loss of self-respect to either giver or receiver. In conception the National Health Service is a precise expression of the Christian ethic. Our task is now to match the conception with performance, in which task the hospital administrator has a vital part to play.

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[2] Taylor, S. *Ibid*, 1952, i, 253.

Special Articles

UNITS FOR THE TREATMENT OF BURNS

THE proper care of burns requires special hospital arrangements, as the work of the Birmingham Burns Unit has demonstrated. The Ministry of Health [1] have now asked regional boards and boards of governors of hospitals to consider together the establishment of burns units in each region, and to give the problem priority. The units, they say, are needed not only to provide an ordinary peace-time service, and to disseminate knowledge of newer methods of treatment, but to serve as training centres in this particular aspect of Civil Defence.

In any one year, it is estimated, 17,500 patients with burns and scalds need admission to hospital in England and Wales—that is 1 case in 2500 population. About two-thirds of these cases are the result of accidents in the home. (The Ministry note that with proper safeguards these home accidents could probably be reduced by half.) If the average stay in hospital is reckoned to be 35 days, each region will need at least one bed per 25,000 population; and in fact it is generally believed that the average stay would be longer than this. A unit of twenty to thirty beds in each region is suggested; even where there is one unit already, as in the Birmingham region, the Minister favours the establishment of a further unit. Industrial and heavily populated areas, where large numbers of burns may be expected, should be chosen, and regional boards and boards of governors are asked to consider together the hospitals in which units can best be developed. Existing units will serve as a guide when units are being set up.

THE QUARTERS

The Ministry base their proposals for accommodation on the recommendations set out by Dr. Leonard Colebrook, F.R.S., in his book,[2] though they point out that, with the present building restrictions, his full design cannot be attempted. It should be possible to adapt existing buildings or to establish a unit in huts, and the capital cost need not then be large. Wards will be needed for men, women, and children. In order to check the spread of infection, not less than a quarter of the total number of beds should be in single-bed cells, ventilated as in an ordinary isolation hospital cubicle. The remaining beds, the Ministry say, can be in open small wards or subdivided large wards. There should also be one or more single-bed rooms measuring 10 ft. by 12–15 ft., for the treatment of shocked patients during the first 24–48 hours. In addition one, or preferably two, rooms, measuring 15 × 16 ft. or at the very least 14 × 12 ft., are needed for the dressing of burns.

The Ministry insist that the dressing-rooms should be air-conditioned. It will be remembered that Colebrook emphasised the importance of this, to prevent the spread of infection. Infection, of course, is not only a common cause of death from burning, but delays healing and the opportunity for skin grafting. The system chosen should provide 12 air changes an hour, and the air-temperature should be thermostatically controlled at 70–75°F. The circular says that draughts must be avoided, but does not specifically recommend the air-locks proposed by Colebrook.

The cost of air-conditioning such a room is surprisingly low: thus a suitable system for a room measuring 15 × 16 × 13 ft. (with louvred inlet, filter of the throw-away type, heater battery, fan, and ducting to high-level damper-controlled fresh-air inlets, and low-level extract fan discharging to the external air) is only about £200 to instal, plus the cost of any necessary supporting arrangement for the plant. The maintenance cost is between 5*d.* and 6*d.* an hour. The Ministry regard it as desirable, but less important, to provide similar ventilation for the shock rooms. The extra cost of extending the plant and ducting to serve more than one room would be £50–100.

THE TEAM

The Ministry insist that the unit must be under the direction of a small team specially designated for the purpose. This, they suggest, should consist of one or two surgeons (general, traumatic, and possibly plastic) who, in addition to their other duties, are willing to engage part-time in this work. They think it unlikely that any surgeon would agree to spend all his time on the treatment of burns. This has not been the experience of the Birmingham unit; and it will be remembered that Colebrook believes it to be important to place the unit under the charge of a director, supported by a full-time team. He also thinks it essential that new cases should be seen and assessed within a few moments of their arrival at hospital by a senior and experienced member of the team.

Besides the surgeons, the team suggested by the Ministry would consist of a whole-time registrar or senior registrar, seconded from the regular staff for 6–12 months, who could be relieved or assisted from time to time by other registrars in the hospital; and one house-surgeon or senior house-officer who could be relieved or assisted by the other residents. Full pathological services, the Ministry note, will of course be necessary, and there should be close liaison with a plastic unit.

This arrangement has the drawback that the doctor on the spot will never have had the long experience of burn cases which is necessary if the best results are to be achieved; and the picture as a whole falls far short of the team trained for the job envisaged by Colebrook. But it might in time lead to that, if a sufficient number of keen men become interested in this difficult subject.

As the Ministry point out, the medical profession has only recently become fully convinced of the need to provide specially for the treatment of burns; and a burns unit in every region may therefore serve as a valuable demonstration. In modern warfare there would probably be large numbers of burns among the population; and improved methods of treating peace-time burns would provide valuable experience in such an emergency. They therefore think that surgeons, senior registrars, and registrars should be seconded for 2–3 months to the regional burns unit from other hospitals. But the boards will need to meet any capital costs this year, for establishing burns units, from the capital sums already allocated to them, and this year's maintenance costs must be met from funds allocated for revenue expenditure.

NEW COLOURS FOR GAS CYLINDERS

THE Medical Defence Union, the Association of Anæsthetists, and the British Oxygen Company, acting under the ægis of the British Standards Institution, have been studying the prevention of accidents caused by giving the wrong anæsthetic gas. Dr. Robert Forbes, secretary of the Medical Defence Union, informs us that action will shortly be taken to put their recommendations into effect.

The possibility of using a non-interchangeable valve, which would make it extremely difficult to give the wrong gas, has been considered, but no decision has yet been reached. But changes in the colour of gas cylinders have been agreed to on an international basis.

The colours that have been given to cylinders in this country conflict with those used for similar gases in other countries, and serious errors and fatal accidents have resulted. To remove this danger a list of standard colours, names, and symbols for medical gas cylinders has been prepared. This involves changing the colours of most of the cylinders at present in use in the United Kingdom.

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[1] Circular R.H.B.(52)69, B.G.(52)66.

[2] A New Approach to the Treatment of Burns and Scalds. London, 1950; see *Lancet*, 1952, i, 908.

Suppliers of cylinders will make the necessary changes, and they are arranging to collect and repaint cylinders as quickly as possible. Close coöperation between suppliers and users will be necessary to reduce the change-over time to a minimum and to avoid the dangers of having in use for even a short time cylinders of two different colours containing the same gas.

One particular gas will be dealt with at a time: the first cylinders to be altered will be those containing nitrous oxide, which are at present painted black. The colour will be changed to French blue, and repainting will begin on Aug. 1, 1952. Suppliers should be told at once when empty cylinders are ready for collection, and any nitrous-oxide cylinders that are unlikely to become empty in the immediate future should also be returned.

When all the nitrous-oxide cylinders have been changed, the repainting of other cylinders will begin. Hospitals will be told about this by the Ministry of Health, and further particulars will be given by the suppliers.

During and for some time after the transitional stage, a gas must be identified by reading the name or the chemical symbol on the cylinder, and not by colour alone.

A new colour chart will be issued to hospitals. Those who would like copies now may obtain them from the British Standards Institution, 24, Victoria Street, London, S.W.1.

Hospital authorities are being asked to display the following notice in all places where gas cylinders are handled or gas is used:

> "Starting on Aug. 1, 1952, changes will take place in the colouring of medical gas cylinders; to identify the gas, reliance must be placed primarily on the name of the gas or the symbol stencilled on the cylinder and not on the colour of the cylinder."

Copies of the notice should be given to every doctor, dentist, nurse, and midwife engaged in the hospital, and to all porters and other persons who handle gas cylinders.

Every medical gas cylinder arriving in the hospital, and every cylinder already in stock, should be marked with a red tie-on tally bearing in heavy black type the words:

> *DANGER:* COLOURS ARE BEING CHANGED. READ THE LABEL AND CHECK THE SYMBOL AND NAME OF GAS.

Hospital authorities should see that frequent inspections are made to ensure that the tallies are in position on all cylinders.

Anyone about to use an anæsthetic machine should first verify the couplings of the apparatus. Safety can be achieved only by observing the following rules: (1) Read the name of the gas or the symbol on the cylinder. (2) Check the coupling of the anæsthetic apparatus. (3) Test the gas for identity at the delivery end.

WORK OF THE KING'S FUND

H.R.H. the DUKE OF GLOUCESTER, presiding at the annual meeting of King Edward's Hospital Fund for London on June 25, announced that the Queen has consented to become patron of the Fund.

The main lines of the present phase of the Fund's work were, he said, becoming fairly clearly defined. By visiting the hospitals and making grants for a great variety of purposes it had been able to lend a helping hand in many different ways. ("The list includes, I am glad to say, a number of grants to mental hospitals, mostly for the improvement of the recreational facilities.") If and when times became easier it might be practicable to look at rather larger projects. Meanwhile the Fund was glad to be able to expand its activities in other directions to meet what were generally felt among the hospitals to be real and pressing needs.

"The plans made four or five years ago are now taking effect; last year saw the opening of the Hospital Administrative Staff College at Palace Court, the School of Hospital Catering at St. Pancras, and the conclusion of an extensive special survey made by the Convalescent Homes Committee. We are now about to submit to the Ministry of Health the conclusions of our investigation into the possibility of cost accounting in hospitals. In this current year, too, the foundations are being laid for a course designed to bring a fresh approach to the work of the hospital matron, taking account of recent changes in outlook on the technique of management."

Two more of the Fund's homes for the aged sick had been opened recently, one at Ealing and one at Sydenham, and another would be opened at Blackheath the same afternoon by the Duchess of Gloucester. Work was in progress on other homes.

SIR EDWARD PEACOCK, the treasurer, said that the Fund's total receipts during the year had come to over half a million pounds. It was very satisfactory that the receipts from legacies should continue to be so well maintained. Grants to hospitals and convalescent homes reached a total of £170,000, and over £132,000 was expended on setting up and administering special services. Sir ERNEST POOLEY, chairman of the management committee, said that no-one could read the annual report without realising the enormous importance of voluntary effort not only for hospitals but for the country generally. Mr. MALCOLM MCCORQUODALE, M.P., speaking as chairman of the Hospital Administrative Staff College, reported that in the first complete year 112 administrative officers, many of senior rank, had followed one or other of the courses. The students of the first full training course had just completed four months' study at the college and were now about to enter on a period of hospital practice under supervision. They would return later to the college for further study and would, after that, again be placed in suitable hospitals to complete their practical training. It had always been the intention to use the college as a centre for the study of hospital problems as well as for the provision of courses of instruction, and already there was a group actively engaged on the question of "making the best use of hospital beds."

Mr. J. W. BOWEN, chairman of the North-East Regional Hospital Board, endorsed to the full the passage in the report: "It seems clear that with the continuance of straitened circumstances hospitals will increasingly find that the relatively small sums that can be made available by the Fund are nevertheless often the means of achieving ends disproportionate to their size."

THE DURHAM DISPUTE

REPRESENTATIVES of Durham County Council and of the Joint Emergency Committee of the Professions agreed on June 26 to ask the Minister of Labour and National Service to appoint a board of arbitration with the following terms of reference:

> "It being accepted by the parties that the professional employees of the county council represented by the Joint Emergency Committee of the Professions—namely, dentists, doctors, professional engineers, midwives, nurses, and teachers—should not as a condition of employment be required to belong to a trade union or professional organisation, the board are asked to determine:
>
> (i) whether the present regulations of the council governing the making of applications for extended sick pay are in conflict with the principle of voluntary membership of a trade union or professional organisations and should therefore be withdrawn; or
>
> (ii) whether the regulations are made in the present exercise of the discretion vested in the council in the granting of extended sick pay and are not in conflict with the principle of voluntary membership of a trade union or professional organisation."

Both the county council and the Joint Emergency Committee of the Professions undertook to accept and implement any award of the board of arbitration.

The teachers' organisations decided to withdraw forthwith the notices of resignation which had been handed in by them on behalf of their members, and the county council decided to suspend immediately the operation of the regulation which had given rise to the dispute. Further, the professions agreed to take all other necessary action to close the dispute.

The Minister has since appointed Sir John Forster Q.C., to be chairman and Prof. D. T. Jack and Mr. J. W. Bowen to be members of the board of arbitration, which will meet in London on July 15.

Sir John Forster is president of the Industrial Court. Professor Jack holds the chair of economics at Durham University. Mr. Bowen is a former chairman of the London County Council.

In England Now

A Running Commentary by Peripatetic Correspondents

AN interest in history is no doubt one of the signs of middle-age; I must own that when I had rooms in the medieval court of Corpus Christi College, Cambridge, I neither knew nor cared whether it was the first court built in an English university. All the same, when I joined in the college's sexcentenary celebrations last week, and looked up at the lovely Saxon church of St. Bene't, or Benedict, I realised that the beauty of the place and its setting had left its mark on me for life, though I did not appreciate it at the time. From this court, thirty years ago, we medical students set out to hear lectures by, among others, two future presidents of the Royal Society—Gowland Hopkins and E. D. Adrian. Perhaps we did not realise that we were getting a university education as well as a medical one. I was lucky enough to have a practising physician as my supervisor of physiology; when I met him at the celebrations he repeated an old argument of his that the Cambridge undergraduate's education is often too medical and too good. Everyone agrees that it is too medical—but who dares take the first step to make it less so? It is too good when a man has only to remember what he is told, and need never think for himself to pass his exams.

One of Corpus's most famous sons made his name by thinking for himself—about blood-pressure. Many rank Stephen Hales's discovery with Harvey's; but it was in the versatility of Hales's mind that his real genius lay—he constructed an instrument to slow down the motion of the heavenly bodies; he produced a leaden cast of the bronchial tree; he invented an instrument to whip cream and another to ventilate prisons; he measured the pressure of the rising sap; and, as every Corpus man should know, he timed the growth of bone before John Hunter was born. Many of us are still following Stephen Hales's example in testing "unsatisfactory conjectures" and trying to make history as well as study it.

* * *

It was noteworthy that Potter, in his recent radio talk on Doctorship, did not mention its newest branch, Non-Smokership, which has developed out of all recognition since the discussions in these columns 18 months ago. Lifemen who, like myself, had already given up smoking years ago because we could not *afford* it, can now make a virtue of necessity. As our plutocratic friend proffers his gold cigarette case we can achieve wonders with a mere raising of an eyebrow, a look of surprise, and a more-than-usually emphatic "No, *thank* you." Observing the effect of such an approach is one of the keen pleasures of true Doctorship. The victim may show slight but unmistakable signs of truculence; or he may make an uneasy attempt to laugh it off, remarking, "I shot my bolt long ago, Old Boy." The correct counter-ploy here is, "I'm sorry you take that attitude, Old Chap." As X. Odoreida has pointed out, the strength of this riposte lies in the words "Old Ch[illegible] ith the protagonist's "Old Boy"; if [illegible] this phrase will imply that the Lifeman is a generation wiser and more self-disciplined than his companion.

The serious practice of Non-Smokership offers as much scope as any branch of Doctorship—indeed, it covers almost the whole vast field of Lifemanship. One word of warning, it can be carried too far. As Potter himself would say: *One Must Know When to Stop.*

* * *

A geneticist friend of ours finds himself in an interesting position. From his youth he has been aware that in the matter of vomiting he is not as other men. Not for him the cough, the retch, the beads of sweat, the partial tearing of the abdominal muscles. All he has to do is switch in some hypothalamic overdrive and *up* it all comes. His wife, it seems, is cast in more fragile clay, and vomits in a routine manner. They have two children, both as a rule possessed of cast-iron stomachs. Nevertheless, the boy has succumbed to various infections, and our friend has been interested to observe on these occasions that his vomiting follows the maternal pattern. It is with the girl, however, that the future rests. In earliest infancy she was a good regurgitator, but for the last two years nothing would induce her to vomit. The other day she obliged on the dining-room sofa, and our friend was delighted to recognise at once a kindred spirit. He is now chattering happily about fourth-generation siblings, and he has already reserved a little black square for himself at the head of the family tree to be published in THE LANCET of A.D. 2052.

* * *

It was as a schoolboy that I first learnt of the traditional inability of doctors to express themselves without using long technical terms. An example was the medical witness who said his patient had "sustained a severe contusion of the integument under the left orbit, causing extensive abrasions of the cuticle, with local extravasation of blood and ecchymosis into the subcuticular tissue"; to which the learned judge remarked "You mean he had a black eye?" For fifty years (and God knows how long before that) this monstrosity of pathological hyperbole has been employed to flagellate us for our stupidity.

Whenever a book on forensic medicine or an article or lecture on medical evidence is published, one looks with confidence for this venerable example of supposedly customary practice. I have always regarded the doctor who was originally responsible as a lineal descendant of Mrs. Harris—the choice perfection of the phraseology smells too much of the lamp. But since it is just possible that it really issued from the lips of a colleague with more fluency and love of accuracy than sense of proportion, I always write to ask for chapter and verse. So far there has been no response; nor do I anticipate one to my latest inquiry on its reappearance only last week. It will live for ever—unless someone can invent another example which is equally striking and slightly more probable.

* * *

After a couple of stillbirths and a miscarriage or two, Mrs. D at last had a daughter, born by cæsarean section. As she left the hospital sister expressed the hope that she would be coming back some day. Mrs. D thought this over but concluded that she didn't know: "After all I've been through," she said, "I'll be a bit precautious."

* * *

I took it hard when a patient of mine told me that the osteopath she works for as secretary had given her sulphacetamide drops for her sore eye. Not that I objected to his treatment, which was successful, or to his interference, which was kind. My point was that this osteopath had used the orthodox weapons he pretends to reject. If he had manipulated her cervical spine he would at least have been consistent. Heretics must have the courage of their heresy if they want other people to take them seriously.

* * *

Looking for a cheap hotel in a north Italian town last summer I came across one that looked just what I wanted—clean, at least relatively so, and simple. In a ground-floor window there was a large placard advertising the virtues of the restaurant in four languages. At the top the announcement was given in Italian: "*Pránza al prezo fisso. Cucina del casa.*" Next came its equivalent in German, and below that in French: "*Repas à prix fixe. Cuisine familiale.*" Last came the English version: "*Meal at fixed price. Familiar cook.*"

* * *

Conversation before operation:

"When you were off work for 18 months, did you have a pain?"—"Yes, Doctor."

"Where?"—"My doctor said it was round my heart."

"I see. Show me just where it was."—"Round my heart, Doctor."

"Yes, but point with this finger to where the pain was worst."—"I can't do that, Doctor."

"Why not?"—"I don't know where my heart is."

Letters to the Editor

RESISTANT STAPHYLOCOCCI

SIR,—The article by Dr. Clarke and her colleagues (June 7) is one of several recent reports on the increasing number of drug-resistant staphylococci in hospital infections. We are apt to forget how much more heroic some branches of surgery have become under the protection of antibiotics, and it would be a tragedy if we allowed the present trend to continue.

The following points regarding hospital staphylococcal infection are important:

1. Staphylococci far exceed all other pathogens as the cause of secondary infection.

2. Wards which have patients with chronic staphylococcal suppuration build up a reservoir of drug-resistant staphylococci.

3. The most important mode of spread is: contaminated dressings → floor → blankets → fresh wounds. It is true that many of the staff may be transient or even permanent carriers: but masking and a no-touch technique in wound dressing reduces the nose → finger → wound spread, and in my opinion droplet spread is of minor importance with respect to staphylococci.

4. The measures taken to prevent cross-infection in many hospitals appear to be concerned almost exclusively with respiratory and streptococcal infection. Adequate bed-spacing, face masks, and bowls of 'Dettol' have no doubt contributed to the eclipse of the streptococcus. But when a staphylococcal infection is treated in the ward, contaminated particles from the dressing are commonly swept from one end of the ward to the other, alighting on bed-clothes from which they are thrown up to descend on fresh wounds when these in turn are exposed.

5. This mode of spread may have little importance in acute surgical wards, but is of very great importance in orthopædic wards. The sum of misery and frustration brought about by the ubiquitous staphylococcus is still very high. Amyloid disease still arises from unnecessarily infected tuberculous sinuses; spinal grafts are still extruded, screws are loosened, and tendons destroyed; chronic osteomyelitis still occurs, and is still one of the most distressing of all diseases.

As we are not controlling the staphylococcus by antibiotic therapy, we must consider how to stop the spread of this organism in chronic surgical wards. The measures I would suggest are:

(*a*) Separation of infected from non-infected patients. Separate wards may be impossible, but there is no need to put a patient with a tuberculous abscess requiring aspiration in a bed adjacent to one with a discharging osteomyelitis.

(*b*) Dressing-rooms for all dressings and examinations. No peeping at wounds in the open ward.

(*c*) No dry sweeping. A vacuum-cleaner suitable for hospital wards is an urgent necessity.

(*d*) Careful supervision of the disposal of infected plasters and dressings in the theatre as well as in the ward.

(*e*) A patient in an orthopædic ward, discharging staphylococci that are resistant to the antibiotics in common use, should be isolated.

Royal National Orthopædic Hospital, Stanmore, Middlesex.
CHARLES H. LACK
Pathologist.

PERIPHERAL FACIAL PALSY

SIR,—Mr. Terence Cawthorne's article (June 20) on peripheral facial palsy and his observations on its pathology in an earlier communication[1] provide a valuable contribution to our knowledge of this condition.

Particularly interesting is the analysis of the ætiology in 129 cases in which the lesion was intratemporal, and in which the facial nerve was exposed at the upper level of the lesion. One infers that no case of Bell's palsy was met with in which a lesion could be demonstrated in the tympanic segment or upper vertical segment (as he has named them), whereas 53 cases were found in the lower vertical segment.

Does Bell's palsy ever involve the facial nerve as high as the geniculate ganglion? Mr. Cawthorne says that between the geniculate ganglion and the level of the chorda tympani there is no guide as to the site of the lesion except the cause. Does he consider the stapedius reflex of any value in localisation? If the patient complains of hyperacusis as well as facial palsy and taste disturbances, would this constitute a dependable indication that the level of the lesion is above the level of the nerve to the stapedius? It would seem theoretically that the presence of hyperacusis should provide a guide for lesions suprachordal but infrageniculate (provided lacrimation is normal).

I have at the moment in general practice a schoolmaster, aged 40, who experienced a feeling of tightness not amounting to pain in the left ear and overnight developed complete left peripheral facial palsy. In addition he complained of painfully loud hearing on the same side, particularly painful when using the telephone. There was smarting of both eyes but not one more than the other. He had a feeling in the left side of his tongue anteriorly as though it had been scalded by hot fluid. These complaints developed concurrently with the palsy.

The palsy is very obvious, there being pronounced dropping of the angle of the mouth, inability to close the eye, and loss of forehead furrows on the affected side.

Examination of the ears shows nothing abnormal. Weber test normal. Rinne's test positive on each side, but air-conduction lasts longer on the left than on the right side and some sounds are painful. Hearing is normal for conversation and whisper. The tympanic membrane is normal: there are no herpes spots. Taste tests are inconclusive, all the front of the tongue being unreliable. Blood-pressure and central nervous system normal. Wassermann reaction not yet known.

In such a case is one entitled to conclude that the lesion of Bell's palsy extends from the stylomastoid foramen to the geniculate ganglion, and that if decompression had to be carried out the lesion would be found in the tympanic part of the nerve or above?

All authorities agree that it is impossible to give a reliable prognosis in the first week or two after the onset of a complete Bell's palsy even with the help of electromyography, &c. Has Mr. Cawthorne, from his survey of 325 cases, gained any hint as to prognosis based on an assessment of the clinical features in the early days of the palsy? Thus is there any suggestion that a severe case such as I have described carries a worse prognosis as regards recovery of full function than a case of complete peripheral facial palsy without evident involvement of the chorda tympani, stapedius, and lacrimal gland, or with involvement of the chorda tympani only?

It seems unsatisfactory indeed that the only indication for the operation of decompression is the absence of clinical or electric evidence of returning function a month or more after the onset of the palsy. One would imagine that meanwhile irreparable harm would have overtaken the nerve.

Sheffield.
E. C. ATKINSON.

⁂ We have shown this letter to Mr. Cawthorne whose reply follows.—ED. L.

SIR,—The term Bell's palsy implies a lesion of the facial nerve-trunk in the lowest part of the vertical segment just above the stylomastoid foramen. Since first recognising at operation the characteristic appearance of the nerve-trunk in this situation, it has been noted in all but 4 of the cases of facial palsy submitted to decompression. The swelling and discoloration of the nerve-trunk in Bell's palsy has never been seen to extend higher than 1 cm. above the stylomastoid foramen. It remains to be seen whether in severe cases the swelling extends higher than this; and if so whether it is the same disease. Only by looking and seeing can this be found out.

That the lesion is in the lowest part of the intratemporal part of the nerve is suggested by the effect on taste; for in many cases taste is unaffected, although the chorda tympani nerve joins the facial less than 5 mm. above the foramen. Loss of taste is often experienced in cases which subsequently recover spontaneously; and very occasionally when it is unaffected complete recovery does not take place.

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[1] *Lancet*, 1951, ii, 593.

The stapedius reflex is disappointing as a localising sign; for the undue sensitivity to loud sounds which might be expected to follow paralysis of this muscle rarely happens, even when the nerve to stapedius is affected. This may be because its work is taken over by the other intratympanic muscle, the tensor tympani, which also contracts in response to loud sounds, and which receives its innervation from the fifth cranial nerve.

The prognosis in Bell's palsy depends upon the extent of the paralysis and the ability of the nerve to transmit an electrical stimulus. Of 45 cases in which the paralysis was incomplete, 44 had shown improvement within two months. On the other hand, of 107 cases in which the paralysis was complete, 58 showed no sign of recovery after two months. Of 92 cases in which the nerve retained its ability to conduct an electrical stimulus, only 1 failed to show any sign of recovery within two months; whilst of 60 cases in which the response was lost only 3 showed any sign of recovery within two months. Though severe pain and loss of taste often accompany the more serious lesions, I have noted both these phenomena in incomplete paralysis where spontaneous recovery is the rule.

I wish that I could give more definite answers to Dr. Atkinson's interesting and pertinent questions; and I feel, as I think he does, that early decompression offers the best chance of preventing irreversible damage to the nerve.

At present the most that can be said in the earliest stages is that where the paralysis is complete the chances of total spontaneous recovery are evenly balanced with the prospect of eventual partial recovery or none at all. Confirmation, by electrical tests, of the severity of the lesion must wait for two weeks, during which time, as Dr. Atkinson says, irreparable harm may have been done. I sincerely hope that it will not be long before we can tell within a day in which cases decompression is needed.

London, W.1. TERENCE CAWTHORNE.

SUCCINYLCHOLINE

SIR,—I hasten to thank Dr. Bourne and his colleagues for their excellent and significant contribution, published in your issue of June 21.

There is, however, one procedure described by them that should be acted upon only with caution and full knowledge of the mechanisms involved. After suggesting that, at the end of an operation in which *d*-tubocurarine chloride or gallamine triethiodide has been given to provide relaxation, succinylcholine may be used when the abdomen is to be closed, in order to avoid the further use of the longer-acting agents, they proceed to recommend the administration of neostigmine "even in a full 5 mg. dose" "when the succinylcholine has worn off, if there remains any doubt whether the patient has sufficiently recovered from the curare or gallamine." This procedure is safe provided that one can be absolutely sure *that all the succinylcholine* has been hydrolysed. It is, however, my suspicion that after large doses, or repeated small doses, of succinylcholine the return of *some* respiration does not necessarily mean complete removal of all the drug; for we have observed and recorded a case which has, in fact, returned to a state of apnœa following a dose of neostigmine, and the cessation of respiration lasted for a not inconsiderable time.

There is another sequence of drugs in which the unwary may be inclined to indulge and which may lead, I believe, to serious results. It is conceivable that there may be circumstances in which, at the end of an operation, after the administration of anæsthesia which includes *d*-tubocurarine chloride or gallamine triethiodide and neostigmine, the surgeon may for some reason decide to reopen the abdomen—for example (although this may seem far-fetched with modern methods of checking) to find a missing swab. The anæsthetist may then be tempted to produce temporary relaxation with succinylcholine. I have, for quite a different reason, given this sequence—*d*-tubocurarine chloride, succinylcholine, atropine, neostigmine, succinylcholine—and although the last dose of a succinylcholine was, in fact, only 25 mg., there resulted a most alarming bradycardia (pulse-rate in the region of 30 per minute) followed by vomiting of what appeared to be recently secreted stomach contents. This picture did not appear until immediately after the administration of the succinylcholine. Conceivably the bradycardia was unrelated to the succinylcholine but a possible mechanism would be an intense inhibition of tissue cholinesterase due to the combined action of neostigmine and succinylcholine. The previously administered dose of atropine (1·3 mg.) was evidently insufficient to prevent this.

I believe that there may be a place for the administration of more than one relaxant agent to a patient in order to attain a desired result. This polypharmacy, however, must be practised only with full realisation of the interaction of these agents and of the relation they bear to other drugs which may be administered; otherwise there will be danger of the anæsthetist losing that complete control of the situation which is one of the great advantages resulting from the advent of these valuable agents.

Department of Anæsthesia,
University of Liverpool. T. CECIL GRAY.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—I read Miss Humphreys's letter (May 24) on nurse-cadets with considerable sympathy, but I must challenge her statement that "this is the considered opinion of my colleagues in the teaching profession."

The Association of Head Mistresses have discussed nursing-cadet schemes on many occasions, not only among themselves, but also with the Association of Hospital Matrons. While sympathising with the difficulties that such schemes are designed to solve, both in hospitals and for girls leaving school at 15, it is the considered opinion of the Association of Head Mistresses that they are not the best solution of these difficulties and, indeed, that they create additional problems for both hospitals and girls.

AGNES CATNACH
Past-president of the Association
London S.W.18. of Head Mistresses.

COTTON SUTURES

SIR,—I read with interest the letter from Dr. Patrick (June 7).

We have always understood that the primary *factors* in surgical sutures should be uniformity of *gauging*, maximum tensile strength, and absence of tissue *irritants*. Whilst we agree that economy should be exercised in the use of all materials in hospitals, it *is surprising* that, when such high standards are demanded from the recognised manufacturers of suture materials, the surgical profession are prepared to purchase reels of cotton, &c., from the ordinary haberdasher.

Cotton thread seems to have little following in this country; but we should be quite prepared to investigate the possibilities of supplying a similar material manufactured under strict control, ensuring reliable gauge and tensile strength. You will appreciate that firms marketing ordinary cotton and linen thread for domestic and industrial purposes are not obliged to announce any changes in their manufacturing procedures which might involve change of dye, filling, &c.; and a change of this kind might have serious complications for patients into whom the thread was implanted.

From information that we have received—albeit somewhat vague—as to the cost of major operations—expenditure on suture materials seems to represent little more than 1½%. Thus the saving in buying "uncontrolled" suture materials would be a fraction of 1% of the cost of the operation and thus an infinitesimal percentage of the total cost of the hospital services.

Ethicon Suture Laboratories Ltd.,
Edinburgh.

W. J. WARD
Product Manager.

MONILIASIS

SIR,—Your annotation (June 21) accompanying two reports of moniliasis draws attention to this condition following treatment with antibiotics. You suggest that, before starting treatment, precautionary measures should be taken: "First, before starting therapy with aureomycin, chloramphenicol, or terramycin, it is wise to ascertain, whenever possible, the bacteriology of the condition (where it is desirable to start treatment before the bacteriological report is known, penicillin or sulphonamides can be used in the first instance)."

Stuart[1] and Hulse[2] both reported serious infections of the bovine udder with yeasts of the candida species following treatment of the udder with penicillin. It might be questioned, therefore, whether penicillin is much safer in this respect than the other antibiotics.

Ministry of Agriculture and
Fisheries, Veterinary Laboratory.
Weybridge, Surrey.

A. W. STABLEFORTH.

SUDDEN DEATH IN INFANCY

SIR,—Your leading article last week rightly stresses the changing outlook on the cause of sudden and unexpected death in infancy, and mentions a number of current views on the probable causes. While you confine yourself largely to the type of case that comes before the coroner, the same problem is present in many of the deaths that occur in hospital.

Excluding cases of gross congenital deformity and of diseases that occur throughout life, such as meningitis, we know extremely little of pathological processes in children. In such cases we are commonly hindered by attempting to interpret gross necropsy findings in terms of adult pathology. You write: "At necropsy the thoracic viscera were congested and often covered with petechial hæmorrhages. These findings suggest asphyxia, but . . . the clinical picture was that of severe respiratory infection." Such petechial hæmorrhages are so common in infancy and occur in such diverse conditions that in my opinion they do not indicate asphyxia or necessarily even any respiratory disorder.

The cause of death in these infants dying suddenly will not be known to us until we know considerably more of the functional pathology of infancy—such as factors promoting pulmonary œdema or bronchial secretion.

A point that is often overlooked in cases of "sudden death" is that questioning of the parents privately and at leisure reveals that very few of the children were in fact "perfectly well when they went to bed and found dead in the morning"; and a history obtained by an enlightened social worker, such as a children's hospital almoner, is frequently found to be quite different from that obtained under the stress of the coroner's court. The term "unexpected death" describes these cases, rather than "sudden death."

While interchange of ideas would be extremely useful, at our present state of knowledge more will probably be learned by a few people doing very detailed investigations in different centres than by a coördinated investigation such as you suggest; for this type of investigation is only likely to produce large figures based on current pathological concepts.

Department of Pathology,
Children's Hospital, Sheffield.

JOHN L. EMERY.

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1. Stuart, P. *Vet. Rec.* 1951, 63, 314.
2. Hulse, E. H. *Ibid*, 1952, 64, 210.

ANATOMICAL NOMENCLATURE

SIR,—At the International Congress of Anatomists, held at Oxford in the summer of 1950, it was resolved to set up a committee, comprising three members from each of the countries (or groups of countries) represented, to make recommendations to the congress to be held in 1955 in France for the establishment of an agreed international anatomical nomenclature.

Hitherto there has not been an *agreed* international anatomical nomenclature. The B.N.A. (1895), despite the fact that it has been gradually adopted by most countries, was essentially the work of a small committee of exceptionally able German anatomists, and the fact that one British and one Italian anatomist were coöpted during its preparation did not make the B.N.A. an agreed international nomenclature. In 1933 the Anatomical Society of Great Britain and Ireland approved the revision of the B.N.A. carried out by British anatomists with the intention of bringing it up to date, and this revision has been in use in the anatomy departments of universities and medical schools in this country for nearly twenty years. The corresponding German society (Deutsche Anatomische Gesellschaft), working quite independently, published its own revision of the B.N.A. in 1936. Since then advances in knowledge, particularly in the section of neurology, have made it desirable for the whole position to be reviewed with the authority attaching to an international committee of anatomists.

With the sympathetic and material support of UNESCO and its appropriate branch, the Council for the Coördination of International Congresses of Medical Sciences, it proved possible to hold a meeting in London of one duly accredited representative from each country (or group of countries) concerned.

This meeting was held in the week May 26–31, 1952, when representatives were present from France (representing Belgian and French-speaking Swiss anatomists), Germany (representing Austrian and German-speaking Swiss anatomists), Great Britain (representing British, Irish, and Commonwealth anatomists), Holland, Italy, Scandinavia, Spain and Portugal (including the Spanish and Portuguese-speaking countries of South America), and the U.S.A. An invitation had been issued to the anatomists of the U.S.S.R. but no representative attended.

The principal object was to determine whether the proposal to attempt to establish an agreed international anatomical nomenclature at the present time was in fact practicable, and the matters discussed were, to a very large extent, matters of principle. Throughout the six sessions there was an atmosphere of cordiality and friendship which was not only encouraging but expressed itself in a willingness to compromise, whenever compromise could be considered reasonable and justifiable. As a result the committee came to the conclusion that the establishment of an agreed international anatomical nomenclature was practicable and it was decided to proceed therewith.

As a first step it was agreed unanimously that the B.N.A. (1895) should form the basis for an agreed international anatomical nomenclature and that the changes to be effected in it should be restricted as far as possible to those considered essential. The principles which had been adopted in the B.N.A. were fully discussed and, with a number of minor modifications, were unanimously adopted. Further, it was unanimously agreed that each country should be at liberty to translate the official term, which would be in Latin, into its own vernacular for teaching purposes, if it desired to do so, but the committee was very strongly of the opinion that in scientific publications, in anatomical or other medical journals, it was most desirable that the official Latin terms should be used—especially in the titles—to avoid ambiguity or uncertainty.

The detailed work will be carried out by a series of subcommittees and it was agreed to make a special effort to submit a report to the International Congress of Anatomists to be held in France in 1955.

While the committee felt that the revision of anatomical nomenclature was properly the responsibility of anatomists, they were well aware that it was most important to obtain the sympathetic coöperation of all who are actively concerned with the teaching of medical students in any branches of medical science, for it would patently be absurd to lay down for anatomists that each structure in the body should be designated by one term only, if no attempt were made to persuade physiologists, pathologists, clinicians, and others concerned, to use the same terms. It is, therefore, hoped that those who are interested in this matter will communicate their views to me, and I will gladly undertake to put them before the appropriate committee.

In an endeavour to make known as widely as possible that this revision of the B.N.A. will be an agreed international anatomical nomenclature in actual fact, each member of the committee has undertaken to make a similar communication to this in the responsible medical journal, or journals, in his own country and to forward to me such communications as he may receive.

Anatomists are most anxious to avoid antagonising any of their colleagues and they earnestly seek their coöperation both now and in the future. The B.N.A. (1895) has been gradually adopted in this country, and the aim of the committee is to restrict changes to be effected in it to the minimum, while recognising that in some respects, and especially in the central nervous system, the B.N.A. is outdated. It is apparent that such changes as it may prove necessary to introduce will take time to become absorbed into general medical terminology: but such terms as "dorsal vertebrae, Poupart's ligament, musculospiral nerve, internal lateral ligament of the knee-joint" have in the space of forty years almost entirely been replaced in this country by the terms "thoracic vertebrae, inguinal ligament, radial nerve, and medial ligament of the knee-joint" respectively.

Guy's Hospital, London, S.E.1. T. B. JOHNSTON.

INSULIN HYPOGLYCÆMIA AND EOSINOPHILIA

SIR,—Dr. Shattock and Mrs. Micklem (June 21) describe an eosinophilia after hypoglycæmic treatment in mental patients. Over twenty years ago I described eosinocytosis (perhaps a better word) from insulin injections without any hypoglycæmia.[1] I ascribed this to local reactions to an injected foreign substance. No doubt insulin is purer now and provokes less local reactions. But this local factor should be considered and ruled out by controls before eosinophil changes are ascribed to hypoglycæmia and reactions thereto in cortical and other hormone glands.

Diabetic Department,
King's College Hospital, London. R. D. LAWRENCE.

SICKLE-CELL ANOMALY IN GREECE

SIR,—In answer to Dr. Caminopetros's letter (June 14) I should like to make the following remarks.

I insist that the bone lesions in Cooley's anæmia are not specific to that disease but can also be found, in lesser degree, in other anæmias. I believe, today as in the past, *that there is probably an ætiological relation* between malaria and Cooley's anæmia. The nature of this I do not know.

Dr. Caminopetros writes that, together with Dr. Roumanis, he found several patients with "the typical mongoloid facies of Cooley's anæmia" in the villages of Petromagoula and Scripou. We have not seen one. Moreover, using Singer's method for testing the alkali resistance of hæmoglobin our clinic has examined[2] the patients with sickle-cell anæmia in these villages and found percentages of resistant hæmoglobin between 5 and 19—values which fall within the limits reported by Singer in Negroes with sickle-cell anæmia. The values in patients with Cooley's anæmia have been found to be so much higher that this test can be used in the differential diagnosis between sickle-cell anæmia and Cooley's anæmia.

We disagree fundamentally with the ideas of Dr. Caminopetros on sickle-cell morphology.

University of Athens. K. CHOREMIS.

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[1] *Brit. med. J.* 1929, i, 597.

[2] Zannos, L. To be published.

THE DANCKWERTS AWARD

SIR,—I do not suppose I am the only elderly G.P. who has suffered loss in two wars and then of private practice, and so has of late found hard the struggle to make ends meet. To us the Danckwerts award has been as welcome as it was unforeseen, giving hope of some relief from anxiety, and the prospect of being again able to obtain the little luxuries for so long beyond our reach. Our thanks are due to those whose efforts have brought about this most happy consummation.

London, W.C.1. PRACTITIONER.

SHUNTING IN THE HUMAN KIDNEY

SIR,—The letter from Dr. Solymoss and Dr. Molnar in your issue of March 15, in connection with our article,[1] is very stimulating. We wish to clarify certain points which are raised there.

To study the vascular pattern of the kidney we have followed the histological technique described by Pickworth[2] who appears not to have based his method on Lepehne's[3] work. American workers[4] have called the technique the Lepehne-Pickworth method and not simply the Lepehne reaction or benzidine reaction, while elsewhere[5] it has been accepted as Pickworth's stain. We feel that "Pickworth's stain for blood-vessels" does itself imply the benzidine reaction as developed by Pickworth, whereas simple "Lepehne" or "benzidine" reaction may leave one guessing *about the technique followed—all the more so since at least* one other modification has been described.[6]

We regret that Solymoss's paper[7] escaped our attention. This was partly due to the fact that there was no mention of shunting or corticomedullary diversion or intrarenal redistribution of blood in its title, which had suggested to us rather a case-note relating anuria with cortical ischæmia. Franklin[8] has also cited this paper as providing evidence of correlation between anuria in abnormal pregnancy and cortical pallor.

Dr. Solymoss's article was based on a single case of eclampsia. The suggested engorgement of the vasa recta cannot be clearly appreciated owing to absence of a control picture. The exact vascular channels through which the cortical blood is diverted have not been defined. The vasa recta are said to be derived "from efferent vessels of juxtamedullary glomeruli"; but no such glomerulus can be made out in the photomicrograph, nor is it described in the text. If direct anatomical demonstration of the "Trueta phenomenon" (as *Dr. Solymoss and Dr. Molnar call it*) simply means demonstration of cortical ischæmia with medullary congestion, then we suggest that Maegraith and Findlay[9] were the first to do this from the plain macroscopic appearance of the cut surface of the kidney in blackwater fever, even *before* the experimental works of Trueta and his co-workers.[10] We believe that clear anatomical demonstration of shunting in the human kidney requires histological demonstration of cortical ischæmia and of the exact alternative channels through which the blood is diverted. *Certainly Dr. Solymoss*[7] has clearly demonstrated histologically cortical ischæmia *in the human kidney with the* vascular stain, but the exact pathways of diversion have not been defined. Trueta[11] has himself described and depicted most clearly the prominent juxtamedullary efferent vessels breaking up into pencils of vasa recta, but no cortical ischæmia was demonstrable in his cases.

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[1] De, S. N., Sengupta, K. P. *Lancet*, 1951, ii, 1100.

[2] Pickworth, F. A. *J. Anat.* 1934, 69, 62.

[3] Lepehne, G. *Beitr. path. Anat. allg. Path.* 1919, 65, 163.

[4] Lillie, R. D. Histopathologic Technic. Philadelphia, 1948; p. 119. Mallory, F. B. Pathological Technique. Philadelphia, 1938; p. 257.

[5] Blackwood, W. *J. Path. Bact.* 1940, 52, 209. De, S. N. *Ibid*, 1950, 62, 197.

[6] Doherty, M. M., Suh, T. H., Alexander, L. *Arch. Neurol. Psychiat.* 1938, 40, 158.

[7] Solymoss, A. *Lancet*, 1949, i, 957.

[8] Franklin, K. J. *Proc. R. Soc. Med.* 1950, 43, 467.

[9] Maegraith, B., Findlay, G. M. *Lancet*, 1944, ii, 403.

[10] Trueta, J., Barclay, A. C., Daniel, P. M., Franklin, K. J., Prichard, M. M. L. *Ibid*, 1946, ii, 237. Studies of the Renal Circulation. Oxford, 1947.

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S. N. De
K. P. Sengupta.

CONTROLLED HYPOTENSION DURING SURGICAL OPERATIONS

Sir,—Since my paper on this subject (June 28, p. 1286) was submitted for publication, estimations of cerebral venous oxygen content have been made, at arterial pressures of 60 mm. Hg and less, on blood samples taken during neurosurgical procedures. These have shown that cerebral vasodilatation very nearly compensates for the fall in arterial pressure, so that under the conditions used by us cerebral anoxia does not occur.

Department of Medicine,
University of Otago, Dunedin, N.Z.
J. W. Saunders.

TREATMENT OF RHEUMATOID ARTHRITIS WITH BUTAZOLIDINE

Sir,—Just over a year ago 'Irgapyrin' (Geigy) appeared in this country. This substance contains amidopyrine and butazolidine in equal parts, 12½ grains of each in one intramuscular injection of 5 ml. In some cases of rheumatoid arthritis and osteo-arthritis little effect was obtained, but most patients' symptoms were relieved, and this relief was occasionally striking. It seemed to Currie[12] that the relief obtained was greater than could be expected from the amidopyrine content alone. He therefore tried the effect of the solvent, 1 : 2-diphenyl-3 : 5-dioxo-4-n-butylpyrazolidine (G 13871 or butazolidine; also known in the United States as phenylbutazone), and we understand that you are publishing his results this week.

At Dr. Currie's suggestion we began investigating the effects of this substance in the rheumatism unit of this hospital at the end of last year. 16 patients have had courses of butazolidine lasting five to fifteen days; 2 received 800 mg. daily by mouth in divided doses, and the remainder had 1 g. (5 ml.) daily by intramuscular injection. Our first supplies came with control ampoules, and we were unaware which substance was control and which butazolidine. All patients received both substances one after the other in varying order. In treating the first 4 patients we soon recognised the active substance, for it relieved pain in all 4, though there was no reduction in swelling as measured in the fingers by jewellers' rings (Hart and Clark[13]). The other 12 patients gave similar results; in most cases reduction in pain and consequent improvement in function were seen, but no objective changes were produced except in the 3 cases described below. Relief of pain usually wore off within a week of stopping the drug.

Case 1.—Mrs. A, aged 50, had early generalised rheumatoid arthritis of only four months' standing. Her swollen fingers did not improve after full salicylate therapy, control substance, or butazolidine, each given for five days. A sixteen-day course of adrenocorticotropic hormone (A.C.T.H.) by six-hourly injection, 60 mg. daily gradually decreasing to 28 mg. daily, reduced finger swelling by 11 ring sizes. The usual rebound followed the withdrawal of the drug, and finger swelling increased by 30 ring sizes in the next fortnight. Butazolidine was then given intramuscularly for nine days, during which time the fingers diminished by 6 sizes, and in the next five days by a further 19 sizes. Five months later a ten-day course of butazolidine following a control period produced no reduction at all. In retrospect it is likely that the apparent improvement was in fact a spontaneous one following an A.C.T.H.-withdrawal exacerbation.

Case 2.—Mr. B, aged 40, had had generalised rheumatoid arthritis for three years. Swelling of the proximal interphalangeal joints diminished by 10 ring sizes after a nine-day course of butazolidine, but relapse followed when the drug was stopped.

Case 3.—Mr. C, aged 40, had had rheumatoid arthritis for just over a year. After intramuscular butazolidine for ten days, his fingers were reduced by 6 sizes, and in the next four days by a further 4 sizes. Within eleven days of stopping treatment the swelling was as great as before, the fingers having increased by 10 sizes. This rebound, seen in some cases only, is of interest because it suggests that there may occasionally be a true reduction in swelling.

In the other 13 patients no significant reduction in finger swelling was seen when compared with the effect of the control injections. Subjective improvement though usual was not invariable: 3 patients obtained no relief from the short courses given. One further case is worthy of note.

A man, aged 32, had had recurrent swelling and stiffness of various joints for many months. These bouts had become very frequent, and pain, swelling, and stiffness in one or more joints were to be seen every day. On oral butazolidine (2 g. six-hourly for eleven days) the swelling disappeared, but recurred on the second day after withdrawing the drug.

It seems that in this case butazolidine prevented the occurrence of swelling. Our impression is that it is more effective in relieving the pain of rheumatoid arthritis and osteo-arthritis than in other conditions. Several patients with other types of pain found it inferior to the usual analgesics, and Dr. Currie makes the same point.

No toxic effects (such as have been reported in the United States after prolonged therapy), gastro-intestinal upsets, purpura, œdema, or drug rashes were seen. The toxic effects that have been described usually followed oral dosage.

In the United States experience with much larger series has been entirely similar to our own: the drug has excellent analgesic properties whether given by injection or by mouth in long or short courses, but little or no evidence of true antirheumatoid activity has been found, and sedimentation-rates have been unchanged.

The bulk of available evidence suggests that we have in butazolidine a drug which definitely lessens the pain of rheumatoid arthritis but which has no constant antirheumatic effect. It deserves further study.

Westminster Hospital,
London, S.W.1.
F. Dudley Hart.
Alan M. Johnson.

SURGERY OF PEPTIC ULCER

Sir,—I was interested to read the comments of Sir Heneage Ogilvie (May 31) and of Mr. Patey (June 7) on this subject.

When ulcers have been large or highly placed on the lesser curve I have, for some years, "timed" the operation of gastrectomy, by awaiting complete or almost complete healing as shown by X-ray examination. I have seldom treated these patients medically in hospital and seldom kept them away from work; healing has taken place according to the natural history of the disease. Even the largest ulcers seem to heal with time alone, and the time of healing is probably not very much changed by intensive treatment. Perhaps the time of healing of an ulcer, from the moment the physician or surgeon first sees the case, is related more to the stage of its development in relation to its natural history than to any treatment used.

In cases of duodenal ulceration X-ray examination is often not reliable as evidence of healing, since in so many there is gross deformity of the duodenal cap. Freedom from symptoms and absence of tenderness are not, in my experience, sure signs that the duodenal wall is healthy enough for suture. I regard prepyloric closure with mucosal ablation as so safe that I seldom attempt to "time" the operation. In a series of some 350 cases of gastrectomy for duodenal ulceration, done by my registrars and myself in two hospitals, there has been no case of stump leakage since we first used the Bancroft

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11. Trueta, J. *Glasg. med. J.* 1950, 31, 217.
12. Currie, J. P. Personal Communication. 1951.
13. Hart, F. D., Clark, C. J. M. *Lancet*, 1951, i, 775.

operation in 1947; this operation has been done in some 40 of these cases.

Very rarely the exclusion operation may be the method of choice. Otherwise it should be mentioned only to be condemned, for it has no advantage over the Bancroft operation and is usually followed by a second operation to excise the retained antrum. I did, in a small series of cases, use this operation before I came to know how very safe is prepyloric closure with ablation. I did not follow it by a later operation to excise the antrum; for I believed that, if this retained segment of stomach caused jejunal ulceration, then its excision would cure that ulceration. Oddly these few cases have not yet developed this condition, although it is now some years since the operations were done.

Sir Heneage is right when he states that the operation of prepyloric closure with mucosal ablation is "slightly untidy." The patient is, however, asleep when the operation is done: he lives only to know its worth.

London, W.1. HAROLD BURGE.

SIR,—An article from the pen of Sir Heneage Ogilvie is invariably refreshing and inspiring. His address on the First Part of the Duodenum is fully deserving of the tribute paid him by Mr. David Patey.

Much as I respect Mr. Patey's surgical views, I am surprised at his strong advocacy of milk—particularly its administration by the drip method—in the treatment of acutely inflamed duodenal ulcer. The giving of milk from "on high" by the drip method certainly anchors the patient to bed, and often exercises a peculiar fascination for him. Some of our cases have become veritable milk-drip addicts, offering occasional difficulty in weaning!

At best, however, milk is a weak antacid, and some of my colleagues and I have found that patients derive just as much benefit from the rest in bed and a mixture of the type advocated by Dr. Arthur Douthwaite as a preliminary to operation.[1] One of the disadvantages of milk is that the patient tends to put on so much weight, and recently a surgical colleague found to his disgust that he had to deal with the unrepentant ulcer of a patient who had gained three stone after an extended course of this treatment.

Incidentally it is remarkable how many doctors there are, afflicted with duodenal ulcer, who are content to have medical treatment for their relapses, rather than face the prospect of a gastrectomy.

London, W.1. MICHAEL J. SMYTH.

APPOINTMENT SYSTEMS IN HOSPITAL OUTPATIENT DEPARTMENTS

SIR,—In the article (May 31) by Brigadier Welch and Mr. Bailey two important factors appear to have been overlooked: (1) patients who make an appointment and fail to arrive; and (2) patients who make an appointment which is not recorded. At a large teaching hospital I attended this year, three appointments had been made for 10 o'clock and no record of them could be found on the consultant's appointment-sheet.

London, S.W.11. AUBREY H. CARTER.

AUTOGENOUS VACCINE

SIR,—I have a patient under my care in hospital for whom I asked the appropriate laboratory to make a vaccine. I was met with a refusal to do so on the ground that the organisms discovered were not likely to make a useful vaccine. These organisms were a streptococcus of somewhat indeterminate character and the patient's own brand of *Micrococcus catarrhalis*. He suffers from bronchitis and asthma which have proved very resistant to ordinary remedies. Can you, Sir, tell me where I can learn how the potentialities of any particular autogenous vaccine can be discovered otherwise than by its clinical use?

Sevenoaks, Kent. GORDON WARD.

HOSPITAL COSTING

SIR,—Your leading article on this subject (June 21) pointed out some deficiencies of the present method of hospital costing. In particular, you questioned the credentials of the practice of counting five outpatient attendances as the costing equivalent of one inpatient day. I suggest that a source of greater error is the failure to adopt a standard unit to measure equivalent amounts of work done in the various departments. Reference to note (ii) on page 6 of the report *Hospital Costing Returns*[1] shows that "one outpatient attendance" is not, for the purpose of costing, the same as "one patient attending the Out-Patient Dept. once." Other items such as "treatments or examinations in physiotherapy, pathological, radiological and similar departments" are also included.

This report refers to the financial year ending March 31, 1951, and the statistics on which the costing is based were obtained mainly from various returns of the Ministry of Health for the year ending Dec. 31, 1950. At that time there was considerable confusion both at the Ministry and in the hospitals as to what constituted a "unit" in pathological and similar departments. As the Ministry had not been able to produce satisfactory definitions to cover these points, there was great diversity in interpretation which led to the same examinations and treatments being valued at different rates in different hospitals. This invalidates the costing figures based on these statistics, since an elementary rule of comparative costing is to compare "like with like." The instructions on how to compile these costing figures issued by the Ministry (R.H.B.[50]66) to boards and management committees should have been included in full in the report since the merits of any statistical report can only be judged on the reliability of the source data; and not everyone who may wish to use this report will have easy access to official files.

Later, in an attempt to clarify the situation, the Minister of Health issued a circular (R.H.B.[51]59) from which we learn that "for the purpose of costing" the following services are rated as equivalent to *one outpatient attendance*: (1) X-ray examinations enumerated on the basis of the "requests" received from clinicians, irrespective of the number of films used or the time taken to complete the examination; (2) a single pathological specimen of blood, urine, cerebrospinal fluid, &c., regardless of the number or quality of the tests performed on it; (3) a treatment in the physiotherapy department, simultaneous treatments to be counted as one but group treatments (e.g., remedial gymnastic classes) to be counted as *one for each patient attending*; (4) even more surprisingly, a necropsy is counted as one outpatient attendance, but histological or other special examinations should be counted as one for each organ even where more than one block or specimen is examined from the same organ. In view of this heterogeneous collection of so-called "units" you will no doubt agree that the exact ratio employed to equate these to one inpatient day is hardly of practical importance. It is well to note that the costing statistics for the financial year ending March 31, 1952, will be based on figures compiled in accordance with these instructions. Whether or not the Ministry will have revised its definitions of costing units in time for the 1952/53 financial report is as yet unknown.

There is a tendency among the members of the medical profession to regard all questions relating to costing as the concern of the administrative side of the hospital service. But in fact it is the concern of us all; for in these days of financial stringency the whole policy of administration of the health service may depend on costing statistics. At no time in the foreseeable future will money be so plentiful that costing will be unnecessary, so that whether or not we regard costing as desirable it is certainly inevitable. If the medical profession realistically accepts the necessity of comparative costing then it would be to its advantage to ensure that the figures bear at least some relation to the truth.

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[1] Douthwaite, A. H. *Brit. med. J.* 1951, i, 291.

[1] National Health Service: Hospital Costing Returns, year ended March 31, 1951. H.M. Stationery Office, 1952.

London, S.E.5. VERA NORRIS.

MALARIA IN EX-SERVICEMEN

SIR,—We are engaged in a war in which our troops are fighting in malarious theatres—Korea and Malaya—whilst others are stationed in more peaceful malarious places, such as West Africa. The incidence of malaria in all these theatres is within reasonable bounds and on the whole is surprisingly low. Various preventive measures are used but considerable emphasis is laid on 'Paludrine' as a prophylactic, the experiences with which have been satisfactory.

Paludrine, in common with other drugs, may only act as a suppressant of benign tertian malaria, and clinical attacks may occur when it is discontinued. Benign tertian malaria is the predominant malaria of Korea, and it is therefore to be expected that a number of attacks of malaria will occur amongst soldiers who have returned from that theatre. The numbers recorded are low, the total in this country last year averaging only 16 per month; and, the disease being benign, there is no immediate grave risk to the individual. It is, however, inevitable that some of these soldiers suffer relapses after demobilisation which may occur quite quickly after their return from Korea, and it has been brought to my notice that a number of cases amongst demobilised men have only been diagnosed after prolonged examination and treatment for other diseases, neither the doctor nor the patient having considered the possibility of malaria.

A strongly worded warning is given to soldiers on their return of the possibility of a relapse, but in the cases referred to this mechanism has failed for one reason or another to put men on their guard. If practitioners meet cases of acute febrile illness amongst recently demobilised men they should bear the possibility of a malarial relapse in mind, seeking early confirmation of the possibility either by referring the patient to an appropriate hospital or by arranging for the rapid examination of blood films.

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London, W.C.1.

G. MACDONALD
Hon. Consultant
in Malariology
to the War Office.

SIR,—During the past few weeks we have had under our care several cases of benign tertian malaria in men returned from military service in Korea. In each instance the history has been that the patient has taken regular prophylactic paludrine whilst overseas and has remained in good health. The paludrine has been stopped during the voyage home, the patient has returned to civilian life, and some weeks or months later he has developed a tertian fever which, with one exception, has not been suspected as being due to malaria until it has continued for upwards of three weeks, by which time the patient has become considerably debilitated and anæmic. The exception referred to was a regular soldier who had had a previous experience of malaria and came to us on his own initiative on the fourth day of his illness.

This long delay between the onset of symptoms and the recognition of the nature of the disease magnifies what should be a trivial episode of ill health into quite a serious illness. Much time, money, and anxiety can be saved if it is remembered that benign tertian malaria is a likely explanation of a fever occurring within twelve months of a visit to Korea.

A. R. D. ADAMS
D. R. SEATON.

Liverpool School of Tropical Medicine.

Public Health

Economy in Local Government

THE Ministry of Housing and Local Government has sent to local authorities a circular reinforcing the call by the Chancellor of the Exchequer, in his budget speech, for "economy in the sphere of local government as well as national government."

With regard to urban water-supply and sewerage where work is proposed on grounds of public health, an appendix to the circular states:

> It must be established that the scheme is not merely desirable but is essential on public health grounds. The fact that existing conditions are unsatisfactory in some respects may not mean that they are necessarily a danger to health. Examples of schemes which will be considered on this count are those for replacing works or machinery that are in danger of breakdown with consequent failures of supply; work for obviating pollution of water-supplies that may give rise to disease; sewerage schemes designed to relieve flooding inside dwelling houses; and the improvement or replacement of sewage works that are overloaded or obsolescent to an extent that may give rise to conditions that will affect the health of people in the areas concerned. Any claim that works are necessary on grounds of public health must be supported by a report from the Medical Officer of Health on the nature and extent of the danger.

Statistics for 1950

The civil tables volume [1] of the Registrar-General's report for 1950 shows that during the year the birth-rate in England and Wales was 15·8 per 1000 population; this was a decrease of 0·9 per 1000 from the previous year's rate. Stillbirths amounted to 23 per 1000 total live and still births. Of the legitimate maternities 40·2% were to mothers with no surviving previous children, 32·2% to mothers with 1 surviving child, and 14·7% to mothers with 2 surviving children.

The First Quarter in Scotland

The Registrar-General for Scotland [2] reports that in the quarter ended March 31 this year the birth-rate was 18 per 1000 population, which was 0·8 below the rate for the corresponding quarter of 1951. Stillbirths amounted to 29 per 1000 live and still births. The death-rate was 14·5 per 1000 population—3·3 less than in the first quarter of 1951. The infant-mortality rate—38 per 1000 live births—was 8 below that for the corresponding quarter of 1951. The neonatal death-rate was 23 per 1000 live births, which was 2 below that for the corresponding quarter in 1951. The death-rate from tuberculosis was 47 (respiratory 41) per 100,000 population, compared with 58 (respiratory 51) in the corresponding quarter of 1951.

Housing in Edinburgh

An interesting light is cast on housing progress in Edinburgh by the first detailed report [3] that has emerged from last year's Census of Scotland.

In the twenty years since the previous census in 1931, the number of occupied private houses has risen from 105,702 to 134,038—an increase of 26·8%, compared with an increase in the private-household population of only 5·6%. On April 8, 1951, the average number of persons for each house was 3·29, compared with 3·95 in 1931. In 1931 and 1951 the population was distributed as follows:

No. of persons per room	*1931* (%)	*1951* (%)
Not more than 2	72·1	89·0
More than 2 but not more than 3	17·4	8·8
More than 3 but not more than 4	6·9	1·6
More than 4	3·6	0·6

The number of one-roomed houses has fallen from 7123 (6·7%) to 5173 (3·9%). Two-roomed houses have fallen from 33,591 (31·8%) to 31,255 (23·3%). Three-roomed

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1. The Registrar-General's Review of England and Wales for the Year 1950. Tables, part 2, civil. H.M. Stationery Office. Pp. 176. 5*s.*
2. Quarterly Return of the Registrar-General, Scotland: Births Deaths; and Marriages Registered in the Quarter ended March 31, 1952. H.M. Stationery Office. Pp. 30. 2*s.* 6*d.*
3. Report of the Fifteenth Census of Scotland: vol. 1, part 1. H.M. Stationery Office. 7*s.* 6*d.*

houses have increased from 26,934 (25·5%) to 44,475 (33·2%), four-roomed houses from 15,687 (14·8%) to 28,293 (21·1%), and five-roomed houses from 8114 (7·7%) to 11,537 (8·6%).

With regard to conveniences, the figures for households, in percentages, are as follows:

	Exclusive use	*Shared use*	*None*
	%	%	%
Kitchen sink	90·3	8·9	0·8
Piped water-supply ..	89·5	10·2	0·3
Cooking stove or range ..	88·3	6·9	4·7
Water-closet	80·3	19·5	0·2
Fixed bath	60·4	7·4	32·3

59·7% of households had exclusive use of all five conveniences; and of the total of 141,472 households 39 had no conveniences at all.

Of the 134,038 occupied private houses, 5874 (4·4%) were occupied by *two or more households*. Of these 5874 houses, 4809 (81·9%) had two households, 660 (11·2%) three households, and 405 (6·9%) four or more households.

Parliament

Hypnotism Bill

In the House of Commons on June 27 Mr. **Somerville Hastings** moved the third reading of the Hypnotism Bill, which as amended in Standing Committee prohibits absolutely demonstrations of stage hypnotism on persons under 21 years of age. Demonstration is permissible on those over 21 in certain circumstances. Where places in which demonstrations are intended to take place are licensed for music and dancing the demonstrations are permissible provided that the authority concerned is agreeable.

The Bill was read the third time and passed.

Burns in the Home

On June 27 the House of Commons gave a third reading to the Heating Appliances (Fireguards) Bill, which aims at the reduction of two classes of burn accidents in the home: those caused to children, and those caused by clothing catching in an exposed element or flame. Mr. **Denys Bullard**, in moving the third reading, paid a special tribute to the work of Dr. and Mrs. Leonard Colebrook and to the many other doctors who had aided him.

Royal Assent

In the House of Lords on June 26 the Royal Assent was given by Commission to the Corneal Grafting Bill, the Family Allowances and National Insurance Bill, and the Cremation Bill.

Working Party's Report

The Parliamentary Labour Party has issued the following statement concerning the report of the Working Party[1] which was set up to consider the distribution of the Danckwerts award and the future distribution of the general practitioners' central pool of remuneration:

"The Parliamentary Labour Party does not propose to oppose the Danckwerts findings. However, having carefully studied the report of the working party on the future distribution of the central pool, the Parliamentary Labour Party affirms that a most valuable opportunity has been missed to better the general-practitioner service to the public and to improve the standard of doctoring throughout the country. Moreover, the report fails adequately to improve the position of the young and poorer paid doctors having small lists of patients, and gives the greatest increase of payment to those who are already receiving higher rates of remuneration. Its proposals for the encouragement of group practice are grossly inadequate.

"When this subject is debated in the House, the viewpoint of the Parliamentary Labour Party will be elaborated and constructive modifications will be proposed."

QUESTION TIME

Medical Evidence and National Insurance Claims

Replying to Mr. C. C. **Poole**, Mr. **Osbert Peake**, Minister of National Insurance, said there were no statistics to show in how many cases in the five months ending May, 1952 insurance officers had refused to accept the medical evidence of incapacity supplied in support of a claim.

Mr. **Poole**: What further evidence would the Ministry require in support of a claim, apart from that of the medical practitioner who examined the patient, and on what authority do the officers of the Ministry refuse a claim when such evidence is forthcoming? Mr. **Peake**: In my opinion it would be quite wrong to tie down the insurance officer and compel him in every case to accept a medical certificate without question.

Hospital Staff Economies

Replying to Major **Guy Lloyd**, Mr. **Iain Macleod**, Minister of Health, said that precise figures were not available, but it was estimated that a saving of 5% of establishments so far reviewed would result from the reports of teams investigating administrative and clerical hospital staffs.

Prescription Charges

Replying to Mr. **Richard Ewart**, Mr. **Macleod** said that he was not prepared to exempt from the prescription charge chronic sick patients who required dangerous drugs which were dispensed weekly. When such drugs were prescribed on a weekly basis, they were not usually required for periods so long as to make the ordinary provision for relief of financial *hardship inappropriate*.

Replying to Dr. A. D. D. **Broughton**, Mr. **Macleod** said that the approximate cost of a National Health Service prescription in England and Wales in 1948, 1949, and 1950, accounted for by the payment of the dispensing fee and the cost of the container and of drugs, medicines, and dressings, was as follows:

Period	Av. cost of dispensing fee per prescription	Cost of container allowance per prescription	Av. ingredient cost of drugs and appliances per prescription
1948: July–December	1*s.* 1*d.*	2½*d.*	11*d.*
1949	1*s.* 0*d.*	2*d.*	1*s.* 2¼*d.*
1950	1*s.* 0½*d.*	1¾*d.*	1*s.* 5¾*d.*

Figures for 1951 were not yet available.

Vaccination against Tuberculosis

Mr. **Anthony Greenwood** *asked the Minister of Health* how many local authorities had schemes in active operation for B.C.G. vaccination, and how many persons had been so vaccinated.—Mr. **Macleod** replied: 143 local health authorities have had proposals approved authorising the use of B.C.G. vaccine. Approximately 32,000 persons were vaccinated under approved schemes between October, 1949, and Dec. 31, 1951.

Mr. **Greenwood**, asked what was the present state of medical research in this country in regard to vaccination with the vole bacillus vaccine.—Mr. **Macleod** replied: A large-scale trial with this vaccine is being carried out under the auspices of the Tuberculosis Vaccine Trials Committee of the Medical Research Council.

Hospital Outpatients

Replying to Major **Lloyd**, Mr. **Macleod** said that the total numbers of new outpatients who attended hospital consultative clinics in England and Wales in each of the years 1949–51 inclusive were as follows: 1949, 6,147,825; 1950, 6,193,156; and 1951, 6,298,746.

Appointments

Couch, A. H. C., M.D. Lond., M.R.C.P., D.C.H.: asst. chest physician, Ipswich Chest Clinic.

Fisher, J. D., M.C., M.R.C.S.: appointed factory doctor, West Nottingham district.

Goddard, D. L. H., M.D. Lond., M.R.C.P.: consultant chest physican and deputy medical superintendent, St. Wulstan's Hospital, Malvern.

Marshall, A. G., M.D. Camb.: part-time consultant pathologist, Wolverhampton group of hospitals.

Parish, Christopher, M.B. Manc., B.SC., F.R.C.S.: consultant Regional Hospital Board thoracic surgeon, East Anglian hospitals and the United Cambridge Hospitals.

Rutter, L. D., M.B. Manc.: appointed factory doctor, Yarmouth district, Norfolk.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

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[1] See *Lancet*, 1951, i, 1147, 1155.

Notes and News

NATIONAL INSURANCE CHANGES

An order made by the Minister of National Insurance fixes the days on which the increased insurance benefits and family allowances will come into force. Sickness, unemployment, industrial-injury, and widow's benefits will be paid at the new rates from July 24; the family and guardian's allowances from Sept 2; and the retirement pensions (including widow's retirement pension) from Sept. 29. The higher contribution rates will operate from Oct. 6. The total weekly National Insurance contribution for an employed man over 18 will then be 10*s*., of which he will pay 5*s*. 5*d*. himself.

The Minister has also increased the time allowed for claiming some industrial injury benefits and for obtaining payment of a benefit after it has been awarded. The time allowed for claiming disablement benefit is increased from 1 month to 3 months. Injury benefit must still be claimed within 21 days, but this limit will be relaxed to some extent for hospital inpatients. Payment of a benefit already awarded may now be made up to 6 months after the award, and in the case of disablement and death gratuities the time-limit has been discarded altogether. These changes applied from July 1.

The Ministry has prepared a leaflet, which will shortly be issued to general practitioners, giving details about the medical certificates required for insurance purposes. The amended regulations, which came into force on May 26, make a number of changes in the rules governing certification. Only three types of certificate will be in use instead of five. A copy of the regulations will be sent to practitioners as soon as possible. The leaflet describes the use of the new certificates, but the old certificates will continue to be used until supplies of the new ones have been distributed.

ACTION UNDER THE CORNEAL GRAFTING ACT

The Ministry of Health suggests that those who wish to offer their eyes for use after their death, under the terms of the Corneal Grafting Act, should take the following steps: (1) make a written statement of their wish that their eyes should be used for therapeutic purposes after their death; (2) give this to their family or anyone else with whom they live; (3) give a copy also to any executors appointed to carry out their will; and (4) inform the authorities of any hospital which they may enter as an inpatient of their wish that their eyes should be used after death for this purpose.

University of Oxford

On June 25 the honorary degree of D.LITT. was conferred on William Somerset Maugham, M.R.C.S.

The degree of D.M. was conferred on E. M. Poulton and A. N. Cammock on June 7 and not on March 11 as we stated previously.

University of London

Mr. P. H. Mitchiner has been reappointed deputy vice-chancellor for the year 1952–53. Dr. C. F. Harris has been elected dean of the faculty of medicine for the period 1952–54.

Dr. J. R. Napier, lecturer in anatomy at St. Thomas's Hospital Medical School, has been appointed to the university readership in anatomy tenable at the Royal Free Hospital School of Medicine, from Oct. 1 this year.

University of Durham

The following degrees were conferred on June 27 and 28:

M.D.—W. A. Brown, L. W. Carstairs, W. P. Haigh, M. M. Martin, Alexander Russell, C. B. S. Schofield, J. N. Walton, P. D. G. V. Whittingham.

M.B., B.S.—P. R. Bachrich, A. L. Bass, A. R. Bird, D. H. Blake, D. W. Braithwaite, *James Brotherton, Ann K. Brough, William Brough, *D. D. Brown, A. T. Burdon, D. W. Cammock, W. A. Colling, L. P. Coulson, Margaret L. Coulson, Betty E. Cowling, Alan Coxon, A. J. Coyer, Kenneth Davison, Doreen L. P. Dias, Wilfrid Dickson, Raymond Dingley, Donald Elliott, J. S. Etherington, A. D. W. Farmer, P. G. Fawcett, W. T. Fothergill, June E. Heslop, James Ivory, Frank Johnson, G. S. Jeans, *Elizabeth Jennings, M. H. Kemp, P. E. Kilby, J. C. King, Elsa Little, H. A. McClelland, J. F. S. T. McClory, Peter McElhatton, John McKinlay, I. R. Macleod, C. F. R. Mallett, T. J. Mallinson, R. A. Middleton, D. G. Millar, Betty M. Moody, G. H. E. L. Morpeth, *J. H. Morrison, John Mulroy, R. W. Newmark, N. C. C. Nielsen, S. J. O'Donnell, T. W. Parkinson, I. B. Porteous, John Richardson, *Elizabeth R. M. Rowell, Patricia J. Saunders, Kirt Schapira, Thomas Scratcherd, Arnold Shaw, R. H. Shields, L. K. Simango, A. J. Smith, K. D. Stephenson, Mary E. A. Still, *G. A. Stirling, *Isabelle M. Thompson, T. R. Thompson, R. W. Thomson, Marian S. J. Tuszewski, F. A. Tyce, Raymond Veeder, M. O. Waddell, Desmond Walker, Elizabeth A. Waterhouse, Ann C. Wilby, N. V. Wilkinson, C. F. G. Woodman, Joan Yell, Enid M. Young.

*In absentia.

University of Sheffield

At a degree congregation on June 28, the degrees of M.B., CH.B. were conferred on the following:

R. M. Atkinson, K. C. A. Y. Baldwin, James Banner, A. L. Bloom, R. L. Bojankiewicz, H. W. Chambers, Kathleen H. Chrispin, Marjorie Clifton, J. B. Cole M. B. Collins, G. A. Fieldsend, K. B. Holloway, G. G. Imrie, R. S. Johnstone, H. M. Kidd, P. B. Lambert, Fred Lees, F. W. Leigh, Francis Lothe, Marcel Malden, J. D. Parry, Frances B. Penny, N. E. Pitts, Shelagh M. Richards, D. W. M. Rolfe, N. E. Shaw, Mary L. Stewart, Sylvia H. Swift, F. G. Thorpe, David Tingle, I. J. Waite, I. A. Wood, J. K. Young, S. S. Young.

Royal College of Physicians of Ireland

On June 26 Sir Russell Brain, F.R.C.P. Lond., was admitted to honorary fellowship of the college.

On June 27 the following, having passed the final examination of the Conjoint Board of Ireland, were admitted licentiates in medicine and midwifery:

E. St.G. Anderson, K. A. Barrett, John Biggins, M. C. Botha N. R. O'C. Brennan, Nora E. Casey, L. J. Conway, D. J. Daly, K. E. Dewhurst, R. G. Fricker, Ellen C. Geraghty, J. H. Gower, Aileen G. Grant, Stuart Gray, H. C. Henry, J. G. N. Lagan, Leonard Levy, Joan E. Mackey, Joyce W. Malcolm, A. A. Marinho, J. G. Muldoon, Kathleen M. McManus, Kathleen M. McNamara, J. O. P. Noonan, M. A. Okupe, F. W. Quilty, R. J. Regan, J. M. Rennie, Edward Rogan, Celia D. Thomas, J. N. Udom, Veronica Whitty, J. J. Wilson.

Royal College of Surgeons in Ireland

At a meeting of the college on June 3 Mr. M. P. Burke was elected president, and Mr. Ian Fraser vice-president.

Faculty of Radiologists

The following have passed the examination for fellowship of the faculty:

S. Kramer (radiotherapy), F. G. M. Ross (radiodiagnosis), Paul Strickland (radiotherapy), W. N. Thomson (radiodiagnosis), and H. C. Warrington (radiotherapy).

Royal Society of Tropical Medicine and Hygiene

The society will meet at 7.30 P.M. on July 17 at 26, Portland Place, London, W.1, when Brigadier J. S. K. Boyd, F.R.S., will present a symposium on the new antimalarial drug, 'Daraprim.'

Bovine Tuberculosis in Denmark

According to a statement in the *Manchester Guardian* of June 30, the Danish ministry of agriculture has recently announced that eradication of bovine tuberculosis from Danish herds of cattle is now complete. The campaign against the disease began in 1893 with a State subsidy to provide free tuberculin-testing, but thirty years ago 80% of the herds were still regarded as tuberculous.

Lister Institute of Preventive Medicine

Dr. A. A. Miles has been appointed to succeed Sir Alan Drury, F.R.S., as director of the Lister Institute of Preventive Medicine, London.

Dr. Miles, who is 48 years of age, was elected to an exhibition in natural sciences at King's College, Cambridge, in 1921, and completed his medical education at St. Bartholomew's Hospital. He graduated M.B. in 1928 and became M.R.C.P. in 1929. In 1934 he was appointed to the university readership in bacteriology at the British Postgraduate Medical School. Three years later, in 1937 he was elected F.R.C.P. In the same year he was appointed to the university chair of bacteriology tenable at University College Hospital Medical School. This he retained until 1946 when he went to the National Institute for Medical Research. He is at present deputy director of the institute and director of its department of biological standards. Dr. Miles is also a member of the British Pharmacopœia Commission and chairman of the W.H.O. Expert Committee on [illegible] Together with Prof. G. S. Wilson he r[illegible] *Principles of Bacteriology and Immunity.* [illegible] arlier this year.

War Pensions and the Brussels Treaty

By the Brussels Treaty the signatory countries (Belgium, France, Luxembourg, the Netherlands, and the United Kingdom) agreed to develop their social services along corresponding lines. A statement issued after a conference of senior officials from the pensions ministries of the five Powers, held in Paris from June 23 to 26, says that the initial attempt at international negotiation in the field of war pensions has produced some interesting and, in certain cases, notable results. Recommendations submitted to governments by the committee cover the granting, to nationals of the five countries, of medical treatment in respect of accepted war disablement free of charge on the same basis as to nationals of the country of residence. The causal relations of certain diseases with war service have been explored in detail and a guide to the medical bases of assessment of disablement for war victims has been produced.

Scottish South Eastern Regional Hospital Board

The remaining vacancy on this board (see *Lancet*, 1951, i, 813) has been filled by the appointment of Mr. George I. Scott, F.R.C.S.E., who will remain in office until March 31, 1955.

Third Commonwealth Health and Tuberculosis Conference

This conference, organised by the National Association for the Prevention of Tuberculosis, will be held at the Central Hall, Westminster, between July 8 and 11.

World Federation for Mental Health

The federation's fifth annual meeting is to be held at the Université Libre, Brussels, between Aug. 24 and 30. Further information may be had from the General Secretary, National Association for Mental Health, 39, Queen Anne Street, London, W.1.

Pure-tone Audiometry

A memorandum on this subject has been prepared jointly by the Medical Research Council Committees on Medical and Surgical Problems of Diseases of the Ear and on Electro-Acoustics. This memorandum (M.R.C. 52/478) is intended for the guidance both of designers and users.

Institute of Child Health

This institute, in conjunction with the Institute of Education, is arranging a short course on Child Development. The course, which will be held at the Institute of Education, Malet Street, London, W.C.1, from Sept. 29 to Oct. 3, is open to a limited number of consultant pædiatricians and senior pædiatric registrars. Further details may be obtained from the director of the department of child development at the above address.

Views on Nurses

Addressing the Association of Hospital Matrons in London on June 28, Miss Pat Hornsby-Smith, Parliamentary Secretary to the Ministry of Health, observed that since the start of the National Health Service there had been a steady increase in the number of staffed hospital beds and in the total nursing staff. By the end of last March there had been an increase of over 22,000 full-time and 9000 part-time nurses; and the number of staffed beds had increased by over 30,000. However, we still needed many more nurses and a very great number of mental nurses to bring even existing hospitals up to strength and to open all the non-staffed beds that could be used.

Miss Hornsby-Smith continued: "There is some controversy over the age of entry into nursing. It is claimed, and I think rightly, that no young girl should take up training before the age of 18, and that no-one younger should be introduced to scenes of sickness and hospital life. Some even go further and think the right age to be even later. On the other hand, every year sees more and varied forms of employment opened up to young women. If they are keen on nursing at school and possibly have to leave at 16, they may well take up a worth-while job for the intervening two or three years and then not want to leave it. Competition for the educated, able type of young women needed in nursing is keener than ever today. We must be careful to maintain a balance in our decisions so that we overcome these difficulties." At present wastage was at least 40%; and it seemed that this figure was, if anything, on the increase.

"This is a problem calling for very serious investigation—particularly when one considers how large a proportion of those who enter training are from the 18–19 age-group. The number of girls reaching the age of 18 each year at present is about 25% less than immediately before the war, and because of the low birth-rate during the 1930s this number will not increase substantially until 1960. In consequence, the number of entrants has fallen in the last year or so and may well continue to fall. So it is all the more important that a large proportion of those who do take up training should complete it."

Miss Hornsby-Smith reasoned that there was a good deal to be said for nurses living out; this promoted a greater sense of independence and it brought a nurse into closer daily contact with the world outside the hospital. With regard to the National Hospital Service Reserve, the campaign to obtain recruits had so far been disappointing, only some 24,000 having enrolled. It had been estimated that the plans for the operation of the hospital and first-aid services in war-time would entail at least 100,000 extra nursing staff.

Royal Medical Foundation of Epsom College

The annual meeting of governors is to be held at the offices of the Medical Defence Union, Tavistock House South, Tavistock Square, London, W.C.1, on Wednesday, July 16, at 3.30 P.M.

Ministry's Monthly Bulletin

Dr. J. Balfour Kirk, C.M.G., F.R.C.P., has succeeded Dr. J. Alison Glover as editor of section 1 of the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service.*

At the Medical Golfing Society's summer meeting held at the Berkshire Club on June 26, THE LANCET Cup (Scratch) was won by Dr. J. Park, the Henry Morris Cup (Bogey) by Dr. J. Park, and Foursomes by Dr. H. L. Rayner and Dr. Ivor Evans.

Diary of the Week

JULY 6 TO 12

Tuesday, 8th

ROYAL COLLEGE OF SURGEONS
5 P.M. Prof. David Slome: Surgical Research at Downe. (Buckston Browne lecture.)

Wednesday, 9th

IMPERIAL CANCER RESEARCH FUND
5 P.M. (Royal College of Surgeons.) Dr. Peyton Rous, F.R.S.: Carcinogenesis.

BRITISH MEDICAL ASSOCIATION
2.30 P.M. (Royal Institution, Colquitt Street, Liverpool.) Dr. Donald Stewart: Medicine and Employment. (Mackenzie industrial health lecture.)

Thursday, 10th

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. Ralph Phillips: Neuroblastoma. (Hunterian lecture.)

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5 P.M. Prof. Norman Dott: Subarachnoid Pouch Formations and Allied Conditions of the Cerebrospinal Fluid Circulation.

Friday, 11th

IMPERIAL CANCE[illegible]
5 P.M. (Royal [illegible] Dr. Peyton Rous: Cancer Causes,

Births, Marriages, and Deaths

BIRTHS

[illegible]—On June 24, at Foresterhill, Aberdeen, to Margaret [illegible] of Dr. John S. Caldwell—a daughter.

[illegible] t St. Brenda's Nursing Home, Clifton, [illegible] wife of Dr. A. M. G. Campbell—a daughter.

CLIFT.—On June 21, at Mayday Hospital, Croydon, to Dr. Dorothy Clift (née Newell), wife of Mr. Arthur Clift, F.R.C.S.—a son.

COOKE.—On June 22, at Wokin [illegible] to Mary (née Barney), wife of Dr. G. N. [illegible]

McQUADE.—On June 23, at W [illegible] o Joy (née Manning), wife of Dr. Brian McQuade—a son.

PEARSE.—On June 26, at Hammersmith Hospital, to Elizabeth, wife of Dr. A. G. Everson Pearse—a daughter.

TRIGER.—On June 23, at Goshen, Six Bells, Abertillery, to Olga, wife of Dr. K. Triger—a son.

YORK-MOORE.—On June 25, at the Norfolk and Norwich Hospital, Norwich, to Rosemary (née Williams), wife of Dr. Michael York-Moore—a daughter.

MARRIAGES

MIDDLETON—YUTENKAS.—On June 21, in New York, Peter McKechney Middleton, M.B., to Adele Barbara Yutenkas.

POWELL—WALLS.—On June 21, Peter D. Powell, M.B., of Glasbury-on-Wye, to Jean Mary Walls, of Carston, Ayr.

RUSHTON—FINDLAY.—On June 21, at Chigwell, David H. Rushton, M.B., to Fiona Findlay.

DEATHS

DALGLIESH.—On June 20, at Ipswich Hospital, Frank Bell Dalgliesh, M.R.C.S., lieut.-colonel, R.A.M.C. retd.

LEWIS.—On June 21, in Melbourne, Australia, Ernest Winbolt Lewis, M.B. Edin., late of Codford St. Mary, Wiltshire.

MACLEOD.—On June 22, Neil Ferguson MacLeod, M.B. Glasg., of 61, Uxbridge Road, Hanwell, W.7, aged 34.

SCHAFFTER.—On June 27, Charles Merill Schaffter, O.B.E., M.B. Edin., F.R.C.S.E., of St. Andrews House, Matlock, and late of C.M.S., Isfahan.

STALLARD.—On June 27, Hamilton George Frampton Stallard, L.R.C.P.E., lieut.-colonel, late Egyptian Army and R.A.M.C. retd, [illegible] urt, aged 80.

[illegible] 22, Brigid Stanford (née O'Beirn), M.B. N.U.I., [illegible] d, Scunthorpe, Lincs.

REASON AND UNREASON IN PSYCHOLOGICAL MEDICINE *

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N my first lecture my purpose was to examine the nciple of causality with a view to ascertaining to what ent it could be made to apply in the field of medicine general and in that of psychological medicine in ticular.

learly, the law of causality requires to possess some vancy and validity if medicine is to maintain any tus in the hierarchy of the natural sciences. It was gested, however, that, if the 19th-century convention almost compulsively searching for efficient causes *usae agentes*), with disregard for the other equally nificant factors in the causal pattern, were persisted in, element of unreason would disorganise the scientific ality, without necessarily violating the laws of formal ic. It was further maintained that this had taken place the case of psychological medicine to a dangerous extent.

Even primitive magic relies on the necessity of ablishing a causal sequence, especially if anything has be *done*, seeing that man is a rational animal. For ample, a tribal rain-maker must have the inner con- tion that, when he pours a bowl of water on the und with the appropriate incantation, the next rainfall s a direct causal relationship with his magical cere- ny. A rain-maker who is not so convinced is a bad n-maker. We shall see later that a psychotherapist— any complexion—who doubts the validity of his own rticular system is a bad psychotherapist. Magic velops into science when it can be shown that the ain of cause and effect is false; and this occurs more ten as the result of trial and error (the experimental ethod) than through pure ratiocination. Inevitably, hemy, which, according to Jung, started as a symbolic, bstitute-religious discipline, developed in this way into emistry.

Let us very briefly review some of the assumed chains cause and effect which have at one time or another termined the theoretical and therapeutic aspects of ychological medicine.

Causal Formulæ in Psychological Medicine

For untold centuries any behaviour-patterns which ave gross offence to the dominant culture-pattern and hich appeared to be unrelated to moral responsibility, understood at the time, were accounted for in terms demoniacal possession. A person barked like a dog, ad fits, talked with unseen persons (or what you will) *cause* he was possessed. Therapeutic procedures, all ependent upon the assumption of this falsely appre- ended causal sequence were various, but all were logical: hole might be bored in the skull to provide a mode of xit for the evil spirit. Ritual exorcism by a qualified ractitioner (priest or shaman) might be regarded as the referred method of treatment. The possessed person ight be required to submit to ill-treatment of various inds—beatings, chainings, brandings, mocking and the ke—so that the body which had been acting as the ost of the possessing demon should be rendered so ncomfortable as to persuade the unwelcome intruder to ake his departure. Treatment of this kind existed in ivilised countries in one form or another until a hundred ears ago. Even in the 18th century in this country a isit to Bethlem to watch the lunatics being ill-treated or to pelt them with filth of all kinds was as popular a Sunday-afternoon expedition as is today a visit to the Zoo to see the sea-lions fed.

The first important departure from this type of magical thinking came with Mesmer's work. This strange 18th-century figure took his medical doctorate in Vienna with a purely astrological thesis, the Effect of the Planets on the Human Body. Mesmer, as you will all know, believed that there was a mysterious vital force, which he called animal magnetism, that could be used to benefit patients suffering from all kinds of mental and bodily disorders. In fact, the term mesmerism has again featured prominently in the general press of this country. A curious, although inverted development of this doctrine is to be found in Christian Science (so called) which still claims many loyal adherents, especially in the United States.

The first serious attempt to formulate some kind of medical-psychological principles and to make use of them to propound a new, relevant causal formula was that of the early hypnotists, especially the members of the so-called Nancy school. They rejected Mesmer's conception of animal magnetism in favour of that of suggestion. They believed that the therapeutic successes of Mesmer and his followers could be accounted for in terms of human suggestibility and that this could be exploited to the best advantage in that altered state of consciousness which they called hypnosis—in preference to the mesmeric trance. It is noteworthy, however, that no satisfactory definition of "suggestion" in scientific psychological terms was forthcoming. It remained almost as mysterious a phenomenon as Mesmer's animal magnetism or Mrs. Eddy's "malicious animal magnetism."

The causal formula was a simple one: mental well-being and acceptable social conduct are the result of "good" suggestions; mental disorder and many forms of delinquency spring from the unwitting acceptance of "bad" suggestions. The logical form of treatment then is, by appropriate counter-suggestions—at first with the use of, at a later date without, hypnosis—to convert "bad" suggestions into "good" ones. In this country, until the beginning of World War I, treatment by suggestion in one of the many forms which it came to assume—hypnotic suggestion, suggestion in the waking state, persuasion (Dubois), re-education (Déjérine and T. A. Ross)—was the main therapeutic standby of the specialists who bothered about treatment at all; and they were few and far between.

During the last quarter of the 19th century great strides were being made in neuro-anatomy and to a lesser extent in neurophysiology. In fact, so much was being found out about the structure of the nervous system and the way it worked that, encouraged by the philosophical climate (materialistic monism and positivism), it was confidently felt in the higher reaches of orthodox medicine that the time was fast approaching when explanations in terms of cause and effect, but of a purely mechanistic nature, covering the whole field of human thought, feeling, and behaviour, would be forthcoming. At one time Oskar and Cecilie Vogt at the old Kaiser Wilhelm Institut, where I visited them once, were engaged in cutting literally millions of sections of the human brain in such a search. I could only admire their ant-like industry, even if I were sceptical as to where it would lead them. (Incidentally, these grand old single-minded research-workers are still alive.)

At the same time, the brilliant researches of Pavlov and his co-workers into the physiology of the conditioned reflex made it appear even more likely to my generation that the naïve approach of Watson in America and his fellow behaviourists would be confirmed by careful physiological observation and experiment. The idea that one can have a psychology without a psyche is anot example, of course, of a failure to apprehend in

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The second Croonian lecture for 1952, delivered before the Royal College of Physicians of London on May 8. (Abridged.) Lecture I appeared last week.

entirety the principles of causality about which I spoke in my first lecture.

Modern variants of this type of thinking are to be found in Wiener's "cybernetics" which likens the mind (strictly speaking, I suppose, I should say the brain; but people who think on these lines equate the brain and the mind) to an immensely complicated electronic computer. The work of McCulloch is comparable, but endocrinology and biochemistry in general figure more largely in the total schema. Academically less important and well-grounded, but coming out of the same stable, we have Salter's work on "conditioned reflex therapy," and the curious claims of L. R. Hubbard, the transatlantic inventor of "dianetics."

Let me say from the start—i.e., before I embark upon a more detailed and more critical exposé of psycho-analysis—that all these formulations are valuable in so far as they establish partial causal relationships, if only by analogy; and, as we have seen, the causal principles which I have outlined have an important place in their system for *analogical* thinking. It is, I think, unfortunate that most of these original workers and thinkers are or were still thinking in terms of simple paired efficient cause and effect.

In the first of my yearly routine lectures to the students at Barts I warn them that everything that I shall tell them in the first half-dozen lectures is little better, or even nothing more, than an analogy, a parable, a simile, a metaphor, or a mythological construct. This is important, for the kind of psychopathology that I find it justifiable and convenient to teach is a sort of "Freud-without-tears." And I repeat the warning from time to time.

Before Freud

Let me again indulge in a short, somewhat amorphous digression: in my student days we were fully aware of one kind of psychiatrist, the asylum medical officer who had reached medical superintendent status, and more vaguely conscious of another type of mental specialist, the psychotherapist. Those were the early days of the Tavistock Clinic, whose founder and first medical director, Dr. Hugh Crichton-Miller, was even then beginning to put eclectic analytical psychotherapy on the map. There were also at that time a few courageous pioneer workers in Freudian psycho-analysis. The majority of us students regarded this second category as "mystery men" whom we treated with a certain amount of amused respect, but failed to take quite seriously. The first category were acceptable in view of the fact that all that they had to teach us was descriptive psychiatry, which did not compel us to indulge in any strenuous thinking for ourselves. Even then it must be admitted that we regarded our few compulsory attendances at a mental hospital for lecture-demonstrations more as a diverting tea-fight than as a serious part of our studies. I think that it would be fair to say that in those days, at least, the most successful mental specialists were those who could demonstrate psychotic "case-material" most effectively, or, to put it less gently, were the best showmen.

Even today the climate surrounding the practising psychiatrist is somewhat anomalous. Nowadays even those who have never heard of Freud are thinking altogether differently from those who lived in pre-Freudian times. Every now and then geniuses appear who reshape our pattern of thinking in this way. Such names as Newton, Karl Marx, Sherrington, Einstein, Planck, occur to us in this connection. The result is that, whereas in the times that I have just described Freud and his courageous followers, if they were heard of at all, were looked upon as prurient-minded cranks, today Freud's basic teaching is not only regarded as being respectable but is taken for granted—i.e., uncritically accepted. In those days it would have been ungallant and "reactionary" to have attacked psycho-analysis—many did so, however; but now that psycho-analytical theory and practice have become modern orthodoxy, it is perhaps a duty on the part of those who feel that their long experience has given them grounds for relevant criticism to speak without fear or favour.

It must not be forgotten that Freud's basic training was neurological and that he was at one time a pupil of Charcot in Paris. It is therefore not surprising that, when he came to think independently, he should have done so in the terms of simple cause and effect derived from the physical sciences. This reliance on formal logic, however falsely based, proved very attractive to the scientific mind and finally succeeded in overcoming the violent opposition—largely based on prejudice and prudishness, as it was at the time—to which it had given rise.

It must not be supposed that the concept of unconscious mental processes originated with Freud. The notion is to be found in the writings of St. Augustine and St. Thomas Aquinas; and, in Freud's own time, von Hartmann had attempted to base a philosophical system upon it. However, Freud was undoubtedly the first to conceive of the immense possibilities of applying this notion to the problem of human motivations in health and disease and thereby revolutionising for all time the whole of normal and abnormal psychology.

This is obviously neither the time nor the place to attempt to summarise the whole corpus of Freudian doctrine and practice. It should, however, be emphasised from the start that Freud's ingrained habit of searching for a simple efficient cause to account for a sequence of effects, however complicated, led to a doctrine of psychological and philosophical determinism of a more far-reaching kind than had ever been previously known, and to the triumph of the principle of unreason in psychological medicine.

The Triumph of Unreason

It never seems to have occurred to Freud or to his disciples, orthodox and dissident, that science and philosophy can accept and make use of the factor of random chance, and that a system of psychology that excludes the fact of human volition from serious consideration is bound to come to grief sooner or later, if only for the reason that it fails to conform to human experience.

The extent to which Freud's teaching on this point is most clearly shown is perhaps best exemplified in his little book, *The Psychopathology of Everyday Life*, a work which became so popular that it was even issued as a "Penguin." If I leave my umbrella in a friend's house, it must be (not it may be, mark you) because I harbour an unconscious desire to have a respectable excuse to revisit the house. If the maid (when Freud was writing, there were such things as maids) breaks the best china teapot, it must be because she is giving expression to her unconscious resentment at being in service at all. All forgetting is purposeful even if the purpose remains unconscious.

We are thus presented with a psychological schema which is more teleological than anything that the most rigid moral theologian could devise, and a doctrine of causality borrowed from physics (without there being any obvious recognition of its analogical nature) which baulks at the First Cause. (It will be remembered that the First Cause is taken out of its causal framework and nonchalantly presented to us on a Freudian plate as a mere skyward projection of the "father-image.")

The life of man, like that of any other animal, is governed by the pleasure-pain principle, and in the last analysis by nothing more. This means that our sole motivations can be reduced to the desire to experience pleasure and to dodge pain; or, expressed in more "neurophysiological" terms, to avoid unbearable tensions. It is interesting that the prophet of the primacy of ex (for all pleasure, according to Freud, is ultimately sex-derived) should have lost sight of the fact that man alone of all the animals can artificially create almost unbearable tensions just in order to relieve them, and that the tension is just as essential a factor in the total pleasure-complex as its relief. An explanation of this apparent paradox by making use of such terms as sado-masochism is, in the opinion of many, a semantic trick and not a true explanation.

"TREATMENT OF CAUSES"

As indicated earlier, the great advantage of the Freudian system was that, in its therapeutic application, it claimed to treat the causes of symptoms rather than symptoms merely. The great disadvantage of the suggestive methods was that, although they were often successful in abolishing the troublesome symptoms of the moment, they were apt to return after a while either in their previous or in some other form—but not always, be it remembered.

Every patient who starts an analysis is told, explicitly or implicitly, that his symptoms have a meaning (i.e., a cause), that this causal relationship exists at that level of the mind which we call the Unconscious (with a capital U), and that he will be relieved of his symptoms once and for all as soon as this relationship is brought into consciousness with emotional conviction, even if the search takes many years, as it may well do.

The analyst, on the other hand, goes to work with a somewhat different formula: the cure of any neurosis, psychosis, or psychosomatic illness depends on the conversion of the *actual* neurosis into a *transference* neurosis and the subsequent resolution of the latter. According to the psycho-analysts, a special kind of dynamic relationship is set up between the analyst and the analysand (patient, or sometimes trainee-analyst). Almost from the start, the analyst becomes identified with one or other of the important figures in the primal childhood drama—usually the mother or the father or a parent-substitute, or each in turn. In the course of analysis the primitive emotions with their polar opposites are *transferred* (hence the term "transference") to the person of the analyst, who is in turn extravagantly loved and equally extravagantly hated. Since these early ambivalent attachments contain a strong (repressed) incestuous element, the attitude of the analysand to the analyst comes to be sexually over-determined. This constitutes the transference neurosis, whose final resolution (largely by active interpretation), if it ever takes place, terminates the analysis. The "actual neurosis," which in the course of successful analysis is replaced by the transference neurosis, is represented by the intolerable symptom-complex for which the analysand is seeking permanent relief.

In view of the incestuous element invariably present in the child-parent or inter-sibling relationship already mentioned, the well-known Œdipus complex (and/or its inversion) is ineluctably disclosed in the course of analysis. In fact, no analysis can be said to be complete until this happens, since failure to resolve the Œdipus complex is said to be the final cause of most mental disorders.

The readiness with which the transference neurosis can replace the actual neurosis depends on the principle of repetition-compulsion, which states that, once a subjectively uncomfortable or socially unacceptable form of canalisation of these infantile, sex-derived emotional dispositions has established itself, it will continue to repeat itself in an increasingly adult setting until the actual neurosis crystallises out as a stable construct. There is no way of meeting this impasse other than through the analytical procedure just described.

I know that this account of the Freudian attitude to the therapeutic aspects of their discipline is a gross over-simplification; but it is not inaccurate. Further, my future critics will complain that I am giving a wrong definition of or a wrong twist to such terms as transference-neurosis or repetition-compulsion. However, this is inevitable, for Freud himself over the length of the years and in his rich output gives different connotations to the terminology of his own coinage; and no two psycho-analytical writers seem to agree exactly on correct usage. The way in which convinced analysts meet scientific and philosophical criticism will call for some comment later.

Many of the assumptions of psycho-analysis which contribute to the element of "unreason" in psychological medicine will already be apparent; others will require further exposition.

It may be said, however, that this remarkable and admirably worked-out *closed* system provides a ready-made (or a potentially prefabricated) answer to all the problems of man's action, feeling, and thinking patterns both in health and disease. Anxiety (whatever the actual situation might be which makes anxiety inevitable) is due to guilt arising out of the unconscious residua of out-of-date psychosexual dispositions. Depression is caused by repressed aggression (itself a by-product of sexuality) directed against the ego. Hysteria depends on a "fixation of the libido" at a pregenital level, obsessive-compulsive neurosis on anal-erotic dispositions (likewise depression, incidentally). Schizophrenia is rooted in primary narcissism and is hence psychogenic. Homosexuality (like almost everything else, in the last analysis) depends on a failure to resolve the Œdipus complex. And so on, and so on.

All these answers depend on the assumption that the questions themselves can be put in the form: "what is the efficient cause of this or that effect?" There is of course the further assumption that the efficient cause is invariably psychic.

As my main thesis is that specifically human situations cannot be stated in terms of simple cause and effect, and, as I regard the principle of multiple ætiology as valid throughout the field of medicine, I am bound to reject much of psycho-analytical doctrine as an irrational system and to regret its *unselective* application as a therapeutic instrument.

THE PRAGMATIC TEST

In the long run, the only sound test for the therapeutic aspects of any branch of medicine is the pragmatic one. If orthodox psycho-analysis could pass this test, it could afford to snap its fingers at its armchair critics. What are the facts? Significant statistical data are lacking, but it would seem that, even in the best hands and with the treatment unhampered by lack of time, psycho-analysis can claim only 22–25% of satisfactory cures. This is disappointing, to say the least, in the case of a system which states that, once the simple chain of cause and effect has been established in the depths of the psychic structure, cure is automatic and inevitable. If this belief is shared by analyst and analysand alike, treatment may well continue indefinitely or until the patient's financial resources are exhausted. That must be so if cure is always thought to be just round the corner. In 1934, for example, I knew of an obsessive-compulsive neurotic patient who had been attending a reputable psycho-analyst for five one-hour sessions a week for the past eleven years. For all I know, he is still undergoing psycho-analysis.

How then are we to account for the 25% of successes (taking the higher figure)? So far as the less well-established *psychoneurotic* formations are concerned, it may be said that some 25% of patients appear to benefit considerably from psychotherapeutic procedures which are unrelated to depth-psychology in the Freudian sense, and that it seems likely that analytical psychotherapy which regards itself as free to depart widely from the orthodox psycho-analytical technique and is sceptical about large parts of Freudian theory can claim a considerably larger number of satisfactory successes than those obtained by rigid orthodox analysts.

CAUSE OR PHASE ?

I am one of those who maintain on the grounds of experience that concepts such as the Œdipus complex, infantile sexuality, and the like mean something and are valuable. However, the use to which they are put by practising analysts is often unfortunate. Freud himself in parts of his writings describes these potential patterns of conduct and feeling as belonging to the natural history of development. In other places, the inference is that these repressed elements are inevitably pathogenic; and the average orthodox analyst pounces on indications of these ontogenetic psychic residua with glee, as they crop up in dreams and free association, as ineluctably providing important clues to the *causation* of the actual neurosis. In my opinion, psychic elements of this kind, as in the case of all kinds of human experience (actual or potential), *may* figure in the pattern of faulty adaptation which we call a psychoneurosis, but analysis may equally well be uncovering traces of natural history possessing no kind of pathogenic significance. To be a little more specific: an analyst over a few years, let us say, analyses half a dozen obsessive-compulsive neurotics and (with or without a certain amount of tendentious suggestions) discovers evidence of buried anal-erotic dispositions in all of them. The immediate inference for this analyst, who is steeped, let us suppose, in Freudian doctrine, is that anal erotism (so called) is the efficient cause or one of the *causae agentes* of obsessive-compulsive neurosis. If, however, "we turn to another page of the book," we find that anal erotism is one of the stages of libidinal development through which we all pass; and it is a logical inference that a control group of normal analysands would also provide evidence of their anal-erotic components. This is only a polite way of expressing the homely truth that one cannot always have it both ways.

In the same sort of context, let us examine the generally accepted psycho-analytical theory of the genesis of homosexuality (in the male, let us say, to keep things as simple as possible). Psycho-analysts maintain that the efficient cause of homosexuality is failure to resolve the Œdipus complex, with the result that after puberty all women become unconsciously tarred with the incestuous brush, causing the adolescent male to regress to the homosexual phase of libidinal development—which, incidentally, and I think with a certain amount of correctness, is postulated as a bit of natural history—and remains stuck, or "fixated," to use Freudian terminology. That formulation, nevertheless, leaves several very important questions unanswered, especially if one is thinking in strictly causal terms. For example, why is this particular boy "mother fixated"? Is it not equally likely that this boy, in view of his asthenic temperamental endowment, established an over-strong emotional dependence on his mother, needing from the start a greater measure of protection from "the slings and arrows of outrageous fortune" than his more robust brother? This would provide an equally valid part-interpretation of homosexuality in terms of constitutional temperament and genetic equipment; and it could not be maintained, I think, that it would be possible to reduce a gene or a constellation of genes to their psycho-analytical terms.

MULTIPLE ÆTIOLOGY

These considerations justify my pointing out in slightly greater detail to what an extent rigid psycho-analytical theory violates the principle of multiple ætiology that I mentioned in my first lecture: for example, Freud himself was by no means blind to the genetic factor. For instance, realising, as he did, that elements of this kind could prove resistant to his technique, he warned his followers against employing it in the case of the psychoses. Many psycho-analysts since then have been less cautious. It could not be denied, I think, that schizophrenia would not develop in the absence of a specific major inheritance factor. Whether this gene predisposes to a certain kind of biochemical perversion at the level of the hypothalamus, as seems quite likely in the light of our present knowledge, or whether it brings about a fragmentation of the personality-structure in other ways is hard to determine. Nevertheless, the only factor which lends itself to psychological analysis (and the psycho-analytical method proves itself to be an inefficient and clumsy instrument for such an analysis) is the precipitating factor; and the analysis would show that the component elements were just as much social or environmental as psychological. In spite of Dr. J. R. Rosen's interesting claims, I would take leave to doubt whether the benefit that his schizophrenic patients derived from his technique could be explained in the strictly causal terms demanded by Freudian theory.

Again, the genetic element in cyclophrenia (as I prefer to call manic-depressive psychosis) is equally definite; and the biochemical determinants of involutional depression are clearly important. Yet the fanatical psychogeneticists amongst the psycho-analysts are bitterly opposed to electroplexy and all physical methods of treatment in these and in other psychotic disorders. The grounds for their disapproval are interesting: they object to therapeutic measures which are empirical in nature (i.e., do not appear to be expressible in terms of simple causality); and they also resent the fact that, if one cures the depressive or the manic attack of the moment without employing the psycho-analytical method, one gets to learn nothing about the psychopathology of cyclophrenia—and this quite regardless of the fact that psychopathology may well represent a glaring irrelevancy. The statement (already mentioned) that in depressive states aggression is directed against the self instead of being projected on to elements in the outside world is a descriptive account and in no sense an explanation in causal terms, as alleged. Furthermore, this provides an instance of the objectionable facility with which psycho-analysts concretise the abstractions of their own devising, so that they come to think of "aggression" as though it were some kind of corrosive fluid under pressure capable of being conducted into this or that channel. In point of fact, of course, there is no such *thing* as aggression; all that there is is an angry man prepared to launch an attack—in other words, an actual or potential pattern of conduct or feeling.

Other instances of the concretisation of psycho-analytical abstractions which are in the last analysis nothing more than semantic conveniences will occur to all of you readily enough. The various divisions of the psyche in the Freudian schema—ego, super-ego, and id—are apt to be regarded as such concrete realities that their representation in terms of cerebral architectonics is occasionally sought for, at least in fantasy.

Towards the end of this lecture I will give my own views of the road which our vast ignorance of the real determinants of mental and emotional disorders entitles us to follow. But, whilst humbly recognising the great debt which psychiatry owes to Freud, I find it necessary to point out here that the psycho-analytical formulations by no means exhaust even the psychological possibilities.

SHORTCOMINGS OF THE PSYCHO-ANALYSTS

You will remember that, in his approach to "depth-psychology," Jung is less interested in clear-cut, sex-derived dispositions arising out of individual experiences, and pays more attention to the balance or tensions associated with the "faculties." Blake, with the vision of the mystical prophet and inspired poet, approached the endopsychic drama in a strikingly similar way. Let me quote from Professor Blackstone's book, *English Blake*, in illustration of this. He is commenting on Blake's *The Four Zoas*:

> "The Eternal Man who is 'in the beginning' lives ideally in enjoyment of every aspect of his being. Of these aspects four are prominent: the imagination (Los), the reason (Urizen), the passions (Luvah), and the instincts or body (Tharmas). So long as these aspects are held in fluid interplay, all is well. But Man (Albion) is led astray by his passions, and begins to worship them. He permits himself to be dominated by Luvah, and only recovers in time to appeal to Urizen for help. But already the balance of consciousness has been disturbed—the excess in the direction of passion has to be remedied by an excess in the direction of reason. Urizen seizes all power into his hands, banishes Luvah, and initiates the egotistic universe of matter. Tharmas is precipitated in a material form as the ocean, and Los, separating from his emanation Enitharmon (inspiration), is engaged in an eternal struggle from now on to redeem man from the effects of his folly. This involves warfare with Urizen. Man falls into the world of generation, and the phenomenal universe is detached from his body."

The psycho-analysts, over-fascinated as they are by the natural or psychopathological history of the early libidinal drives, remain blind to psychological possibilities of this kind, which seem to me to represent equally important features of the human situation.

Before we turn from this brief, critical survey of the orthodox psycho-analytical position and consider other aspects of psychological medicine from the standpoint of reason or unreason, may I present you with another quotation, this time from my introduction to Roland Dalbiez's *Psychoanalytical Method and the Doctrine of Freud*. I regard my comment as being of some importance, because it perhaps serves to show how it came about that the work of Freud and of his more gifted collaborators which would have benefited so much from honest scientific and philosophical criticism was protected therefrom:

> "The psychoanalytical movement itself, however, has developed on extraordinary lines. It has come to resemble a cult more than a scientific discipline. It has its canonical literature, its apocryphas, its orthodoxies and heterodoxies, its inquisitors and its apostolic succession. Orthodox psychoanalysts are compelled to submit their will and reason to as stern a discipline as any members of a Religious Order. Thus it comes about that many psychoanalysts inhabit a little world of their own that is apt to be quite out of touch with systems of thought which are foreign to them."

Physical Methods in Psychiatry

I will have very little to say about the physical methods of treatment which have found a place in the modern practice of psychological medicine. The way in which they fit into the categories of reason and unreason is clear enough. The more prudent protagonist of any of these methods would not claim that they are rational; they are all empirical, and many of them developed out of observations and hypotheses which subsequently turned out to be irrelevant from the strictly rational point of view. This is nothing new in medicine, of course. We need only remind ourselves of the false premises on which Wassermann erected his test. These physical methods will survive for so long as they pass the pragmatic test, until they are superseded by other methods which give better therapeutic results; or, to use an Americanism, they will be used so long as they continue to "deliver the goods."

I, for example, am satisfied that the best method we have today of treating the depressive syndrome in carefully selected cases is by electrically induced convulsions, provided that the technique is sound and that apparatus is used which reduces the risk of damage to neurones to an absolute minimum. However, I recognise the fact that the introduction of a more satisfactory procedure might cause me to reverse this opinion at any moment. As other examples: the popularity of hypoglycæmic coma in the treatment of schizophrenia is on the wane, especially in the United States, where it enjoyed its peak-boom; and I would venture to prophesy, perhaps rashly, that the time is not far distant when prefrontal leucotomy will have been relegated to the museum of grim, outmoded neurosurgical curiosities, even though the procedure is justifiable today, in certain cases.

The Rational Basis

To revert once more to orthodox psycho-analysis in relation to the pragmatic test: it is a curious, but undoubted, fact that the psycho-analytical method can claim the least number of successes in the very field in which its theory is rooted. The number of "cures" of patients exhibiting clear-cut psychosexual anomalies is disappointingly small. I have, for example, yet to come across a case of well-established sexual fetishism which responded satisfactorily to psycho-analysis. The late Dr. Stekel, a non-conforming psycho-analyst, in his two-volume study of fetishism, makes no clear claims to therapeutic successes, although he enjoyed great prestige as a successful psychotherapist in other fields.

I do not wish to give the impression that it is impossible to establish a simple cause-and-effect relationship at the psychological level, but it is likely that this occurs about as rarely in this field as in that of general medicine. As an example, I might quote the following case:

> A young man complained of nausea and vomiting in taxis. It was not a case of ordinary car-sickness, since he was affected only in cabs in this way. The following history was elicited under hypnosis: at the age of 12 on the way home from school he had smoked a cigarette in the taxi and had promptly vomited. At the time smoking by preparatory schoolboys was regarded as a considerable crime; his guilt-sense (presumably) caused him to repress the memory of the incident together with its emotional investment. The knowledge of the "meaning" of his monosymptomatic neurosis led to its abolition.

It is just as legitimate to think of a neurotic symptom of this kind in terms of conditioned reflexes and its cure as the extinction of a conditioned reflex, as to rely on an interpretation based on the Freudian concept of repetition-compulsion.

At the very beginning of his independent work in the field of psychological medicine, Freud employed hypnosis in this way, in the belief that there was always a causal relationship between a repressed traumatic incident and the presenting symptom-complex. That is one of the reasons, perhaps, why, even after he was able to throw light on the immense complexity of the depths of the human psyche, he stuck to his over-simplified notions of causality.

What is to be done to avoid the element of unreason in analytical psychotherapy, and is it really of any practical consequence to do so? To answer the second half of this question first: in the case of psycho-analysis, at any rate, it is important to review its rational basis, for psycho-analysis claims to be more than a corpus of knowledge forming the basis of a therapeutic technique. It claims to act as a guide for the bringing up of children and their subsequent education, to act as a substitute for dogmatic theology, to offer reliable rules for literary and artistic criticism, to reinterpret history, to provide a solution in psychological terms for the problem of war, to reformulate the moral principle of human responsibility, and much else. Quite apart from these general considerations, which are of no immediate interest to the physician, it seems likely that a therapeutic discipline in which the practitioner is unable to differentiate between reason and unreason is bound to give equivocal and incalculable results.

To answer the first half of the question: it seems to me necessary to state the problem itself in simple terms. If one's primary formulation is elaborate, the answers that follow are likely to be so complex that the philosophical framework that should contain them breaks up.

I would be content to say, with Curran and Guttmann, that a mental illness represents a failure to adapt to the situation of the moment, and to commit myself no further so far as definition is concerned. Such a simple formula allows one to employ deduction and induction, and argue *a priori* and *a posteriori* as the occasion demands. It also has the great advantage of conforming to the principle of multiple ætiology. For, clearly, a failure to adapt to a given situation may depend primarily on bodily, psychic, constitutional, genetic, social, or (I would be so bold as to add) spiritual factors.

Furthermore, this formulation makes it essential to take the current conflict into account in arriving at an assessment of the total situation. The psycho-analysts attribute secondary significance only to current difficulties. They regard them merely as representing a trigger or a precipitating factor for starting machinery which is already assembled in the unconscious. The unreason involved in such a notion should, I think, be sufficiently obvious. The problems of infancy, early childhood, pubescence, married life, involution, and senescence, and those associated with approaching bankruptcy, shall we say, or threatened divorce proceedings, imprisonment, or a loss of religious faith, are fundamentally different in kind one from another; it is not just a difference of degree. It seems to me foolish to maintain that early libidinal frustrations are not only the paradigm of more adult discontents but that, in accordance with the psycho-analytical mystique, the pattern is endlessly repeated.

In a sense, the situations to which we are required to adjust are the same throughout our lives, if we reduce the subjective unease involved to its simplest terms: we have to learn by means of foresight to sacrifice the satisfaction of vital (immediacy) values to more realistic needs projected into the future. However, the social setting in which this occurs and the equipment which enables us to try and meet the challenge vary so much from life-phase to life-phase, that it is both irrational and unpractical to insist on the identity. Thus, the failure to adjust to the total situation in the case of a young man who is, say, unconsciously seeking a mother-substitute instead of a mate is in no truly meaningful sense identical with the similar problem which was presented to our hypothetical patient in early childhood. Nor is there any compelling reason to suppose that putting the wheel of time into reverse by taking him for a ride in the psycho-analytical time-machine and forcing him to review his infantile conflict in fantasy is in itself—however skilfully the transference-situation is handled—going to help him to make a satisfactory adjustment to actuality.

Furthermore, it must be remembered that certain acquired psychosomatic patterns have the character of irreversibility; in other words, the psychotherapist is not omnipotent, whatever instrument he may choose to employ. As an example of an irreversible pattern of this kind: an able psycho-analyst has recently shown that the lengthy separation of an infant from his mother or an accepted mother-substitute can so vitiate the emotional organisation of that child that he can never thereafter enjoy proper human relationships.

DIAGNOSIS

As in general medicine, then, so in psychiatry: accurate diagnosis must precede treatment; nor does diagnosis mean merely the neat attachment of a nosological label to a symptom-complex. Such labels are eventually necessary for the compilation of statistical tables, but as a guide to treatment they are even less helpful in psychological medicine than they are in the general field. A patient may be exhibiting anxiety together with its somatic accompaniments as the main presenting syndrome, but it would be unwise in the extreme to make a lightning diagnosis of anxiety neurosis; for a fuller investigation may show that the correct diagnosis may well be early thyrotoxicosis, or incipient schizophrenia, or concealed endogenous depressive psychosis; in fact there are a hundred and one diagnostic possibilities in every case. After he has taken a full history, a psychiatrist should be able to provide answers to all the questions which arise naturally from the principle of multiple ætiology.

TREATMENT

In treatment, then, a psychiatrist must be prepared to try to influence the total situation on several fronts, which include the somatic, the psychic, and the environmental (in its most inclusive sense). Constitutional and genetic factors must be carefully considered in the ætiological assessment, even though they may not be modifiable.

For example, after the initial interview a psychiatrist may decide that all that is required to enable a child who is reacting neurotically to the actual situation is to arrange for a change of school or foster-parents, and that consulting-room methods of treatment, such as interpretative play-therapy, might be positively contra-indicated. Nevertheless, it must, in my opinion, be taken as a general rule that the psychotherapy of adults should always include a careful analysis. This analysis should invariably embrace the total situation of the moment together with all the associated current conflicts. It will in most cases soon become apparent whether the analysis should be extended into the depths of the psyche. It must always be gratefully remembered that even for a proper psychological appreciation of the actual situation we shall always have to rely to a large extent on the pioneer studies in depth-psychology of psychopathologists of genius such as Freud, Jung, and Adler. Nevertheless, it must not be forgotten that in many cases of psychoneurosis all that can be established is the operation of diffuse psychic tension or a non-purposeful psychic content which is reacting on the autonomic nervous centres in such a way as to bring about considerable psychic disequilibrium (Kretschmer).

When we are making use of any of the analytical techniques which have proved of value—and they are many—we should always try to be clear in our own minds whether we are employing *analogical* thinking or dealing with "true" causal sequences.

Further, a psychiatrist should feel free to employ all non-analytical methods as the occasion demands. These will include the physical methods, re-educative methods, direct and indirect suggestive methods, abreactive methods with the use of hypnosis or drugs, conditioned-reflex therapy (Salter), Yoga-like methods such as Schultz's "autogenes training," and Kretschmer's fractional hypnosis, and many others. There is, needless to say, one essential proviso: the practitioner must be a past-master of the technique which he is employing and have a complete belief in its efficacy for the task in hand. Furthermore, every psychiatrist should be a competent general physician with a considerable knowledge of neurology and biochemistry. It will be apparent that I uncompromisingly reject the admission of medically unqualified practitioners into psychological medicine. Certain well-trained and especially gifted lay men and women may, however, render valuable assistance in some highly specialised fields such as play-therapy.

The Psychiatrist

Before I conclude these lectures, even at the risk of appearing to introduce an irrelevancy, I should like to mention one more result of the holding of a *credo* of unreason: both in this country and in the United States there are many posts in mental hygiene which are advertised with a clause limiting applicants to those who have undergone a personal analysis. This implies that we have reached a stage in our social evolution when a new kind of aristocracy, "the fully analysed," has appeared on the horizon, together with a novel sort of proletariat, those who have not done their drill on the psychoanalytical barrack-square and those who have seen fit to dissociate themselves from the Freudian chiaroscuro. Holding the views that I have endeavoured to set out here, I am always embarrassed when other members of a selection committee on which I may happen to be serving ask a candidate for an important psychiatric post whether he has undergone a personal analysis or not. An affirmative answer, as things are at present, is bound to count unduly in his favour with some and to damn him out of hand with others.

The psychiatrist today is in a peculiar position vis-à-vis his professional colleagues in other branches of medicine. As I hinted earlier, thirty or more years ago there was one class of alienist who was called in to certify one's insane patients. Between whiles for the most part such a practitioner did no more damage than prescribe too much bromide, thereby occasioning a few cases of undiagnosed bromide intoxication. Another class of mental specialist exercised custodial functions behind the high walls of mental hospitals and organised cricket matches. The modern psychiatrist presents a challenge; and the attitude to him is curiously ambivalent: at the same time as he is regarded with a considerable measure of suspicion, and accordingly comes in for a fair amount of (sometimes rather ill-natured) banter, he is quite confidently expected to work therapeutic miracles, and in double-quick time; and, strangely enough, he often comes up to expectation.

It must be remembered that from the scientific point of view psychiatry is some fifty years behind general medicine. If psychiatrists will only bear this in mind and not expose themselves to the charge of being "enthusiasts," in the 18th-century sense of the word, they will realise that this double-edged attitude is inevitable for the time being. To console themselves, they can tell themselves that the future of psychological medicine is bright indeed, perhaps brighter than in any other field, and that its rate of progress is such as should satisfy even the most impatient.

DEGENERATION OF THE SPINAL CORD ASSOCIATED WITH CERVICAL SPONDYLOSIS

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Stookey in 1928 described degeneration of the spinal cord in association with cartilaginous protrusions into the cervical region of the spinal canal. These he then called chondromas, but later (1940) he accepted the view that they were the disc protrusions originally described by von Luschka (1858). Further studies of the syndrome have been made by Russell Brain et al. (1948), Epstein and Davidoff (1951), Spillane and Lloyd (1951), Allen (1952), and others.

In most instances the syndrome develops not in relation to an isolated disc protrusion but as a part of severe spondylotic changes in the cervical spine, which may or may not show much protrusion of the degenerated intervertebral discs. The mechanisms whereby the cord degenerates in relation to this spinal disease are often quite uncertain. The case reported here illustrates some of the many factors which have to be considered in attempting to unravel the causes of the myelopathy.

CASE-RECORD

Mrs. A, aged 71, during the autumn of 1949 complained of pains which "started from my toes and ran all the way up the front of my legs." Between these paroxysms of pain there was a dull ache in both legs, not confined to the joints. As far back as 1946 she had had acute attacks of pain in the legs, which had subsided spontaneously after a few days.

Towards the middle of 1950 she complained of weakness of the legs as well as of pain, and of numbness of the right hand and forearm. Incontinence of urine developed in December, 1950, and severe constipation led to her admission to the Radcliffe Infirmary with intestinal obstruction. Enemata relieved the bowel difficulty, but by then bed-sores had developed. She was sent home on Jan. 4, 1951, and admitted to Cowley Road Hospital on Jan. 30, 1951.

Neurological examination revealed spastic paresis of both lower limbs, especially the right, which was powerless and had developed a flexion contracture (correctable to 170° with pain). The ankle-jerks were brisk, but the right knee-jerk was absent and the left sluggish. The right plantar reflex was extensor, and the left doubtful. Postural sense was lost over both lower limbs, but pain and temperature sense were lost only on the left, up to about D9, giving a partial Brown-Séquard syndrome. The right upper limb was weak, and there was obvious wasting of all the small muscles of the hand. The right arm reflexes were greatly depressed, while those of the left arm were normal. No sensory loss was detected in the arms, but detailed examination was not possible.

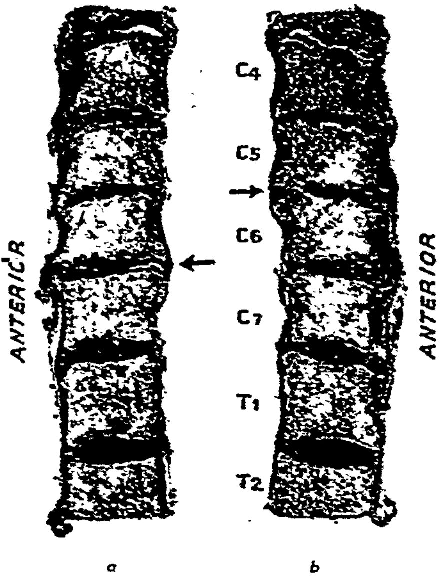

Fig. 1—Parasagittal sections of cervical spine through the two protrusions seen in fig. 4 (marked by arrows): *a*, left; *b*, right, showing degeneration of discs and osteophytic lipping. T1 (left) shows protrusion of degenerated disc material into vertebral bodies (Schmorl's nodes).

Lumbar Puncture.—The lumbar cerebrospinal fluid (C.S.F.) on Jan. 30 was under a pressure of 120 mm. of water. On jugular compression there was a very slow rise of 40 mm., followed by a similar slow fall on release. The C.S.F. contained total protein 90 mg. per 100 ml. and 1 cell per c.mm.; the Lange curve was negative, as also were the Wassermann and Kahn reactions. Re-examined on Feb. 19, the C.S.F. contained 105 mg. of protein per 100 ml. and 2 lymphocytes per c.mm.

Blood Examination.—The serum-protein level was 6·8 g. per 100 ml., and a blood-count showed 10,000 white cells per c.mm. and hæmoglobin 77%. The erythrocyte-sedimentation rate was 116 mm. in 1 hour. The blood Wassermann and Kahn were negative.

Radiography on Feb. 1 showed elevation of the right diaphragm with partial collapse of the right lung; and well-marked degenerative changes in the spine with narrowing of the disc spaces and osteophytic outgrowths at many levels. These were most conspicuous in the lumbar region, but in view of the clinical picture the changes in the cervical vertebræ were thought to be the more significant.

Treatment.—The patient was unfit for laminectomy. An attempt was made to apply neck traction, but death occurred on May 20, 1951.

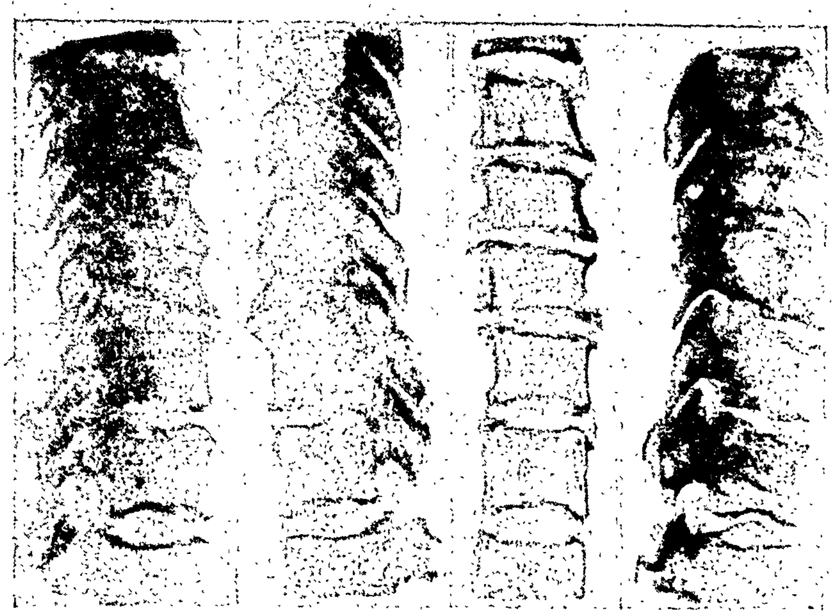

Fig. 2—Lateral radiographs of cervical spine (removed): a, intact specimen; b, left, centre, and right slices obtained by two parasagittal sections.

Necropsy confirmed the severity of the spinal disease in the cervical region. Though nearly all the cervical intervertebral discs were somewhat prominent when viewed through the opened spinal canal, those between c5 and c6 and between c6 and c7 projected most and formed well-marked ridges which expanded laterally into two discrete osteophytic protrusions (fig. 4b), that on the left between c6 and c7 being the larger and projecting about 4 mm. The 7th cervical nerve passing over this spur was stretched and atrophic. Sections through the vertebræ showed that all the cervical discs were degenerated and thinned, and that the prominences were formed by protrusion of the discs covered by bony outgrowths (osteophytic lipping) from the edge of the vertebræ. This change had taken place *not only on the posterior surface* but also round the whole rim of the vertebral bodies, and was in some cases accompanied by severe sclerosis of the bone (figs. 1 and 2). Laterally the process had encroached on the intervertebral foramina, and oblique radiographs of the specimen (after section) showed well the amount of narrowing and distortion (fig. 3). These are the changes of spondylosis *deformans, known in the past as osteo-arthritis of the spine.*

The spinal theca was adherent to the posterior longitudinal ligament at the level of the protrusion at c6–7, and it had been held against the bone firmly enough for the spurs to cause indentation (fig. 4). The spinal cord throughout the whole extent of what should have been the cervical enlargement was much shrunken, as is well seen in fig. 5, and in the 7th and 6th *segments the anteroposterior diameter of the cord was reduced* to 0·4 cm. There was, however, no kinking of the cord, and in spite of the slight protrusions into the spinal canal the theca lay quite loosely over the dorsal surface of the wasted cord.

PATHOLOGY

Microscopy of the cord showed some interesting features. The *chronic degenerative lesion of the cord* was most severe in the 5th and 6th cervical segments, with secondary degeneration ascending and descending from it. In these two segments there was degeneration of both the grey and white matter, with diffuse loss of nerve-cells and severe gliosis (fig. 6). It will be noticed in this figure that the pia mater, especially the denticulate ligament, is thicker and more cellular than usual.

The general pattern of the lesion was best seen in sections stained for myelin, and in fig. 7 transverse sections at several levels provide a general picture of the state of the cervical cord. This figure shows the gross reduction in size of the cord at the affected segments, *although the general configuration is preserved.* One naturally looks for evidence of pressure on the anterior or posterior surface of the cord, but in spite of the *obvious flattening* these aspects show relatively little demyelination.

In the 5th and 6th cervical segments *the demyelination is greatest* on the right side of the cord, where the striking feature is the degeneration in the lateral columns *spreading medially* from the attachment of the thickened denticulate ligament. There is also a prominent *area of demyelination in the anterior* part of the posterior columns. This unusual appearance is unlike a vascular lesion because it does not coincide with the territory of any vessel but is continuous across the posterior horn with the degenerated zone in the lateral column and with the denticulate ligament. Furthermore, the median septa are here shifted to the right, and, although this last may be partly an artefact, all these appearances together suggest that traction on the cord by the right denticulate ligament has played some part in the ætiology of the cord degeneration.

In the 7th cervical segment there is the same wedge of demyelination in the right lateral column as in the two segments above, and at this level also there is a similar relationship to the denticulate ligament. The demyelination in the posterior-root zones is particularly noticeable at this level. The cord at the 1st dorsal segment, below the lesion, is much more normal in size and appearance, but there is obvious descending degeneration in the right lateral column from the lesion above, and this could be traced through the lower dorsal and lumbar segments of the cord. In the upper cervical segments the cord also had a normal shape, and sections showed only ascending degeneration from the lesion below, which, however, in this case has led to a rather unusual appearance of the *posterior columns* (fig. 7). In each posterior column there are two areas of degeneration; the more medial, lying immediately adjacent to the median septum, *is secondary to the posterior-column destruction* at c5 and c6, whereas the more lateral band-like zone is a secondary ascending degeneration of the fibres of the

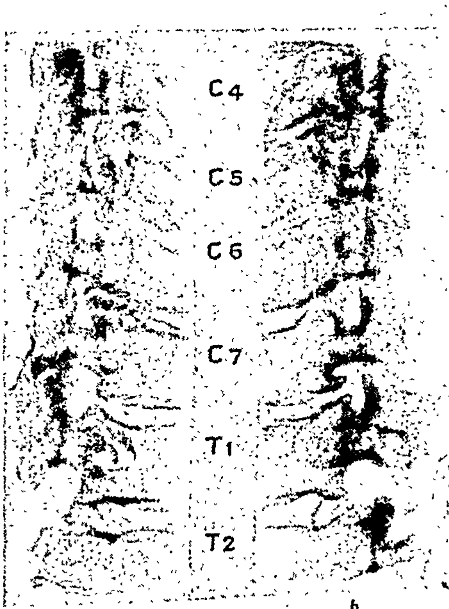

Fig. 3—Oblique radiographs of cervical spine (removed) to show intervertebral foramina.

th, 6th, and 7th cervical nerve-roots. Between this and e posterior horns the well-myelinated ascending fibres f the 3rd and 4th cervical nerves are seen. The great idth of the nerve-roots at entry and their rapid arrowing as they pass upwards are worth noting.

It is clear from these myelin-stained sections that ithin the cord there has been severe degeneration of the ntering nerve-roots in the most affected segments c5 and c6) and in the 7th segment, where at necropsy he left nerve had been seen to be stretched over a bony pur. *Outside the cord the roots of the 6th and 7th nerves* ere much thickened and degenerated, as is visible even n the myelin-stained sections (fig. 7). In these nerves here was a great increase in the collagen surrounding he individual nerve-fibres and an increase in the number of Schwann cells. There was also great variation in the size of the fibres and in the amount of myelin present. Lindblom and Rexed (1948) have described these changes more fully, and we agree with them that the patchiness of the degeneration is striking, some fasciculi being almost entirely degenerated, while neighbouring ones are comparatively unaltered.

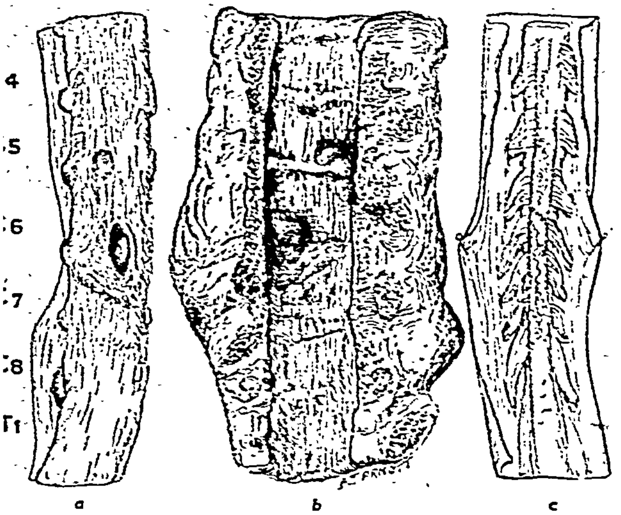

Fig. 4—Cervical spine and cord: *a*, cord and theca from in front after removal, showing site of dural adhesion and indentations of theca by protrusions; *b*, posterior aspect of vertebral bodies, showing the two main protrusions and line of dural adhesion; *c*, posterior aspect of cervical cord, showing wasting of segments 5–8.

It should be noted that the most severely degenerated segments of the cord were those at, and just rostral to, the dural adhesion, and that this was also the level at which the nerve-roots were most damaged. These findings suggest that traction on the cord by either or both these structures may have been an important factor in the ætiology of the condition.

The main spinal blood-vessels were patent. The veins on the dorsal surface of the cord, however, were prominent at the level of the lesion; hence it is possible that the vessels in the intervertebral foraminæ were compressed. Within the cord the walls of the vessels were thickened, and, as is usual, the thickening was most marked in the degenerated areas. The areas of degeneration did not correspond to the distribution of any of the major vessels; so it seems unlikely that ischæmia from vascular disease had played any great part in the pathology.

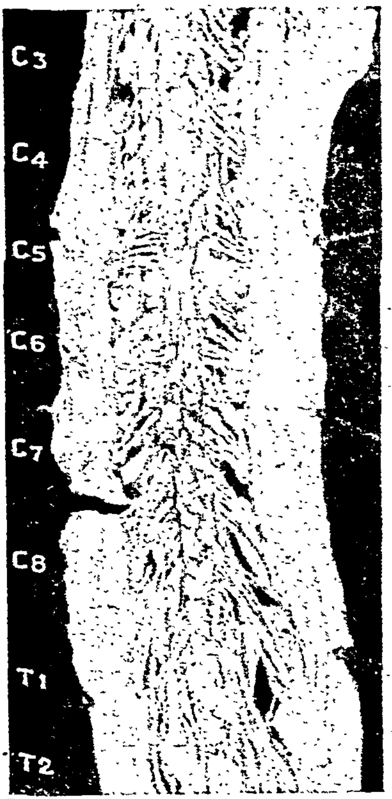

Fig. 5—Dorsal aspect of cervical cord, showing severe wasting most marked between segments 5 and 8.

DISCUSSION

The underlying disease in this case was that often called "osteo-arthritis of the spine"; the term spondylosis deformans, is, however, now generally accepted, and we have called it by this name. Schmorl showed that it was not an inflammation but a degeneration of the intervertebral discs with subsequent characteristic changes in the vertebræ, and it was he who devised the name spondylosis deformans as being more appropriate. Schmorl's work has been summarised in English in a monograph by Beadle (1931).

Cervical spondylosis has long been recognised as a factor in the development of brachial pain syndromes (Mettier and Capp 1941, Lund 1945, Philip 1950); and, as has already been mentioned, the occurrence of cord lesions in relation to cervical spondylosis is being given increasing attention by clinicians.

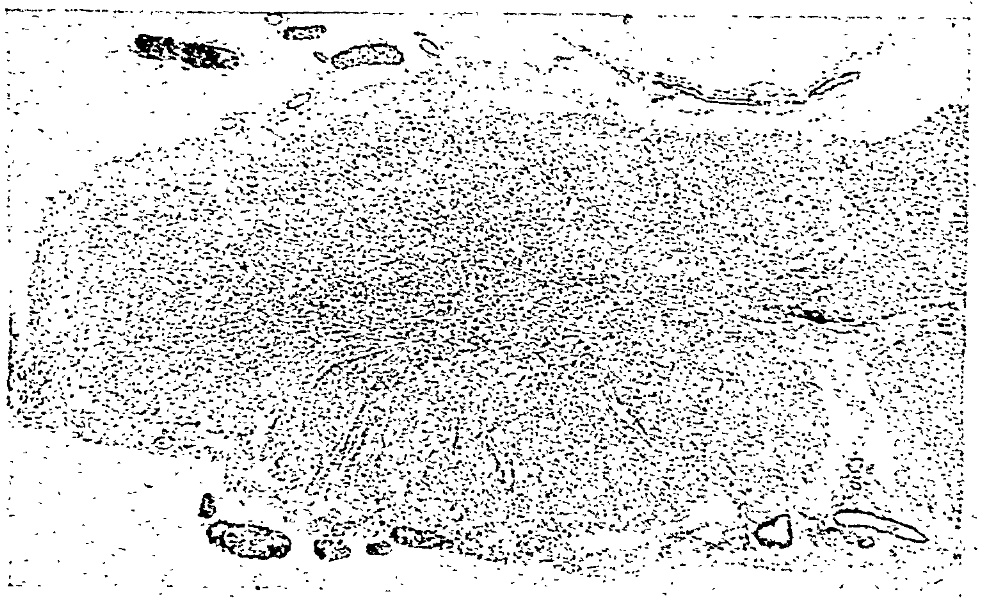

Fig. 6—Transverse section of right half of cord at C5.

Published reports of necropsy findings in these cases, however, seem to be very few.* In the case reported here an old woman slowly developed paralysis of her legs and weakness of her arms. During life the lesion was attributed to severe spondylotic changes in the cervical spine and at necropsy spinal-cord degeneration was found to involve at least three cervical segments (c5, 6, and 7) in close relation to the spondylotic lesions.

It is therefore reasonable to attribute, in some way, the progressive myelopathy to the spondylosis, but how the lesions are produced is uncertain. Here we may turn to the clinical observation that the spinal-cord signs recede in some of these cases if the neck is prevented from exercising its normal movements, which suggests that the cord may become vulnerable to normal neck movements. Further, Allen (1952) has observed, while operating on similar cases, that the spinal cord may blanch when the neck is flexed. The lesion usually develops gradually, and in our case at least there was no reason to inculpate the spinal-cord blood-vessels in the ætiology. A direct traumatic and self-inflicted lesion of the neurones is the most likely explanation, and this suggestion fits in well with the slowly developing characteristics generally observed. It should be emphasised, however, that not all cases showing this clinical syndrome are alike pathologically.

The microscopical sections from the present specimen suggested that the thickened denticulate ligament and the most degenerated nerve-roots were both closely related to the area of cord degeneration, and it seems likely that a tethering of these structures had played some part in the production of the myelopathy.

As regards treatment, the present case makes little contribution except to emphasise the difficulties involved in either surgical or conservative treatment of such a case. It may be possible safely to remove the bony spurs, as Allen (1952) advises, or the denticulate ligament may be divided, as suggested by Kahn (1947). Epstein and Davidoff (1951) strongly deprecated efforts to remove the bony ridges, owing to the danger of causing further cord damage. In this connection Allen (1952) emphasises the dangers of operating with full flexion of the neck and advises an extrathecal approach with a very cautious technique to avoid stretching the cord.

Fixation of the cervical spine by wearing a collar has proved its value in some cases. This, however, also presents difficulties, because long-continued fixation may cause osteoporosis, and most patients not only tire of wearing a collar sooner or later but also may be sceptical of treatment directed to the neck when their symptoms are in the legs. In some cases even a spinal fusion is worth considering.

It is evident, as the present case shows, that handling these patients presents many problems which are not yet fully solved.

SUMMARY

A case is reported (with post-mortem findings) in which there was degeneration of the spinal cord at the 5th, 6th, and 7th cervical segments in relation to cervical spondylosis.

It seems probable that abnormal fixation of the cord may render it vulnerable to normal neck movements. In

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* Some cases have just been published by W. Russell Brain, Douglas Northfield, and Marcia Wilkinson (*Brain*, 1952, 75, 187).

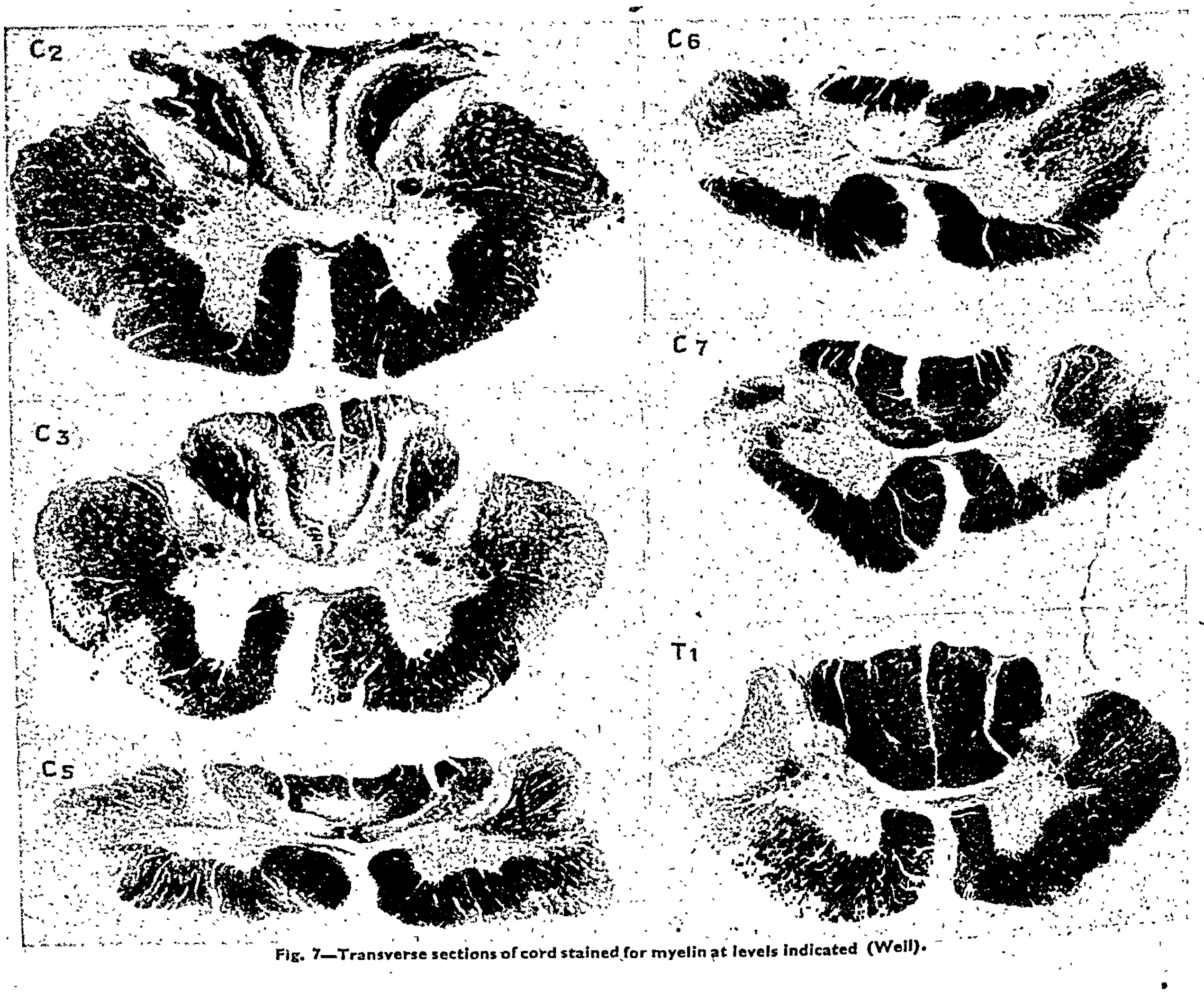

Fig. 7—Transverse sections of cord stained for myelin at levels indicated (Weil).

this case there was evidence of unusual tension on the thickened denticulate ligament and fibrous nerve-roots, and in addition the theca was adherent to the posterior longitudinal ligament. The ridges due to the spondylosis did not seem, per se, to have compressed the cord.

The implications for the treatment of these cases are discussed.

We particularly wish to thank Dr. J. G. Greenfield and Dr. Peter Daniel for all their help with this case, and Miss M. L. Prichard, D.PHIL., for the photomicrographs.

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FRACTURES OF THE NECK OF THE FEMUR

A SIMPLE TECHNIQUE FOR THE INSERTION OF THE SMITH-PETERSEN NAIL

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ALTHOUGH internal fixation with a Smith-Petersen nail, or one of its modifications, is regarded as the standard method for treating a fracture of the neck of the femur, it should be considered primarily as a method of saving the life of the patient. It is often held that this injury kills elderly people because it confines them to bed. This is not true. Consider the thousands of bed-ridden old people in infirmaries. It is not being in bed that kills them, but being confined to bed *with pain*. Abolish the pain, and they will have the best chance of survival.

For this reason the primary indication for internal fixation is to relieve the pain. It is in fact a life-saving measure, which incidentally also offers a reasonable chance of obtaining union of the fracture.

Age and infirmity of the patient are therefore the most important indications for using this method, provided that the surgical manœuvres that it entails do not add too much additional risk.

The aim should therefore be to develop a method which causes the minimum of shock and disturbance to the patient, rather than one that will gratify the operator by its technical perfection.

At the outbreak of the late war, when all nursing-homes in London were temporarily closed, I was compelled to attempt the operation with the patient in his own bed. To my surprise, an ordinary single bed turned out to be an ideal operating-table for the purpose, and the operation was completed with the minimum of difficulty and very limited assistance. As a result of this experience, a technique of performing the operation without moving the patient from his bed was developed, and has now been used in over a hundred cases. It has proved to be so simple and satisfactory, and so few difficulties have been encountered, that I believe it merits a more general trial.

TECHNIQUE

The patient lies on his back in the centre of a standard hospital bed 3 ft. wide and remains in this position throughout. The operation can be performed in the patient's room or ward, or the bed may be wheeled into the operating-theatre. An X-ray cassette holder is slipped under the patient's buttocks; this is a flat wooden box, 15 in. square and 1 in. deep, open at one side so that the X-ray cassette can be slipped in for the anteroposterior view without disturbing the patient. It may be constructed from two pieces of plywood held 1 in. apart by slats on three sides.

Correct anæsthesia is important. It is necessary to have complete relaxation at the commencement but only for a very short time to allow the reduction to be accomplished easily and without trauma. After that, deep anæsthesia is unnecessary. The initial short and deep anæsthesia is obtained by the intravenous administration of sodium thiopentone 0·5 g. or less. The smallest dose that will be effective, given rapidly, is the ideal to be aimed at. Subsequent maintenance is with gas-and-oxygen, assisted by ether if necessary.

The surgeon "scrubs up" and arranges the sterile towels over the patient so that the affected leg is free though wrapped in a towel. Anæsthesia is not induced until this has been done. Thus the surgeon is ready to reduce the fracture while the patient is completely relaxed under the thiopentone; the limb does not have to be disturbed after reduction to put towels round it, and the pinning can be started immediately. With very nervous patients a screen may be used so that they do not see these signs of the coming operation.

Reduction is effected by the Leadbetter (1938) method: the knee and thigh are flexed to a right angle, and the thigh is then rotated externally and internally alternately, while upward traction is exerted with counter-pressure on the pelvis. This disimpacts the broken bone; and, when full internal rotation has been achieved, it is maintained while the thigh is brought down into a position of extension and abduction. The leg now hangs over the edge of the bed, and will be found to lie naturally in a position of full abduction and internal rotation. As the cassette holder compensates for the sag in the middle of the bed, the hip will also be in a position of full extension. Thus a constant and correct position for the leg is secured automatically.

A vertical incision 4 in. long is made on the outer side of the thigh, starting above at the level of the lowest part of the greater trochanter. The vastus lateralis muscle is split vertically, and two bone spikes are passed, one in front of and one behind the shaft of the femur, the handles being then separated to expose the bone. A blunt dissector is passed up along the bone deep to the muscle until it will go no further. This indicates that the dissector has reached the line of attachment of the muscle to the ridge on the lowest part of the trochanter, which provides a constant and easily identifiable landmark. At a point 1 in. below this level a hole $^3/_{16}$ in. in diameter is drilled through the cortex of the bone. If the fracture has been properly reduced, this hole will be in line with the centre of the inguinal ligament on the same side of the body and the anterior superior spine on the opposite side of the body. The point of a Watson-Jones calibrated guide (Watson-Jones 1936) is inserted into the hole and aimed in this line while being held horizontally. It is slowly pushed along through the bone until the increasing resistance of the head of the femur is felt.

Anteroposterior and lateral radiographs are now taken. For the lateral radiograph the cassette is wrapped in a sterile towel and propped up vertically at right angles to the inguinal ligament and with one edge resting against the iliac crest. The opposite leg is raised out of the way, and the X-ray tube is placed approximately where the knee of this leg lay on the bed. It is aimed so that the rays pass parallel to the inguinal ligament. The radiographs first of all check the reduction: if this is incomplete, which only happens very occasionally, the guide is partially withdrawn, the reduction is corrected by further manipulation, and the guide is pushed home again. Secondly, the radiographs check the position of the guide:

if this is incorrect, a second hole is drilled in the bone, and another guide is inserted before the first one is withdrawn. The desired length of nail is estimated from the position of the point of the guide and the calibration mark visible where the guide emerges from the bone, $^{1}/_{4}$ in. being allowed for impaction when the nail is driven home. The selected nail is threaded on to the guide wire, and oriented so that one fin points directly down the shaft of the femur, before it is hammered in. A further radiograph may then be taken, though this is usually unnecessary. In any event, the wound is closed while the X-ray film is being developed; this saves valuable time, and it is a simple matter to remove the stitches in the unlikely event of this being necessary.

ADVANTAGES OF THE METHOD

The chief advantages of this method are its extreme simplicity and the minimal degree of disturbance and shock to the patient. The only special instruments required are an ordinary Smith-Petersen set, consisting of a set of nails, cannulated for the Watson-Jones guide, two guides, cannulated punch, impactor, a bone drill, and, for peace of mind, a nail extractor. The operation can be performed anywhere, even in the patient's own bedroom, and the whole procedure does not take more than half an hour, including ten minutes for taking radiographs.

After some practice with this method it is justifiable to operate, if necessary, without radiographic control. I have done the operation several times without the aid of X rays, and the average time taken from the start of anæsthesia to the bandaging of the wound was twelve minutes. Although in such cases the nail may not be sited perfectly, it is almost impossible to miss the head of the femur, and it should always be possible to obtain fixation firm enough to relieve pain and make the patient comfortable.

DIFFICULTIES AND FAILURES

As in all surgical operations, difficulties and failures are occasionally encountered. Since some of these are avoidable, it may be of advantage to consider those that have been experienced, and the precautions now observed to guard against them.

Difficulty in Reducing the Fracture

Reduction may be difficult where the fracture is impacted or the operation is undertaken a long time after the accident. Impaction most commonly occurs in abduction fractures, and as a rule no attempt at reduction should be made. In late cases, where there is much upward displacement of the femur, a short preliminary period of traction is sometimes advisable. If the fracture is reduced during the stage of complete relaxation, which occurs immediately after the intravenous injection of sodium thiopentone, there will rarely be difficulty. In my experience incomplete reduction can usually be traced to a failure to secure and maintain full internal rotation of the femur.

Difficulty in Passing the Guide

The resistance to the passage of the guide should steadily increase until the articular surface of the head of the femur is reached. If the firm resistance of cortical bone is felt before the guide has been inserted for 3 in., it usually means that the guide has caught on the calcar femorale and must therefore be withdrawn and reinserted with a rather greater upward inclination.

Apart from this, difficulty in passing the guide is usually due to incorrect reduction of the fracture, and it is therefore better to check the reduction again by further manipulation rather than to continue trying to insert the guide in different directions.

Jamming of the Nail on the Guide Wire

This very trying accident is due to the nail catching on one of the grooved calibrations of a guide which is slightly bent. Unless the mishap is noticed, the guide will be carried in with the nail. While the nail is being hammered in, the punch should be withdrawn repeatedly to make sure that this is not happening. Guides can now be obtained which are calibrated without grooves, and this minimises the possibility of such an accident. It may still happen, however, if the guide is slightly out of true. If it happens, both guide and nail must be extracted together. Attempts to extract the guide only may lead to breaking off the portion extruding from the nail, which may then be left embedded somewhere in the joint.

Wrong Length of Nail

If a second guide has had to be inserted, and the length of nail required has been determined from the X-ray plate showing the first guide, a wrong length of nail may be selected. The only safe method is to feel the point of the guide impinge upon the cortical bone of the head of the femur, and to choose a nail a full $^{1}/_{4}$ in. shorter than the length shown on the guide where it emerges from the femur.

Loosening and Extrusion of the Nail

It is debatable whether any precautions should be taken to prevent the possibility of the nail being gradually extruded. If some of the bone in the neck of the femur is being absorbed, this extrusion may be beneficial; for it will prevent the nail from being protruded through the head of the femur into the joint cavity. On the whole, therefore, I prefer not to use any additional form of fixation of the nail.

Non-union

Though some cases of non-union must be expected, the technique described here helps to reduce this number to a minimum. First, the method of reduction and the position used encourage slight over-reduction of the fracture, thus impacting the upper margins of the fracture and rendering the fracture line more horizontal. Secondly, the method is so straightforward and simple that it is not necessary to transfix the head with several guide wires passing in different directions, a manœuvre which can do no good to the precarious blood-supply that remains to the upper fragment.

SUMMARY

A simple technique is described for the insertion of the Smith-Petersen nail for fractures of the neck of the femur, the essential feature being the use of the patient's own bed as the operating-table; in fact, the patient remains in his own bed throughout.

The method not only enables the operation to be performed anywhere without special apparatus, but also considerably reduces its length and also the disturbance and shock to the patient.

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"It is quite customary to ask the psychologist to predict success of a group of people without specifying the exact nature of the situation in which success or failure will be decided. Thus the subjects who passed successfully through the O.S.S. assessment programme might be detailed to do one of a large number of very dissimilar jobs, ranging all the way from putting on propaganda shows in oriental countries to being dropped as secret agents into enemy-occupied territory. This situation would find an analogue in the physicist's being asked which of a large number of metal bars were likely to fracture, but without his being given any information as to the precise stress which would be applied to each of these bars. . . . Until those who pose the questions gain some insight into the methods of science, and learn to provide suitable conditions for an experimental determination of the answer, psychology will continue to operate at a low level of scientific respectability."—H. J. EYSENCK, PH.D., *The Scientific Study of Personality*, London, 1952, p. 292.

ORAL PENICILLIN IN THE PROPHYLAXIS OF STREPTOCOCCAL INFECTION IN RHEUMATIC CHILDREN

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MANY observers have reported that penicillin given by mouth in various doses, and at various intervals between doses, reduces the carrier-rate of hæmolytic streptococci and the incidence of acute throat infections in rheumatic children (Burke 1947, Maliner 1950, Maliner and Amsterdam 1947, Maliner et al. 1949, Goerner et al. 1947, Massell et al. 1948, Kohn et al. 1950, Pitt Evans 1950). Some of them have reported that the incidence of relapses of rheumatism was also reduced by penicillin; but this is a much more difficult matter to investigate, because relapses are not common, and it is difficult to secure comparable groups large enough to give convincing differences in incidence between those who have had penicillin and those who have not.

Brick et al. (1950) carried out a trial in Canada which was very similar to that described here. They treated 38 children attending a cardiac clinic as outpatients and observed a comparable but untreated group of 38 for two years. The treated children were each given penicillin 50,000 units by mouth half an hour before breakfast and the same dose three or four hours after supper. The children were examined once a month, and throat swabs were taken. In the penicillin group 570 swabs were examined, of which 3 were positive, and in the other group 576 were examined, of which 52 were positive. There were 3 recurrences in the penicillin group and 6 in the other.

METHOD OF PRESENT INVESTIGATION

There is in Bristol a comprehensive scheme for the care of children with rheumatism and heart-disease. The disease is notifiable, there is a supervisory clinic, and there are beds for long-stay cases at Winford Orthopædic Hospital and its annexe at Chew Stoke. It was at first intended to conduct the trial in two parts, one at Winford and the other in the outpatient department, but the number of children admitted to Winford became so small that it was impossible to divide them into large enough penicillin-treated and lactose-treated groups; so the inquiry was confined to children attending the supervisory clinic and some who were discharged from Winford while the experiment was going on. Ultimately 73 children were included in the trial. They were paired as far as possible in respect of sex, age, and date of last attack, and one of each pair was allotted to the penicillin and one to the lactose group by tossing a coin. This was done before the parents were asked if they were willing to help in the experiment.

When the parents were invited to take part they were not told to which group their child had been allocated, but unfortunately more of those allocated to the penicillin group accepted. Another difficulty in securing perfectly matched groups was that some of the children discharged from Winford lived too far from Bristol to attend the outpatient department regularly; and it so happened that there were more of these in the lactose than in the penicillin group.

For these reasons there were 41 children in the penicillin group and only 32 in the lactose group. In the penicillin group there were 27 girls and 14 boys, and in the lactose group 22 girls and 10 boys. The age-distribution (both sexes together) was as follows:

Year of birth	*Penicillin*	*Lactose*
1935–37	21 (*51%*)	16 (*50%*)
1938–40	12 (*29%*)	11 (*34%*)
1941–43	7 (*17%*)	4 (*13%*)
1944–45	1 (*2%*)	1 (*3%*)
Total	41	32

The most important factor in pairing was not appreciated at the beginning of the trial. This was the factor of an initial positive swab. Fortunately the distribution of positive swabs at the first visit was much the same in the two groups: 12 out of 41 (29%) in the penicillin group, and 10 out of 32 (31%) in the lactose group.

At the first visit to the outpatient department throat swabs were taken and the children in the penicillin group were given a fortnight's supply of tablets, each containing 200,000 units, and a bottle of 10% glucose solution (dose 2 teaspoonfuls). The children in the lactose group were given their tablets in a bottle exactly like that used for penicillin tablets and were also given the glucose. The children were usually asked to come up once a fortnight, but where there was some clinical indication they were asked to come in a week and an extra swab was taken. The throats of the children who started at Winford were swabbed once a week while they were in hospital and once a fortnight after discharge. Physical condition and erythrocyte-sedimentation rate (E.S.R.) were examined only where there was some clinical indication.

Throat swabs, which were taken by one of us, were taken to the laboratory and cultured with the minimum of delay—never more than three hours (usually less). They were plated on 5% horse blood-digest nutrient agar containing crystal-violet 1/700,000. The plates were incubated overnight in an anaerobic jar. β-hæmolytic colonies were subcultured on blood-agar and the resulting pure cultures grouped by the method of Maxted (1948). All cultures found to be of Lancefield group A were then sent for typing to the Streptococcal Reference Laboratory at Colindale. They were first tested by the slide agglutination method and subsequently by the precipitin method. Throughout the trial the penicillin sensitivity of the group-A streptococci isolated was determined by comparison with the Oxford staphylococcus on penicillin ditch plates (5 units per ml.). All were at least as sensitive as the control organism.

The children came into the trial at slightly different times, but most of them attended from the middle or end of October, 1950, to the middle or end of May, 1951. There were defaulters both in respect of individual visits and because some of the children started work and could no longer attend regularly. These failures to attend seriously impaired the tidiness of the trial, and the possibility of excluding some of the irregular attenders from the final comparison was considered. It was felt, however, that it would be better to set out the results in such a way that irregularities of attendance were obvious, and this has been done in the accompanying figure. As the children were attending as outpatients, it was necessary to rely on them and their mothers to ensure that they actually took the tablets given.

The average number of swabs taken per child was slightly larger in the penicillin group (14·6) than in the lactose group (12·6) because there were more Winford children in the penicillin group. Swabs were taken once a week while they were in hospital, but only once a fortnight when they became outpatients.

RESULTS

The results of the trial are summarised in the accompanying table. Those in section A are the children in whom treatment had either no effect or possibly some preventive effect; those in section B are those in whom treatment appeared to produce a definite improvement; and those in section C are the "failures."

In the penicillin group 18 (44%) out of 41 children, and in the lactose group 22 (69%) out of 32, had a

RESULTS OF INVESTIGATION

Section	Results of swabs		No. of children in group	
	First	Later	Penicillin	Lactose
A	0	All 0	23 (*56%*)	10 (*31%*)
B	+	All 0	8 (*20%*)	1 (*3%*)
C	0	Some +	6 (*24%*)	12 (*66%*)
	+	Some +	4	9
Total			41	32

positive swab at the first visit or at least one positive swab later. The accompanying figure shows the sequence of events in these 40 children. In a few cases *hæmolytic streptococci* of group C were isolated, and this has been indicated by a C in the figure. It is generally held that these organisms are of no significance in acute rheumatism; so the Cs have been counted as Os in the totals in the columns on the right of the figure.

The effect of the penicillin in reducing the number of positives in the group as a whole is obvious, but some of the individual records are also of interest.

Penicillin Group

Six children (nos. 8, 9, 11, 14, 15, and 16) had a negative swab at the first visit and subsequently had at least one positive. Nos. 9, 14, 15, and 16 had only one positive without symptoms, whereas nos. 8 and 11 had three each, and both had a sore throat.

No. 8 started treatment on Oct. 23. She seemed perfectly well and had negative swabs on Oct. 23 and Nov. 6. On Nov. 12 she went to bed for two days with a sore throat. On Nov. 20 she seemed quite recovered and she had a negative swab on that day, on Nov. 27, and on Dec. 4. On Dec. 18 she had a small sore at the angle of the mouth and a strongly positive throat swab. On Jan. 3, 17, and 29 her swabs were negative, but on Feb. 12 and 26 they were positive. After that her swabs were consistently negative. Unfortunately the culture from the swab taken on Dec. 18 died out and could not be typed, but the hæmolytic streptococci cultured from the swabs on Feb. 12 and 26 were of the same types.

No. 11 started treatment on Oct. 25. She was seen on Oct. 25 and Nov. 8 and 29, when she seemed perfectly well and had negative swabs. On Dec. 9 she went to bed with a sore throat and was seen at home on Dec. 14. Her throat was then a little injected, but she seemed to have nearly recovered, and a swab was negative. She was seen again, as an outpatient, on Dec. 19, when she seemed well, her E.S.R. was 3 mm. in 1 hour, and a swab was negative. On Jan. 9 and 24 she seemed perfectly well but had positive swabs. On Feb. 7 she had a negative swab, on Feb. 21 another positive, and after that her swabs were consistently negative. The hæmolytic streptococci cultured from swabs taken on Jan. 9 and 24 and on Feb. 21 were all of the same type.

Nos. 2, 3, 5, and 6 had a positive swab at the first visit and at least one positive at a later visit. Nos. 2 and 3 had only one positive at a visit other than the first, and neither of them had a sore throat. In both cases the type of streptococcus was the same in the first and later swabs. Nos. 5 and 6 were so irregular in attendance that it seems doubtful whether they should be included in the penicillin group at all. Between them they supplied eight of the twenty positive swabs recorded for the whole group at visits other than the first.

Lactose Group

Most of the positive swabs came from chronic carriers, and it seems reasonable to suppose that some of those in the penicillin group who had positive swabs at the first visit would have been chronic carriers if they had not been treated. There was nothing in the appearance of the throats of the chronic carriers to distinguish them from the other children.

Nos. 23, 27, 32, 33, and 37 gave a series of positive swabs after a series of negative ones.

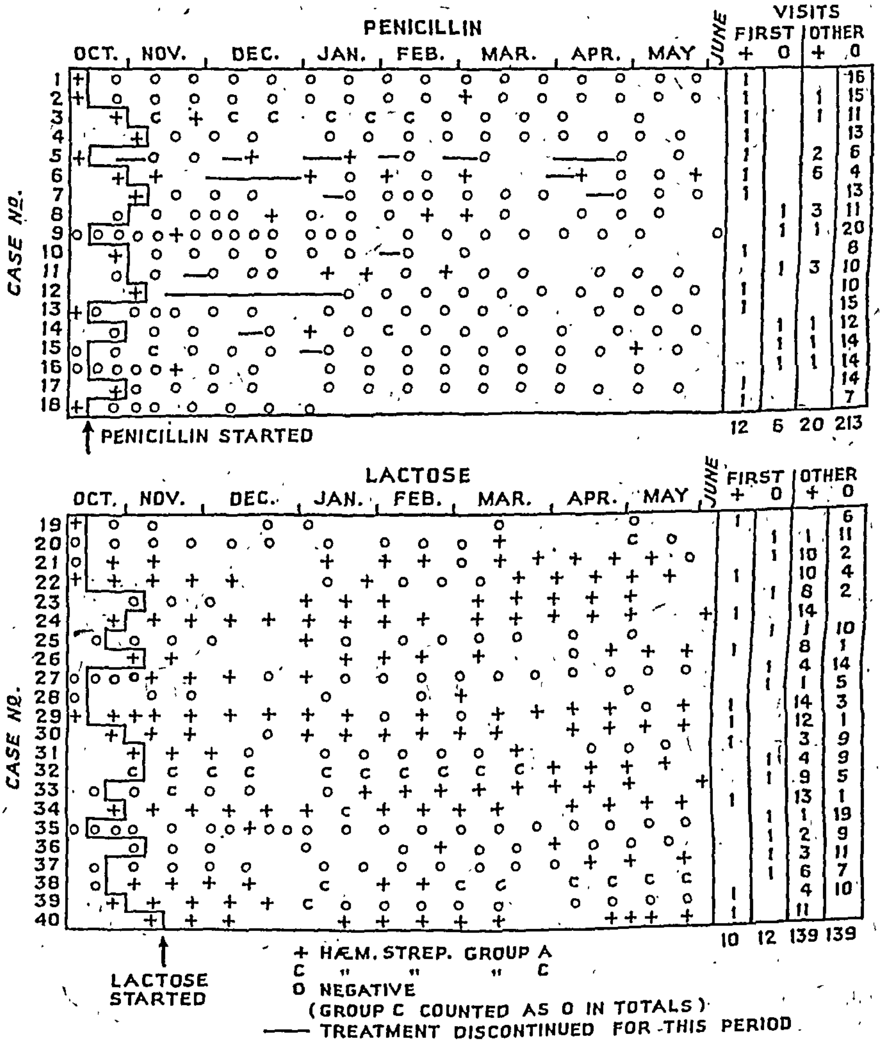
No. 23 had negative swabs on Nov. 1, 15, and 29. About Dec. 13 she had a sore throat and was in bed for three days. On Jan. 3 she seemed well but had a positive swab and later swabs were consistently positive.

No. 27 had negative swabs on Oct. 13, 20, and 27, and Nov. 3. He was discharged from Winford on Nov. 5 and when seen as an outpatient on Nov. 8 he gave a positive swab. Swabs on Nov. 22, Dec. 6, and Jan. 3 were all positive, but one on Dec. 20 was negative. All his swabs after Jan. 3 were negative.

No. 32 had consistently negative swabs till April 17, when they became consistently positive.

No. 33 had consistently negative swabs up to Jan. 22, when they became consistently positive. After the trial she complained of sore throat and painful glands in the neck (June 19), and on July 19 she was admitted to hospital with a slight recurrence of chorea.

No. 37 had consistently negative swabs up to and including April 2. On April 13 she had malaise but no sore throat and



Results in children who had positive swabs at the first or a subsequent visit.

was in bed for a few days at home. On April 18 she seemed well but had a positive swab on that day and on May 2. About May 9 she developed pain and swelling in the left knee, and was admitted to hospital on May 17 with a slight relapse. She had further positive swabs on May 21 and June 7.

It would clearly have been desirable to attempt a comparison between the incidence of sore throats in the penicillin and lactose groups, but in an investigation of outpatients it is impossible to define a sore throat with sufficient precision to give useful comparisons.

None of the children reported any ill effects from the penicillin, and none of the streptococci of group A isolated were resistant to penicillin.

DISCUSSION

This investigation confirms previous work in showing that a daily dose of penicillin by mouth will very considerably reduce the number of throat swabs positive for group-A hæmolytic streptococci in rheumatic children. It leaves unanswered two questions which are more important from the practical point of view: (1) does oral penicillin prevent relapses? and (2) does it prevent acute infections? It is difficult to see how the first question could be answered in a reasonable time with numbers of children of the order available in this investigation. The second question is difficult to answer by an experiment on outpatients. It seems certain, however, that oral penicillin is not a sure preventive of mild throat infections, because at least 2 of the penicillin group (nos. 8 and 11) had them.

SUMMARY

A group of 73 rheumatic children was observed at fortnightly intervals in an outpatient department from October, 1950, to May, 1951. 41 children were given a daily dose of 200,000 units of penicillin with 10% glucose before breakfast, and 32 were given lactose and glucose.

The number of throat swabs positive for group-A hæmolytic streptococci obtained from the penicillin group was very much less than the number obtained from the lactose group.

No conclusive evidence was obtained about the effect of the penicillin in preventing either rheumatic relapses or acute streptococcal throat infections. Only 2 children, both in the lactose group, had rheumatic relapses.

NOTE ON RESULTS OF TYPING

In the lactose group there were 17 children who had more than one positive swab. In 9 of those children the organism was of the same type in every positive swab, in 2 there was a definite change of type, and in the remaining 6 there was some doubt because some swabs produced several types.

In the penicillin group there were 6 children who had more than one positive swab. In 5 of them the organism was of the same type in every positive swab, and in 1 (no. 5) there was a definite change of type. The child who had a definite change of type was irregular in attendance.

We are indebted to Mr. L. J. Waller for much technical assistance; to Dr. R. E. O. Williams and his co-workers at Colindale for the typing; and to Prof. R. H. Parry, medical officer of health for Bristol. The trial was made possible by a grant from the Royal College of Physicians (Miss H. A. M. Thompson bequest).

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ECTOPIC PREGNANCY INSIDE THE UTERINE WALL IN A FIBROMATOUS UTERUS

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THE following case is worth recording because of its rarity.

CASE-RECORD

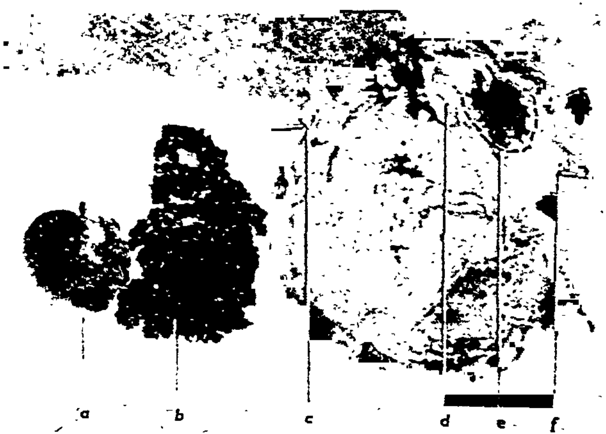
On Oct. 15, 1951, a European woman, aged 41, was admitted to hospital with what appeared to be a ruptured ectopic pregnancy. That day, while having lunch, she had suddenly felt an extremely sharp pain in the umbilical region and left shoulder, and had felt as if "a sharp knife had been pushed into her vagina"; she fell down on the floor, but did not lose consciousness. She had vomited at home twice, and four times on the 75-mile ambulance journey to hospital. Micturition and defæcation were normal. She had menstruated in August, when her period began on Aug. 3, lasted only three days, and was very scanty. In September and October she had menstruated at normal intervals, but only one day on each occasion, and very little.

Past History

She began to menstruate at 12, the menstrual cycle being 8/28 days, and bleeding heavy. At the age of 16 she underwent appendicectomy. At 28 she married, and she conceived soon afterwards. At the time of the first suppressed period she had extremely severe lower abdominal pain and laparotomy was done under spinal anæsthesia. When the abdomen was opened, she heard the surgeon say "she is pregnant," and the abdomen was closed. She subsequently miscarried a $5^1/_2$ month fœtus. After this, her periods became heavier, and each time she lost much blood. Fibromatosis of the uterus was diagnosed, and in 1939 a myomectomy was done, several fibroids being removed. In spite of this operation abdominal pain and distension persisted, and though she became pregnant in 1940 she aborted at 3 months. In 1941, however, she was delivered of a healthy girl. During her pregnancy she had severe hæmaturia every 28 days, lasting 8 days, which coincided with her suppressed menstrual period. Her urine had the same odour and consistence as the menstrual flow, and she "felt very weak."

Immediately after the birth of the baby the periodical hæmaturia disappeared. After $3^1/_4$ years, in 1944, she again became pregnant, and again had periodical hæmaturia. At cystoscopy the bladder appeared to be normal. The hæmaturia was attributed to an anterior low attachment of the placenta and adhesions between the uterus and the bladder. A girl was born at term, and the hæmaturia disappeared immediately after.

The next pregnancy, in 1945, terminated in abortion at 3 months. During this pregnancy, the patient again had periodic hæmaturia, which ceased after abortion.



Posterior view of uterus: *a*, fœtus; *b*, chorionic villi; *c*, pin in left fallopian tube; *d*, fibroma; *e*, opening into gestation cavity; *f*, pin in right fallopian tube.

On Examination

The patient was pale, with temperature 97·8°F, and pulse-rate 84. Her abdomen was slightly distended, very rigid, and extremely tender, especially in the right groin and in the area of McBurney's point. A large oval smooth soft mass could be felt in the right iliac fossa. Vaginal examination revealed no bleeding. The uterus was enlarged to the size of a grape-fruit, soft, and tender, and there was tenderness in both lateral fornices.

Treatment and Progress

As the patient's condition was still satisfactory after her long trip in an ambulance on a rough rubble road, it seemed probable that, if she had a ruptured ectopic pregnancy, the bleeding had stopped. Anti-shock treatment was applied, and the patient observed throughout the night. Next morning her general condition was satisfactory, and she had slept well, but was nauseated and had vomited small amounts several times. Her temperature was 98·4°F, her pulse-rate 90, and a blood-count showed red cells 2,200,000 per c.mm., Hb 32%, white cells 9500 per c.mm. At 11 A.M. her pulse-rate was 100. A ruptured ectopic pregnancy, probably in the right tube, was diagnosed.

Operation

Laparotomy was performed under general anæsthesia at 2.30 P.M. A blood-transfusion of $1^1/_2$ pints was given. On opening the abdomen through a midline incision, clotted and fluid blood was found, especially in the right half of the pelvic cavity. Old dense adhesions covered both appendages and the uterus, and multiple adhesions connected the omentum intestines, and uterus. These were cut and tied off to free the reproductive organs. The uterus, which was as big as two fists, occupied the middle part of the pelvic cavity. No ectopic pregnancy was found in the appendages, but on the posterior wall of the uterus, near the base of the fundus, among dense adhesions, which had at first limited the bleeding from the tear, an opening, 0·5–1·0 c.m. across, was found into which chorionic villi and a shining ovum were protruding. When this aperture was palpated it suddenly became larger, and first the ovum, and then the placenta, prolapsed. As soon as this happened, profuse hæmorrhage took place, which was controlled. In view of the extremely long history of the case, and the present rupture of the uterus, a supracervical hysterectomy was done. The postoperative course was uneventful.

Pathology

The uterus contained several small subperitoneal and intramural fibromata. Old dense adhesions covered its posterior and anterior surfaces, especially at the fundus. Just off centre in the right side of the posterior surface of the fundus, among adhesions, there was a tear in the wall of the uterus about 2·5 cm. in diameter. The left flap of the torn wall was everted medially, and a fibroid as big as a pea was embedded in it. The torn opening in the wall of the uterus led to a cavity 4·5 cm. deep and 2·5 cm. wide containing a fœtus and chorionic villi; it was not lined with decidua. Only a few decidual cells were attached in a corner to the chorionic villi (verified microscopically), and this cavity was separated from the uterine cavity by an intact muscular wall 4 mm. thick. No connection of any kind could be found between these two cavities. The intra-uterine parts of both tubes were separated from the gestation cavity by an intact muscular wall 1·5 cm. thick on the right side and 3·5 cm. thick on the left. The tubes were apparently healthy. The uterine cavity was lined with decidua vera.

DISCUSSION

In discussing the mechanism of this ectopic gestation several possibilities must be considered.

(1) The ovum may have been fertilised and implanted in a mucous crypt inside the uterine wall, or in a diverticulum from the uterine cavity. This is improbable, since the gestation cavity was not lined with decidua, and only a few decidual cells were found in a corner attached to the chorionic villi. In addition, the wall which separated the gestation cavity from the uterine cavity was 4 mm. thick, and there was no connection between them.

(2) The possibility of implantation of the ovum in the intra-uterine portion of the right or left tube, with further expansion into the uterine wall, and subsequent rupture, must be discarded because the interstitial portion of the left tube was separated by intact uterine muscle 3·5 cm. thick, and the right tube by intact uterine wall 1·5 cm. thick.

(3) The third possibility is that the ovum, on its external migration after fertilisation, became implanted on the posterior surface of the uterus, possibly where the epithelium had been damaged by fibromatosis or by dense adhesions. In the further course of its development the ovum burrowed into the uterine wall and, after nearly three months growth, ruptured into the abdominal cavity.

This last mechanism appears the most probable.

I wish to thank Dr. J. M. Cruickshank, Director of Medical Services, Fiji, for permission to publish, and Dr. P. E. C. Manson-Bahr, acting pathologist, for the histological examination.

AN OUTBREAK DUE TO SALMONELLA BRANCASTER

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Salmonella brancaster was first described by Macdonald et al. (1948); it had been discovered in mussels. Subsequently a second strain was isolated from the liver of a dead turkey poult. Although this organism has been found in the stools of a healthy person (Ministry of Health 1951) it has not hitherto been described as a cause of disease in man. An outbreak caused by *S. brancaster* in a children's ward is therefore considered worthy of record.

The organism was isolated, almost simultaneously, from two widely separated sources in the hospital. The first was an infant (case 1 in the accompanying table), an "unidentified salmonella" being grown from a stool passed on Jan. 17, 1951. The second source was an old lady who died on Jan. 19 from "senile myocardial degeneration"; a culture taken from her spleen because it was unaccountably enlarged and soft grew a salmonella. Both cultures were sent to the Salmonella Reference Laboratory and identified as *S. brancaster*.

The ward where the outbreak occurred was used mainly for bottle-fed babies; most of them were aged less than 12 months, but babies were accepted up to the age of 18 months. The ward consisted of a long corridor along one wall, with cubicles and the kitchen opening to it from the other side; on the wall side opened the sluices, bathroom, and sterilising-room. There were 12 cubicles, arranged 6 on each side of the kitchen, which was fitted out as a milk-kitchen also. One of the 12 cubicles was used as the sister's office; the others each held two cots, but often one of a pair could not be used because an infectious patient was in the other. This gave a theoretical capacity of 22, but in practice at least 3 or 4 cubicles were used for infectious diseases, giving a practical maximum of 18 or 19 infants. January was not very busy, but February and March made very heavy demands on our accommodation, and there were often 18 babies in the ward.

The outbreak occurred in two clearly defined periods. The first report of *S. brancaster* in an infant's stool was returned on Jan. 19; positives were often found from then till Feb. 6. This we call "the first positive period." Thereafter the organism could not be found at all in the ward for a fortnight—"the negative period." It was isolated again on Feb. 18, and thereafter was constantly found till the ward was evacuated on April 17—"the second positive period."

On Jan. 19 there were 9 children in the ward, 4 of whom ultimately became infected; the other 5 remained clear. All of these latter left soon after, within the first positive period. Of the infected children, 2 left fairly soon; but the other 2 remained in hospital right through the negative period into the second positive period. Thus they may have carried the infection and later restarted it; but each had had at least 3 negative stool-tests. A further 21 children were admitted during this first positive period, but none of them caught the infection. Only 2 of these stayed on through the negative period, and may conceivably have become symptomless carriers. During the negative period 25 infants were admitted; 2 of these later contracted the infection. During the second positive period 25 children came into hospital, and 4 of them became infected. Admissions were reduced during March; only 5 patients were admitted after March 5, and the ward was closed to further patients on March 18.

The table gives the clinical details of the 10 infected babies.

In the first period 4 babies were involved, 2 of whom had mild diarrhœa without constitutional symptoms; the other 2, in no way disturbed, were found on a search through the ward. The last positive stool of this group was passed on Feb. 5. In the second period 6 babies were infected. All of them showed gastro-intestinal upset, and 2 required parenteral fluids. We had the impression that the infection picked out the seriously ill infants in the ward.

From 5 of the 6 babies concerned in the second period of the outbreak sera were obtained and investigated for the presence of agglutinins to *S. brancaster*. These results also are shown in the table. No significance can be attached to the results from cases 6, 9, and 10. Case 7 showed a fall in titre of 'H' agglutinins between 7 and 22 days after the onset of diarrhœa. Case 8 showed significantly high titres to both 'O' and 'H' agglutinins 7 days after onset, these titres dropping to less than 1:25 after a further 14 days. This drop confirms the diagnosis of infection with *S. brancaster*.

Only 3 nurses were found to be infected:

Nurse A, whose stools were negative on March 24, was found to be passing the organism on April 14. She had no symptoms, and the next three stools were all negative.

Nurse B, who made no complaint and had no symptoms, was found to be passing *Shigella sonnei* in her stools on March 28 and 31; on the latter date *S. brancaster* also was recovered. This organism was subsequently grown on April 14, but the next three stools were negative.

Nurse C was the only one who complained of diarrhœa, and her stools grew *S. brancaster* on one occasion only, April 5.

BACTERIOLOGY

The routine method used at the Whipps Cross Hospital Area Laboratory to isolate salmonellæ from outbreaks of food-poisoning is to make primary cultures of stools or rectal swabs on desoxycholate-citrate agar in a petri dish and on selenite-F broth. Next morning the selenite-F broth-culture is subcultured on to desoxycholate-citrate agar, and the original culture on this medium is examined. Probable pathogens are tested by slide agglutination and subcultured into the fluid carbohydrate media to test their metabolic activity.

S. brancaster grew well on primary culture on desoxycholate-citrate agar, and it was seldom necessary to subculture from the selenite-F broth. The appearance of the 18-hour colony on desoxycholate-citrate agar was characteristic. It was larger (1·5–2·5 mm. in diameter) than, for example, a typical *S. typhimurium* colony, and it showed a faint greenish opacity in the centre. All the colonies were smooth. The biochemical reactions were typical of members of the salmonella group. The organism was slightly sensitive to streptomycin, and fully sensitive to chloramphenicol and aureomycin. By slide agglutination, the organism was agglutinated by standard *S. paratyphi-A* 'O' and *B* 'O' sera, and less actively by *S. typhi* 'O.' None of the 'H' sera in stock agglutinated it. Detailed serological analysis showed that the somatic structure of this organism may be expressed by the symbols I.IV.XII. The somatic structure of *S. paratyphi-A* 'O' is I.II.XII. and of *S. typhi* 'O' is

CLINICAL DETAILS OF BABIES INFECTED WITH *S. brancaster*

Case no.	Born	Cause of admission			Gastro-enteritis			Serology			Discharge		Subsequent examinations	
		Date	Nature	Severity	First symptom	First positive	Severity	Date	Agglutination titre* 'O'	Agglutination titre* 'H'	Date	Stools	Date	Result
1	July 8, 1950	Dec. 22, 1950	Infantile eczema	Severe	Jan. 16	Jan. 20	Mild				March 14	Clear Feb. 16		
2	Dec. 12, 1949	Dec. 13, 1950	Corneal ulcer	Severe	None	Jan. 29	Nil				Feb. 8	Positive	March 7 July 3	Positive Negative
3	Oct. 15, 1949	Jan. 6, 1951	Influenzal meningitis	Severe	Jan. 25	Jan. 29	Mild				Jan. 29	Positive	July 16	Negative
4	May 30, 1950	Dec. 28, 1950	Miliary tuberculosis	Moderate	None	Jan. 29	Nil				March 1	Clear Feb. 16		
5	June 15, 1950	Feb. 9, 1951	Acute bronchitis	Severe	Feb. 15	Feb. 20	Severe				March 16	Positive	May 28	Clear
6	Aug. 2, 1950	Feb. 17, 1951	Pneumonia, empyema	Severe	March 7	March 1	Severe	March 21 April 5	— 25	25 —	April 4	Positive	June 9	Positive
7	Oct. 28, 1950	Feb. 21, 1951	Pertussis	Severe	March 14	March 13	Severe	March 21 April 5	— —	50 —	April 17	Positive	June 1	Clear
8	Nov. 4, 1950	Feb. 13, 1951	Broncho-pneumonia	Severe	(First admission; no gastro-enteritis)						Feb. 28			
		March 8, 1951	Respiratory infection	Moderate	March 15	March 19	Moderate	March 21 April 5	125 —	500 —	April 17	Positive	July 3	Positive
9	Feb. 22 1951	Feb. 24, 1951	For B.C.G. immunisation		March 15	March 27	Mild	March 21 April 5	— —	— —	May 28	Positive	July 3	Positive
10	Feb. 10, 1951	Feb. 28, 1951	For B.C.G. immunisation		March 2	March 31	Mild	April 5 April 24 Aug. 17	— — —	— — 40	May 23	Positive	Aug. 17	Positive

* Titre expressed as reciprocal. —, no agglutination at a titre of 25. "Clear" means that three consecutive stools were negative.

IX.XII. The agglutination observed in sera made from these two organisms is due to the agglutination of antigens common to all three organisms. The somatic structure of *S. paratyphi-B* 'O' is (I).IV.(V).XII., the factors in parentheses being absent from some strains. The somatic structure of *S. brancaster* is identical with that of some strains of *S. paratyphi-B*. The flagellar phase of *S. brancaster* isolated in this outbreak was identified as z_{20}; hence the complete antigenic structure was I.IV.XII : z_{20}.

INVESTIGATION OF SPREAD OF INFECTION

Our efforts to trace the spread of infection followed two main lines: (1) investigation of possible human carriers, and (2) investigation of possible contamination in the ward—e.g., dust, bedsteads, furniture, walls, milk-bottles, and teats.

(1) Doctors, nurses, and ward orderlies, particularly those who had had any contact with the ward in which the old lady had been, were investigated. Fæces or rectal swabs were examined, and serum was sent to the Reference Laboratory for examination for the presence of specific antibodies, but these investigations proved negative except for the 3 nurses mentioned above. Attempts were made to detect agglutinins in the sera from nurses and ward orderlies. Of the 3 infected nurses, only one serum showed the 'O' agglutination to a titre of 1 : 25. Sera from a further 41 nurses were examined; only one agglutinated the 'H' phase of *S. brancaster* at 1 : 25. Sera from 14 ward orderlies were examined, none of which agglutinated *S. brancaster* 'O' or 'H.'

(2) Swabs were taken of brooms and various parts of cots, furniture, and walls within reach of infants occupying the cots, but all these gave negative results. The milk-bottles and teats were boiled before use and found always to be sterile.

Finally, the general antiseptic technique was reconsidered, and 1 : 80 'Lysol' solution was substituted for the weak 'Dettol' solution used in cleaning cots and furniture. After this change no further cases were discovered. It was interesting to compare dettol with phenol by the Rideal-Walker technique, using *S. brancaster* as the test organism instead of *S. typhi*. The phenol coefficient of dettol in distilled water was then found to be 1. When plasma was used as diluent, the coefficient was reduced to 0·075, and when broth was used, to 0·03.

SUMMARY

An outbreak of *Salmonella brancaster* infection in an infants' ward is described.

The infection occurred in two periods with a free interval between them and affected 10 infants.

The clinical picture varied from no gastro-intestinal symptoms to severe enteritis. All the patients recovered, but some babies continued to excrete the organism for several months.

Three nurses also were infected, only one of whom had mild diarrhœa.

About the time that the outbreak started *S. brancaster* was also found post mortem in the spleen of an elderly patient who had died (in a ward remote from the babies) from senile myocardial degeneration. In spite of a careful search no connection could be traced.

It is a pleasure to acknowledge the great help we have received from our colleagues, both medical and auxiliary, in the work of investigating and controlling the outbreak. In particular we wish to thank Sister M. Kent and Mr. Kenneth Podger, laboratory technician, both of Whipps Cross; and Mr. Douglas Miller, technical assistant, of the Salmonella Reference Laboratory.

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LOSS AND RECOVERY OF SIGHT IN MEASLES ENCEPHALITIS

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MEASLES encephalomyelitis occurs, if the figures of the large epidemics of measles are a guide, once in about every 1000–1500 cases during an epidemic (Boehnheim 1925, Peterman and Fox 1933, Hoyne 1939, Geiger and Sappington 1940, Litvak 1947). It seems to be more likely to occur at the peak of an epidemic (Peterman and Fox 1933, Roisman and Rosen 1943) and, conversely, to be less common among sporadic cases; 8 cases in the London epidemic of 1936 were mentioned in the *British Medical Journal* (1936).

The drowsiness, vomiting, convulsions, and meningitic signs which accompany measles encephalitis are unlikely to be overlooked, particularly since they often come on suddenly on the fourth or fifth day after the appearance of the measles rash and after initial improvement in the patient's condition; some cases show predominant cord signs—e.g., paraplegia and ascending paralysis. In either type of the illness the course may be brief or long, but if death takes place it is usually early and may be on the first day in fulminating cases. Zimmerman and Yannet (1930) have computed that 10% of all measles encephalomyelitics die, and that 65% show a final residual mental impairment.

Litvak et al. (1943) suggest that there is no relationship between the severity of the measles and the incidence of encephalitis, or between the severity of the encephalitis and the liability to residual nervous lesions. They suggest that the longer the cases are followed the more noticeable are mental and personality disorders and the less become the neurological findings (cf. Neal and Appelbaum 1927).

The chief pathological lesions are focal perivascular demyelination and diffuse congestion of the brain (Greenfield 1929). One particular focus of demyelination is in the optic nerves with resultant blindness. This rare symptom is generally transient, as appears not only from the case described here but also from those cited by Ford (1928), Hamilton and Hanna (1941), Litvak et al. (1943), and Meurer (1948).

The present case was seen during a measles epidemic in which the weekly notification for the previous month in England and Wales lay between 17,300 and just over 20,000 cases. This occurrence just after the peak of an outbreak has been generally observed in measles encephalitis and suggests the likelihood that the measles virus is causal and not merely an associated neurotropic virus.

CASE-RECORD

A boy, aged 7½ years, developed a typical measles rash on March 16, 1949, after two days' prodromal symptoms. After a further two days the rash began to fade and the child felt better and sat up in bed, but on March 19 he was listless and drowsy, and again without appetite. No further symptoms appeared, but he became more drowsy, and on March 21 he was incontinent of urine.

On examination by me on March 23 he was very drowsy but rousable into coöperation and not appreciably disoriented. His optic discs were clear but showed slight overfilling of the veins. He had severe neck stiffness, a positive Kernig's sign, and severe general spasticity in all four limbs, more especially in the arms, which also showed slight intention tremor. The tendon-jerks were all very brisk; the abdominal reflexes were absent, and the plantar reflexes flexor. The boy was afebrile, but a fading measles rash was still present.

Lumbar puncture showed clear cerebrospinal fluid (C.S.F.) under a pressure of 50 mm. and containing protein 100 mg. per 100 ml. but no increase in cells.

Progress.—Next day (March 24) the boy was much worse; he was flushed and slightly cyanotic, with temperature

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99·8°F, respirations 36 a minute and shallow. He was unrousable, with eyes closed and expressionless face. His limbs showed severe though varying spasticity, particularly in the arms, which also showed attacks of convulsive shaking lasting one or two minutes. During the next two weeks the patient lay speechless and inert, but in the second week he was more irritable and grumbled at times. From March 30 there were spasms of the facial muscles and at times fine nystagmoid jerkings of the eyes. Meningitic signs persisted, and there was constant spasticity with increased response in the limbs and jaw reflexes, particularly in the right arm. The right plantar reflex was now extensor. Muscle power could not be tested, but when requested the patient could partly protrude his tongue. A grasp reflex was present till April 14. A small area of consolidation appeared at the base of the right lung on April 3 and cleared with sulphonamide therapy. The patient took fluids and light solids satisfactorily by mouth.

Lumbar puncture on April 7 produced clear C.S.F. under a pressure of 100 mm. and containing protein 50 mg. per 100 ml. and no increase in cells. A Pandy test was faintly positive.

Further Progress.—From April 11 though still drowsy and incontinent, the patient gradually became mentally receptive and smiled faintly if amused. He ceased to whine on April 16 and was fully rational, though speech remained distant and monotonous. There was possibly a slight intention tremor of his arms, which he often moved aimlessly through the air. On April 19 he could only dimly discern the white coat of the doctor by his bed, and the outer halves of his optic discs were white; his pupils reacted imperfectly to light. His legs, though wasted, showed fair power, and the other nervous signs were little changed, with persisting constipation and urinary incontinence.

Examination of Eyes.—Mr. J. Gibson Moore reported on April 22: “ Early optic atrophy R. and L., L. more advanced. Pupils sluggish, but react to light. Ocular-movements full.”

Recovery.—The patient’s conversation became quite sensible by May 4, and despite poor vision, especially in the left eye, he was bright and cheerful. His optic discs remained very pale and tendon-jerks much increased, but both plantar reflexes were now flexor. Muscular power seemed good and sphincter control normal, and he was allowed out of bed. By May 12 he could walk, though with an unsteady and jerky gait, and he was discharged on May 14. Although at this time his sight was very poor, he could, by peering closely at objects, see all colours but red.

Follow-up.—After discharge he made steady general progress, and on June 2, 1949, he walked well, apart from a little clumsiness in the right leg. There was still a slight increase in all deep reflexes, and the abdominal reflexes were absent. Visual improvement was slower, but on June 24 Mr. Gibson Moore reported 6/60 vision in both eyes, though both discs remained pale. By Aug. 4 the patient could fish, swim, see better, and recognise red objects. By April 19, 1950, he could read the smallest print at two feet, but his mother thought that he occasionally mistook objects at a distance. On Jan. 1, 1951, when the patient had been back at school two terms, Mr. Gibson Moore found 6/12 vision in each eye and bilateral optic atrophy. As at the previous and subsequent examinations, the tendon-jerks were very brisk and the abdominal reflexes absent, but the plantar reflexes were flexor. At the final examination on Dec. 21, 1951, shortly after his 10th birthday, he was very well and alert. Mr. Gibson Moore now found 6/6 vision in both eyes, and though both discs were slightly pale their appearances were within normal limits.

DISCUSSION

This example of a rare complication of measles has been described in detail because it emphasises the potential recoverability of all the lesions of measles encephalitis, a toxic degeneration rather than an inflammation. Though cerebral recovery is less general than optic-nerve recovery, the ophthalmic lesion may cause the greater immediate distress, and it is essential to sustain hope in the patient and his relations during the period of blindness. This condition, however, is not often encountered. Ford (1928), reviewing the reports published in the previous sixty years, found only 111 cases of measles encephalitis, and among these only 6 cases of papillœdema; and Litvak et al. (1943) found 4 cases of papillœdema and 3 cases of disc pallor in 56 cases of measles encephalitis. In Ford’s series only 1 patient became finally “ blind and an idiot.” All the others
in Litvak’s series recovered their s
That recovery of sight is always slo
by Meurer’s (1948) cases. One of his pa
in September, 1942, and had almost recover
two years later; another took ten months to
from bilateral 3/60 to bilateral 6/9 vision. The
nerve lesions are like the other neurological findings
their tendency to disappear if the case is observed for a long time. Fortunately in the present case the converse finding of the slow emergence of mental symptoms has not been noted.

I am grateful to Mr. J. Gibson Moore for his reports on the progress of the eye condition in this case.

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“MILK POISONING” AND “CALCIUM GOUT”

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In the following case sudden and painful swelling of the joints resembling gout occurred repeatedly in a patient who had been drinking large quantities of milk.

CASE-RECORD

First Admission

A man, aged 56, was admitted to the psychiatric wards of a Brisbane hospital on July 10, 1950, complaining of loss of energy, insomnia, irritability, depression, weight loss of 2 st., and loss of libido. These symptoms had been present since January. He had had a duodenal ulcer since 1944 and had been on an ulcer diet, ‘Amphojel,’ and alkaline powders on and off ever since.

On admission he was dejected and tearful and had a pronounced digital tremor. His pulse-rate was 136 per minute and his blood-pressure 140/100 mm. Hg. There were two hard lumps on his left forearm, each about 5 cm. long by 3 cm. across, one over the base of the first metacarpal and the other over the head of the radius. Radiography on Aug. 12 showed deposits of opaque material on the radial side of the left wrist (fig. 1).

On further inquiry the patient said that since January, 1950, he had been drinking about a gallon of milk a day. He had continued taking amphojel and alkaline powders alternately, each for about a month at a time. He had not noticed the lumps until July when an extremely painful, tender

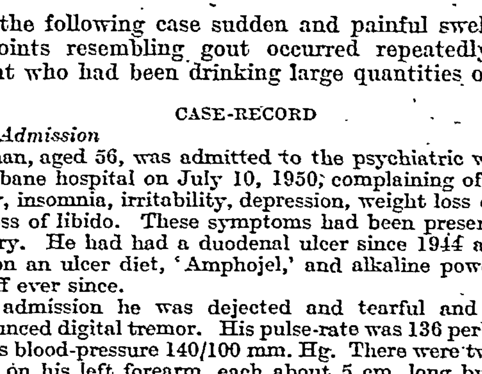

Fig. 1—Radiograph (Nov. 6, 1950) showing calcium deposits on the radial side of the left wrist.

TABLE I—BIOCHEMICAL FINDINGS (FIRST ADMISSION)

—	Serum-calcium (mg. per 100 ml.)	Serum-phosphorus (mg. per 100 ml.)	Alk. phosphatase (King Armstrong units)	Urea (mg. per 100 ml.)	Serum uric acid (mg. per 100 ml.)	CO₂ combining-power (vols. %)	E.S.R. (Westergren) (mm. in 1 hour)
Aug. 22, 1950	..	..	..	138	..	..	..
„ 24 „	12·0	3·9	12	..	..	..	..
Sept. 13 „	12·5	..	6	102	..	..	..
„ 22 „	..	..	..	..	..	86%	..
„ 25 „	..	4·2	..	..	..	..	..
Oct. 5 „	12·3	4·3	8	160	..	..	..
„ 23 „	11·9	..	..	130	..	..	..
„ 31 „	12·0	..	..	135	..	..	..
Nov. 9 „	..	..	..	..	3·9	..	..
„ 21 „	12·4	..	..	125	..	..	..
Jan. 22, 1951	..	..	..	..	..	..	117
„ 24 „	12·6	3·4	10	120	..	..	..
Feb. 6 „	..	..	..	..	..	..	120
„ 14 „	12·3	3·6	9	113	..	..	..
„ 22 „	13·5	3·2	..	72	..	..	..
April 2 „	11·4	..	8	160	..	..	..
May 8 „	..	..	..	151	..	..	..
June 20 „	11·3	3·7	..	137	..	..	105
„ 21 „	..	..	..	..	..	80%	..

swelling developed in the wrist and dorsum of his left hand. The swelling disappeared in about a week, but the lumps at the lower end of the radius remained. The same process was presently repeated at the elbow.

A further physical finding, evident when I first saw the patient on Sept. 8, was the presence of white chalk-like plaques in the sclera of each eye, but the fundi were normal.

Further radiography revealed gross calcification in several other areas, including the iliac arteries and the radial arteries. No calcification could be demonstrated in the renal areas, however, and the renal outlines appeared normal.

The urine was alkaline, with a specific gravity of 1·010, and consistently showed a cloud of albumin. Microscopy on several occasions showed a few leucocytes, a few epithelial cells, and an occasional hyaline cast, but no casts of other types and no red cells. Culture was repeatedly sterile. A urea-clearance test on Aug. 22 showed a maximum concentration of 1·72 g. per 100 ml. and a standard clearance of 16% of average normal.

Numerous blood studies (table I) showed a high level of serum-calcium and CO_2 combining-power (even after alkalis were withheld from the diet), a high serum-urea, and a normal serum uric acid, serum-phosphorus, and serum alkaline phosphatase. The erythrocyte-sedimentation rate was rapid.

Treatment consisted in removing all calcium-containing foods from the diet and withholding all alkalis except aluminium hydroxide. Belladonna and barbiturates were given to help control his ulcer symptoms. On this régime, his general condition improved and his mental state returned to normal. The lumps at wrist and elbow diminished in size and soon were no longer palpable (fig. 2).

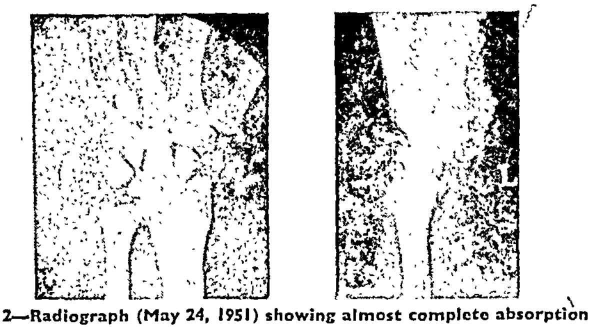

Fig. 2—Radiograph (May 24, 1951) showing almost complete absorption of the calcium deposits seen in fig. 1.

A barium meal on May 17, 1951, showed an ulcer in the first part of the duodenum and some delay in the stomach emptying-time, about half of the barium remaining in the stomach after 8 hours. After 24 hours the stomach was empty.

He was discharged from hospital in June, 1951, with instructions to follow his milk-free, alkaline-free diet. At this time his blood-pressure was 110/70 and a blood examination showed: red cells 3,200,000 per c.mm., hæmoglobin 9·4 g. per 100 ml., white cells 14,000 per c.mm. (neutrophils 83%, lymphocytes 13%, monocytes 2%, eosinophils 2%).

Second Admission

At 2.45 A.M. on July 30, 1951, he reported at the same hospital stating that $3^1/_2$ hours earlier, while in bed, he had developed severe pain in the right groin. He was obviously in intense pain with his hip held in flexion. There was an excruciatingly tender swelling over the hip-joint and the anterolateral aspect of the thigh.

Radiography on the day of admission showed enormous deposits of calcium near each hip-joint. Calcium deposits were also seen in the penis (fig. 3). He said that he had not been adhering to his diet. He had been unable to refrain from drinking milk and, in fact, he had virtually become a milk addict. (On one occasion he even seized the baby's bottle from his infant grand-daughter and drained it at a gulp.) The reason for his curious behaviour apparently was that only milk gave him real relief from his ulcer pain.

Blood biochemical findings during his second admission are shown in table II. His urine contained no albumin or other abnormal constituents at this time.

He was again given a calcium-free diet with olive oil after meals and supplementary amphojel and phenobarbitone. The pain in his hip subsided *fairly rapidly*, and the swelling of his thigh diminished over a period of several weeks. The radiographic report on Sept. 20 said: "The calcium deposit around the right hip-joint appears less and there is probably also some decrease in the mass about the left hip. The penile accumulation is unchanged, and also that in the large arteries."

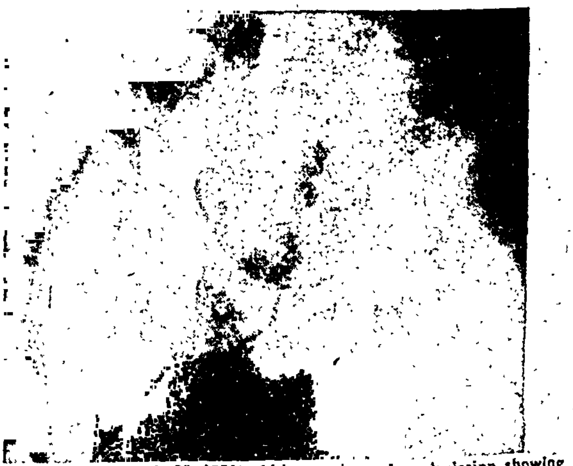

Fig. 3—Radiograph (July 30, 1951) of hips at time of readmission, showing extensive deposits of calcium about both upper femurs. Also calcium deposits in the penis.

DISCUSSION

To turn first to the metastatic calcification. The lesions in the eyes are not unique; they are recognised sequelæ of hypercalcæmia (Walsh and Howard 1947). The manner in which the deposits at the wrist, elbow, and hip (calcinosis) first showed themselves is striking in its resemblance to acute gout. The excruciatingly painful, exquisitely tender swellings, *coming on within*

TABLE II—BIOCHEMICAL FINDINGS (SECOND ADMISSION)

—	Serum-calcium (mg. per 100 ml.)	Serum-phosphorus (mg. per 100 ml.)	Urea (mg. per 100 ml.)	CO₂ combining-power (vols. %)
July 30, 1951	..	..	151	..
Aug. 1 „	12·0	..	..	65
„ 14 „	..	..	..	..
„ 17 „	..	..	135	..
„ 31 „	14·8	3·1	..	..
Sept. 21 „	13·4	3·5	138	..

a few hours, then subsiding only to recur in the vicinity of another joint, invites a comparison with gout strengthened by the similarity of the residual deposits to gouty tophi.

In fact, the sequence of events recalls those I believe to take place in gout (McQueen 1951): the capacity for holding calcium in soluble form having been exceeded, calcium began to be deposited in insoluble form. In this case, as in uric-acid gout, the deposits gave rise to signs of inflammation.

In the differential diagnosis the first condition springing to mind is hyperparathyroidism secondary to chronic renal disease. Several important points are against this diagnosis, however. Firstly the serum-phosphorus was always normal or only slightly raised. Phosphorus retention is thought to be the first step leading to secondary parathyroid hyperplasia (Albright and Reifenstein 1948): the adult cases of Gilmour (1947) and the one case of Richards (1951) all had high serum-phosphorus levels. Secondly, the serum-calcium was raised, not lowered. It is true that the patient's excessively high intake of milk might have counteracted the usual tendency in cases of hyperparathyroidism toward a low serum-calcium, thereby preventing resorption of calcium from the skeleton with consequent osteitis fibrosa. It might also explain the normal serum alkaline phosphatase, but one would have expected this to become raised during the long period in hospital when the calcium intake was negligible. Further, the high CO_2 combining-power, even after cessation of alkalis, is against a diagnosis of secondary hyperparathyroid disease.

Primary hyperparathyroidism cannot be excluded without tests of calcium excretion. However, the absence of skeletal changes, and the normal serum alkaline phosphatase after restriction of calcium intake, make this diagnosis unlikely.

Burnett et al. (1949) have described a syndrome characterised by:

> ". . . a history of prolonged and excessive intake of milk and absorbable alkali; hypercalcæmia without hypercalcuria or hypophosphatæmia; normal serum alkaline phosphatase level; marked renal insufficiency with azotæmia; mild alkalosis; calcinosis manifested especially by an ocular lesion resembling band keratitis; and an improvement in the clinical state on an intake low in milk and absorbable alkali."

The development of this syndrome may not be possible in the absence of renal disease. The only case in Burnett's series which came to necropsy had pyelonephritis (and nephrocalcinosis), although in one of his cases renal biopsy was normal two years before the development of renal insufficiency. My own patient had undergone repeated routine examinations before the onset of his present illness (he had been in hospital for treatment of his ulcer in 1944, 1947, and 1948), and no record had ever been made of a urinary abnormality.

Long-continued and excessive consumption of alkalis may be prerequisite for the development of this syndrome and may possibly be responsible for initiating the renal damage. Burnett et al. (1950) have shown damaged renal function 17 months after acute episodes of alkalosis. Actually there had been no acute episode of alkalosis in the present case; the patient had been taking alkalis for years and there had been no bout of vomiting or other disturbance likely to precipitate alkalosis.

The onset of his present symptoms dated from the time he started drinking an enormous amount of milk. But when milk and other calcium-containing foods were removed from his diet the symptoms and most of the calcium deposits disappeared. I think therefore that this may truly be called a case of "milk poisoning."

I would like to thank the Chairman of the Repatriation Commission for permission to publish this article.

References at foot of next column

Preliminary Communication

RELATION BETWEEN IN-VITRO AND IN-VIVO RESISTANCE TO ISONIAZID

It is now established that tubercle bacilli can develop resistance to isoniazid and related compounds both in laboratory media and in patients undergoing treatment with the drugs.[1] The relation between in-vitro and in-vivo resistance, however, is not clear and there are conflicting reports as to the rapidity with which they may develop. The experiments here described show (1) that resistance can be rapidly developed in vitro by subculture at appropriate intervals, and (2) that organisms made resistant in vitro are resistant to the action of the drug in vivo.

In-vitro Production of a Resistant Strain

A culture of *Mycobacterium tuberculosis* H37RV (obtained from Dr. R. J. W. Rees of the National Institute of Medical Research) was incubated in a series of tubes of Dubos's liquid medium containing falling concentrations of isoniazid. (The concentrations referred to here are the *initial* concentrations. This is an important point, since we have found that the drug is inactivated at 37°C even in uninoculated medium. Experiments demonstrating this effect will shortly be reported.)

During the first 2 weeks of incubation, growth was inhibited at a level of 0·01 µg. per ml., but after 25 days of incubation the tube which had contained initially 1·6 µg. per ml. showed profuse growth. One drop was transferred from this tube to a fresh set containing falling concentrations of the drug. In this series growth was inhibited at first at a level of 1·6 µg. per ml., increasing during further incubation to 8 µg. Subculture was made after 19 days of incubation from the tube which had received 1·6 µg. per ml. into a similar series of tubes, and in this set growth rapidly occurred in as much as 25 µg. per ml. On subculture from this tube after only 10 days of incubation into a fresh set, good growth occurred after only 7 days' incubation in 62·5 µg. per ml. The organisms, therefore, were now about 6000 times more resistant than in the original culture.

A subculture was made from this tube into drug-free Dubos's medium and used for the animal experiments here described. The sensitivity of the actual culture used was found to lie between 8 and 40 µg. per ml.

In-vivo Results

For the screening of antituberculous drugs in vivo the experimental induction of intracorneal tuberculosis in mice has provided the basis of a satisfactory technique.[2] Conditions are standardised so that the mice, under deep ether anæsthesia, are each inoculated intracorneally in one eye with about 1000 viable organisms of *M. tuberculosis.* Thereafter, in the absence of treatment, a characteristic tuberculous lesion appears after an interval of about 11–14 days. Over the ensuing 2 weeks it proceeds to involve the greater part of the cornea, remains stationary for some time and subsequently undergoes some spontaneous regression.

When such mice are treated with an effective antituberculous agent, however, the course of the disease may be modified in various ways. There may be suppression altogether; there may be inhibition while treatment is maintained but recrudescence later with undiminished vigour; there may be some

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[1] See leading article, *Lancet*, 1952, i, 1293.
[2] Rees, R. J. W., Robson, J. M. *Brit. J. Pharmacol.* 1950, 5, 77.

DR. MCQUEEN: REFERENCES

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alteration in the advance of the disease, both in extent and time.

Using this method, the efficacy of isoniazid in the control of experimental tuberculosis has been satisfactorily demonstrated.

In one group of male albino mice, infected intracorneally with a virulent human strain of *M. tuberculosis* (H37RV), the disease followed its expected course and the great majority of animals were eventually involved. Treatment with isoniazid completely prevented the development of any ocular lesions during the period of administration of the drug, a result very similar to that already reported with thiosemicarbazones.[3]

When the same experiment was repeated with the in-vitro resistant strain (described above) the result was entirely different. In all such experiments with isoniazid the mice received 0·3 mg. per mouse per day in the food (equivalent to about 12 mg. per kg. body-weight). The treated animals developed lesions of exactly the same kind as the untreated control mice; in both groups (each containing 10 mice) there was the usual latent period of some 14 days and then the lesions developed rapidly.

There is now a clear indication that resistance to isoniazid does develop in patients treated with the drug, and such results are in fact being obtained in clinical investigations at present in progress at Guy's Hospital. The evidence for this conclusion is, of course, based on measurement of resistance performed in vitro on organisms recovered from such treated patients. The results here described show that such in-vitro data are in fact relevant to conditions in the living body and that such resistant organisms can produce pathological changes in the course of treatment with isoniazid.

We are greatly indebted to Mr. D. E. Seymour of Herts Pharmaceuticals Ltd. for the supply of isoniazid used in these experiments.

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Reviews of Books

Film in Education

ANDREW BUCHANAN, D.LITT., PH.D., F.R.S.A. London: Phœnix House. 1951. Pp. 256. 25*s.*

FILMS are already playing a large part in modern education and cover a number of subjects ranging from science to the fine arts and religious instruction. The possibilities of extension are limited mainly by the cost of production. In medicine, films can never take the place of practical contact with patients, but thanks to their ability to compress time they can usefully illustrate the progress of disease over long periods. They can also be used to demonstrate procedures such as surgical operations, and prolonged physiological studies such as the determination of the cardiac output; and diagrammatic films can clarify such things as complicated biochemical reactions or integrate multiple ætiological factors into a unified scheme of causation.

Dr. Buchanan's book covers almost every aspect of educational film work from production to the details of projection, and it is thoroughly informative. Although he writes as an enthusiast holding clear-cut opinions, he is careful to demand for films no more than their just place as an instrument of a general educational purpose, and does not offer them as a substitute for other methods of teaching. The place of teachers in the use and in the making of film is also set out in this useful and readable book.

Manual of Leprosy. *Supplement to the 1st. edition.*

ERNEST MUIR, C.M.G., C.I.E., M.D., F.R.C.S.E., medical adviser, British Empire Leprosy Relief Association. Edinburgh: E. & S. Livingstone. 1952. Pp. 16. 2*s.* 6*d.*

THIS supplement to the "manual" published in 1948 is particularly welcome, for it brings a rapidly developing subject up to date. Where leprosy is concerned there is a tendency to err on the optimistic side; and emphasis on the cheapness of treatment and the efficacy of present-day drugs may lull the profession into complacency. The discovery of an effective remedy for leprosy does not mean we are yet within reach of its final control. The scheme of dosage of the sulphone preparations recommended by Dr. Muir is in accordance with the regimen now accepted, and he insists that physicians must start with low doses and gradually increase them. Those who follow his detailed instructions should not go astray. For routine use he advises oral diamino-diphenyl-sulphone, but emphasises that this should only be the method of choice for those "who are sufficiently educated and responsible to be trusted to take tablets regularly." He might have given more attention to the toxic signs, particularly with D.D.S., for these are often a cause of concern. Desensitisation is mentioned when a toxic dermatitis supervenes, but not the dosages of aqueous 'Sulphetrone.' Those recommended by Lowe and Davey (*Trans. R. Soc. trop. Med. Hyg.* 1951, 44, 634) are very small—20–200 mg. twice weekly over 4–5 weeks. More space might have been given to reaction in leprosy, and it would have been useful to differentiate between the erythema-nodosum phenomenon, which is passing and generally speaking favourable, and the more serious progressive lepra reaction, which may be much more formidable, and carry a more serious prognosis. It may also be confusing for the general physician, for whom the manual was written, to introduce such drugs as streptomycin, of which the expense and inconvenience have proved to be out of proportion to the results. Thiosemicarbazone is rightly mentioned, but no indication is given of its dosage. The impression left on the reader's mind is that the only sulphone worthy of attention is the parent sulphone, diamino-diphenyl-sulphone; but there are preparations which are almost as cheap and which some workers regard as less toxic yet equally effective.

Ruptures of the Rotator Cuff

H. F. MOSELEY, M.CH. Oxfd, F.R.C.S., F.A.C.S., assistant professor of surgery, McGill University. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 90. 47*s.* 6*d.*

Dr. Moseley's little book is in the American Lectures in Surgery series and as such presents didactically, with a minimum of discussion, his views on the diagnosis and treatment of the rotator tendon injuries at the shoulder. Starting from Codman's emphasis on the supraspinatus, he proceeds to include lesions of the subscapularis tendon; normal and pathological anatomy and operative repair are illustrated by diagrams of great clarity and beauty, though the few photographs of actual specimens are less satisfactory. He relies considerably on the procaine test, advising operation when this restores active abduction but the power of abduction against resistance remains greatly diminished. In this country opinion would usually be against operation unless abduction remained impossible after procaine infiltration. His emphasis on the necessity for operation if a good functional result is to be obtained is not in entire accord with the good results which may be obtained with conservative treatment, or with the finding—by De Palma and others—that perfect function during life may be compatible with massive cuff injuries found at routine necropsy. Good simple methods of measuring shoulder-joint and shoulder-girdle range and power are shown. It is interesting to note that although the Canadian winter prevents the routine use of abduction splints after operation, patients seem to do just as well if the arm is kept—as Codman originally advised—in a sling by the side.

THE LANCET

LONDON: SATURDAY, JULY 12, 1952

Sore Throat and Rheumatic Fever

Acute rheumatic fever is a complication of a group-A β-hæmolytic streptococcal infection of the throat of a susceptible person. This is a proposition which is now well established, and its corollaries seem equally sound—namely, that infection by no other organism gives rise to acute rheumatic fever, and that all patients with acute rheumatic fever have had antecedent streptococcal throat infections. Medical science has a way of finding exceptions to such dogmatic statements, but the general truth of these is widely accepted. It follows that if one can prevent streptococcal throat infections one can prevent rheumatic fever, and this too has been abundantly confirmed. What we do not know is why, of 100 patients with apparently identical infections of this type, 98 recover completely and 2 get rheumatic fever.

To Coburn[1] in the United States, and to Schlesinger[2] and Sheldon[3] in this country, goes the credit for bringing again to general notice the clinical relation of upper respiratory infection to rheumatic fever, the evidence for which was reviewed many years earlier, in 1899, by Pribram.[4] Serological analysis of streptococci by the method of Lancefield[5] has shown that only upper respiratory infections caused by the group-A β-hæmolytic streptococcus are involved, and other evidence for this relationship has been provided by epidemiological studies following the pioneer work of Glover[6] in this field.[7, 8] Yet further evidence is given by a study of the antibodies found in the blood; recently Swift[9] could show that, of a group of patients with rheumatic fever, all showed antibodies to one or other of the antigens of the group-A β-hæmolytic streptococcus in titres suggesting recent infection. But while it has been possible to prove that there is a relation between throat infection and rheumatic fever, we are still uncertain about its nature. The opinion most widely held is that rheumatic fever is a disordered antibody-antigen reaction following the repeated absorption into the body of some product of the streptococcus, analogous to the serum-sickness following injection of foreign serum. The immunology of the group-A β-hæmolytic streptococcus has been extensively studied, but none of the many antigens produced by this organism has yet been incriminated.

However, the man who knows nothing about the chemistry of combustion is none the less able to avoid putting his fingers in the fire, and attempts at preventing rheumatic complications by avoiding or preventing the initiating streptococcal infection have met with striking success. In the past it has been supposed that removal of the tonsils would decrease the incidence of rheumatic fever, but this is not borne out by experience.[10] The recent war, by ensuring that young men were herded together in barracks, camps, and ships, afforded many opportunities for the epidemic spread of streptococcal infections, which left rheumatism in their wake. Pioneer work by Thomas and France,[11] and by Coburn and Moore,[12] in 1939 led to the use of sulphonamides in small doses to prevent this spread of infection, and the incidence of both streptococcal infection and rheumatic fever was reduced. Once a throat infection is established, however, sulphonamide treatment is of no use in preventing rheumatism; and, while it has proved safe enough to use sulphonamide to protect a particular person from streptococcal infection at home or in hospital, long-continued use of this agent in the mass prophylaxis of all members of a closed community has so altered the bacterial environment that, when sulphonamide-resistant strains of group-A β-hæmolytic streptococci emerged, their pathogenicity and spread was actually enhanced—a counter-attack by the organism only controllable because penicillin was now in reserve.[13]

Much of the early work with sulphonamides was repeated with penicillin when this antibiotic grew plentiful; and it became apparent not only that penicillin was equally effective in preventing streptococcal infections[14, 15] but also that early vigorous treatment of exudative tonsillitis could abort these infections quickly enough to reduce the likelihood of subsequent rheumatism. The largest studies on this subject have been those of Rammelkamp and his associates[16] at a large American Air Force training base. In their investigation 1178 randomly selected patients with exudative tonsillitis received penicillin and 1162 patients with the same diagnosis served as controls. In the thirty-four days following the onset of the sore throat 23 of the control patients developed rheumatic fever (an incidence of approximately 2%), but only 1 of the treated group showed this complication—and here there was evidence of an intercurrent untreated reinfection. Rammelkamp[17] emphasises that penicillin treatment should be early and that the case of sore throat caused by the group-A β-hæmolytic streptococcus is usually characteristic enough to make bacteriological confirmation unnecessary before starting treatment. Typically there is a relatively rapid onset with soreness in the throat on swallowing, painful and swollen cervical lymph-nodes, malaise, and fever. Young patients often vomit during this period. On examining the throat one sees general swelling of the lymphoid tissues of the pharynx and a bright-red inflammation of faucial mucosa. On the tonsils, discrete or confluent patches of yellow exudate

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stand out clearly against the red background. The concept of a clinically recognisable group-A β-hæmolytic streptococcal sore throat is supported by the experience of Rantz et al.,[18] but recent careful studies in this country [19, 20] show that there may be considerable overlap between the symptoms and signs of sore throats which yield a positive throat culture for this organism and sore throats which yield commensals. Nevertheless, all observers agree that most of the more severe sore throats are caused by this group of streptococci, and it therefore seems reasonable policy to treat all moderate or severe sore throats with penicillin by intramuscular injection (Rammelkamp [17] recommends at least two injections of 600,000 units of procaine penicillin G in oil with 2% aluminium monostearate at a three-day interval). Mild sore throat, on the other hand, need not be treated unless there is known to be an epidemic of group-A β-hæmolytic streptococcal infection or unless there is evidence of a personal or family predisposition to rheumatic fever. Widespread application of this policy should lower the incidence of rheumatic fever and of rheumatic heart-disease. Indeed the more effective treatment of sore throat may be partly responsible for the decline in the incidence of these conditions in recent years, although this decline began before the era of antibiotics.

What of the patient who has already had one attack of rheumatic fever? Here the situation is somewhat different, for it is estimated that about half of these susceptible people who have further attacks of streptococcal infection suffer recrudescence of rheumatism.[21] Moreover, the infection which provokes the recrudescence may be mild and little more than the symptomless carrier state. Because of this special risk, Rammelkamp thinks it unjustifiable to await symptoms of infection before attacking the organism; treatment should be continuously given to *prevent* infection. It is in this group of patients that a small daily dose of an antibiotic can substantially decrease the recurrence-rate of rheumatic fever; though in some 10% of patients the infection "breaks through" the protecting antibiotic. From the standpoint of protection from rheumatic recurrence there seems to be little to choose between a small daily dose of a sulphonamide (such as 1·0 gramme of sulphadiazine) and a daily oral tablet containing perhaps 100,000 units of penicillin. The sulphonamide is the cheaper to give, but in a small proportion of cases it will give rise to signs of toxicity, which, though they would be promptly recognised and dealt with if the patients were still in hospital, may lead to serious complications in patients at home. Oral penicillin is safer and less liable to breed resistant organisms, but it is more expensive and its absorption from the alimentary tract is somewhat variable, though this can be improved by giving the tablets between meals and accompanying the dose with an antacid.[22] In the régime used by Pitt Evans [23] the rheumatic child received 100,000 units in 5% glucose solution three-quarters of an hour before breakfast.

Children recovering from rheumatic fever should, Rammelkamp suggests, be given chemoprophylaxis with one or other of these antibiotics for at least two years, and some would say even longer. Studies such as that by Bland and Ducket Jones [24] have shown that the rheumatic child runs his greatest risk of developing a recurrence (about 20%) in the first five years after an attack. Since, with the passage of time, the liability to recurrences dwindles, and after the age of puberty [25] falls sharply, a case could be made for continuing chemoprophylaxis until, say, the age of sixteen; but, as Batten [26] recently pointed out, the loss as well as the profit of prophylaxis on such a scale must be accounted for, and to subject children to daily medication throughout their most formative years may well entail avoidable cardiac neuroses. In addition, the practical implications of a general policy of chemoprophylaxis have as yet to be faced. As Dr. Gale, Dr. Gillespie, and Professor Perry point out on another page, chemoprophylaxis of outpatients, as opposed to those children still in hospital or in convalescent homes, may fall short of complete success because of the difficulty of ensuring that patients receive and take their tablets. Moreover, if prophylaxis is to become routine, more supervision will be needed of the large number of children who will require it. The current reported prevalence of rheumatic fever in this country is somewhere between 0·5 and 2 cases per 1000 of the child population, making a total of about 15,000 cases, each of whom would have to be seen regularly for two to three years. At each attendance the child would be examined for recurrence of rheumatic activity or for toxic effects of the antibiotic; and it might be thought necessary to test the urine as a check on whether the tablets were being taken. Outside those centres which already conduct frequent follow-up examinations on children who have had rheumatic fever [27] such work could not be done very readily and it would be expensive. Against this must be set the fact that rheumatic fever and its sequelæ are among the major causes of loss of years of life and of capacity to do productive work—a cost to the country which must, in comparison, be enormous.

It cannot be claimed that these methods, even if widely applied, will ever prevent all cases of rheumatic heart-disease; for about half of those who have rheumatic heart-disease have never had a manifest attack of rheumatic fever. Furthermore, daily chemoprophylaxis of group-A β-hæmolytic streptococcal sore throats is for practical reasons limited to prevention of recurrences in those who have *already* had one attack of rheumatic fever—a procedure which will decrease the mortality and morbidity of recurrences but may not decrease the cardiac damage initiated by the first attack, for the simple reason that prognosis is not closely linked with the number of attacks.[28] Despite these limitations, chemoprophylaxis is the most powerful weapon that we have in the fight against this important disease, and there is now enough evidence to justify its use much more widely than at present.

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Faulty Feet

IN recent years there has been growing awareness that foot health is important, not only to the individual but also to the economy of the nation. During the late war the great prevalence of serious foot defects among young entrants to the Services came as a shock to those who examined them, and caused lively concern to the authorities: paradoxically, while Napoleon could say that an army marched on its stomach, the highly mechanised army of today depends increasingly on the state of the feet of its combatants. In industry, too, the increasing tempo of modern life brings more sharply into focus the economic wastage from the defective foot. Geriatricians, again, find that the state of the feet is one of the larger factors in determining whether old people can continue to lead useful and active lives. Foot ailments have effects out of all proportion to their intrinsic seriousness; and in an ageing population this is a factor of increasing importance. It has been rightly said that foot ailments are one of the major evils of modern society; yet little has been done on a national scale in the way of preventive care, compared with that bestowed, for example, on the teeth and the eyes. Before embarking on large measures, however, we need to know the nature and the extent of the problem. Although a number of surveys have dealt with specific aspects, none has hitherto been undertaken with the object of giving a general picture of the prevalence of the various types of foot ailment in the general population at all ages. To fill this gap, Dr. DYKES and his colleagues [1] made a survey in Luton, and their findings provide illuminating answers to a number of cogent questions. The survey was conducted by means of a questionary which was sent to a random sample of the population, and the replies were checked by personal examination of a sub-sample. The resulting figures lead DYKES et al. to the somewhat alarming conclusion that about 30% of the population have a foot defect of one kind or another. A visible defect does not, however, necessarily entail pain or disability; and it is unfortunate that in this survey defects causing symptoms are not more clearly distinguished from those unassociated with symptoms. For years orthopædic surgeons have held that in the adult the commonest cause of foot disability is not "flat-foot" but defects of the forefoot and toes, and that these conditions originate in childhood. This survey, like others before it, shows that whereas in the 0–14 year age-group the "flat-foot" and "valgus ankle" complex outnumbers forefoot defects by 7 : 1, from the age of 25 years onwards the ratio is reversed at 1 : 5. Moreover, after the age of 14 years the incidence of symptoms from forefoot defects increases rapidly. Since in children mechanical defects have to be quite severe before giving rise to symptoms, the defects themselves must arise at a much earlier age. Thus the most significant facts confirmed by this survey are the great prevalence of foot disabilities in the population, the major rôle of defects of the forefoot and toes, and the early age at which such defects originate.

Clearly the problem can be effectively tackled only by preventive measures in childhood. This implies, first, the organisation of suitable schemes for the inspection of children's feet at various ages, and, secondly, suitable provision for the care and supervision of those noticed to have defective feet. A useful lead is given in a pamphlet just published by the Foot Health Educational Bureau,[2] which puts forward definite proposals for preventive measures that could be undertaken within the present economy of local health authorities. We hope that medical officers of health will study these suggestions and try to adopt those suitable to their own particular circumstances; for it is only by local experiment and experience that a national policy can be evolved.

New Ideas for Cancer Research

AN appeal is often heard for more synthesis and less collection of facts in cancer research; but provided that the facts are new and not mere elaborations and repetitions, they should be welcomed, for all are needed to solve the many problems of this intricate disease. In the 29th annual report of the British Empire Cancer Campaign [3] many new data are added and two welcome attempts are made to blend older information.

Differences between species in susceptibility to induced cancer compel caution in deducing that what is true for one may apply to others; and hitherto these differences have not been explained. The difference in response of man, dog, and the smaller laboratory animals to ingestion of chemicals which in some cause bladder cancer is one that has greatly hampered experimental work aimed at the detection of the substance or substances responsible for industrial bladder cancer in man. The explanation of this particular species difference lies almost certainly in differences in metabolism. It has long been known that β-naphthylamine (now called 2-naphthylamine), an intermediate product in the dye industry, will induce bladder tumours in man by absorption through lungs, mouth, and skin. In dogs oral administration induces such tumours, but in other laboratory animals this chemical seldom has such an effect. The discovery, reported last year by G. M. BONSER and her colleagues,[4] that the compound which is actually effective in the bladder is more likely to be 2-amino-1-naphthol, a metabolite, than the parent amine has now been confirmed and extended. This view rests on the evidence that when in mice 2-amino-1-naphthol was introduced directly into the urinary bladder in pellets, some bladder carcinomas arose locally, even though mice are insusceptible to the parent amine by ingestion. Furthermore, conjugates of 2-amino-1-naphthol are excreted in the urine of the dog in amounts approximately equivalent to the dose of parent amine, whereas under equivalent conditions of dosage they fall from species to species in the order cat, ferret, rat, mouse, rabbit. Again, the conjugates excreted in the urine of the dog are highly concentrated compared with plasma; and traces are found in the urine of dye workers. Last week at a meeting in Glasgow of the Pathological Society of Great Britain and Ireland, the additional information was given that the parent amine itself was ineffective in pellets introduced into the mouse bladder. Here, then, we have a most useful new technique which does not require unusual skill,[5] a synthesis of knowledge which has been patiently garnered over many years, and the first reported explanation of variation in species susceptibility.

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While the story of bladder cancer is well on the way to full substantiation, the second attempted synthesis is still somewhat more speculative. Attention was first drawn by F. D. ASPLIN and E. BOYLAND[6] to the capacity of sulphadimidine to induce hypertrophy and hyperplasia of the testis, with precocious comb growth, in young cockerels. This odd result was independent of bacteriostatic properties or mediation via the anterior lobe of the pituitary. These workers found, in collaboration with W. C. J. Ross, that another pyrimidine derivative, xanthopterin, produced hypertrophy of the kidney of rat and mouse due to a great outburst of mitosis of tubular epithelium. The view was taken that the stimulus to mitosis was direct, and not due to destruction and regeneration with hyperplasia. This is very likely correct because xanthopterin is a natural product in the body. If so it takes its place among the few known direct stimuli of cell division. The hormones and their target organs are other examples. This new observation has led to intensive studies because of the intrinsic importance of xanthopterin in regulating normal cell division and the part that it may play in the continuous multiplication of tumour cells—presumably kidney tumour cells. It is at this point that speculative synthesis is being attempted. Two main hypotheses are being examined by Prof. A. HADDOW and a team at the Royal Cancer Hospital. The first supposes that while xanthopterin is a specific stimulus to division of cells of the renal tubules, other substances, including certain imines, have the same effect by inhibiting xanthine oxidase, and thus allowing the accumulation of xanthopterin as one of its substrates. The second view supposes that xanthopterin itself inhibits xanthine oxidase. If, now, there occurs in a cell a loss of this enzyme system governing xanthopterin production and output, xanthopterin might provide that continuous stimulus to division which is the basic property of tumour cells. Here the unproved assumptions include the loss of the enzyme system and continuous production by renal tumours of xanthopterin. This might readily be settled by the use of Lucke's adenocarcinoma of the leopard frog. It might be found that the virus causing this tumour effects deletion of the enzyme system. Continuous production of xanthopterin after infection of the renal cells might then be sought.

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[5] Jull, J. W. *Brit. J. Cancer*, 1951, 5, 328.
[6] British Empire Cancer Campaign: Annual report, 1947.

Annotations

FACT AND THEORY IN INFLUENZA RESEARCH

IN a most interesting series of talks on the Nature of Scientific Theory, broadcast recently in the Third Programme, Mr. S. E. Toulmin discussed the differences between logicians and scientists in their attitude to scientific theory. Logicians, according to Mr. Toulmin, expect the scientist to do each experiment five hundred to a thousand times; the greater the number of experiments, the more certain the scientist can be of his results and conclusions. This view has arisen, however, from a mistaken idea that scientists are all naturalists who simply observe and record their results. In fact, Mr. Toulmin pointed out, the outlook of the natural historian has little influence on present-day scientific theory, which is more in the nature of a map, showing a range of phenomena as an ordinary map shows a stretch of country. It is seldom necessary for a scientist to repeat an experiment more than three or four times before he can legitimately begin to construct his hypotheses. The speaker was being generous in his estimate; many scientists construct their theories after two, one, or no experiments.

If we may distort Mr. Toulmin's analogy a little, the place-dots on a map may be likened to experimental facts and the contour lines to theories relating these facts. The centre of the map is printed in bold type and describes the body of accepted knowledge, while at the periphery the dots and lines are fainter. We may liken a scientific paper to an attempt to fill in a few more dots and lines at the edge of the map. Some scientists take great pains with their dots, surrounding each with a small circle to indicate their experimental error, and sketch in only a few modest dotted lines, almost as an afterthought. Other scientists draw bold lines which join up a few modest, perhaps even nebulous, dots.

Examples of the different methodologies can be found in the June issue of the *Journal of Hygiene*, which contains two papers describing the results of research on the influenza viruses. Fulton's paper[1] is a careful account of a method for titrating influenza virus neutralising antibodies, using a new technique[2] for cultivating the virus in fragments of chick chorio-allantoic membrane. The precision of the test is matched by its elegance. An interesting outcome of this work is the slight serological relation noted between the WS strain of influenza A and strains of influenza B virus. This result may be another serological coincidence similar to the relation between antigens of proteus and the rickettsiæ, or it may be a faint hint of a common parentage. Hoyle's article[3] is an imaginative account of the structure of the influenza virus in relation to its method of multiplying. The theory follows the author's earlier lines of thought; the virus is conceived of as entering a susceptible cell and breaking up into smaller units of self-replicating soluble antigen which later recombine with specific antigen derived from the original inoculum. This hypothesis demands that the soluble antigen should contain nucleoprotein, since self-replicating units have nearly all been shown to contain nucleoprotein. Hoyle describes experiments which lead him to conclude that the soluble antigen is a ribonucleoprotein. In the absence of chemical estimations, however, the tests with enzyme preparations have to be interpreted cautiously; thus many-times crystallised preparations of ribonuclease have been shown to contain small amounts of protease which might upset the best-laid plans. Hoyle's ideas on influenza virus multiplication are arousing much interest; but they are a long way ahead of the known facts.

One well-known scientist used to suggest that all scientific journals should be printed in two colours—black for fact and pink for imagination—and he added that very little black ink would be needed. Nevertheless, in any scientific work, fact and theory are strongly interdependent, and the one without the other is like meat without drink. It is for the scientist to find the proportion of theory that will stimulate without intoxicating.

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[1] Fulton, F. *J. Hyg. Camb.* 1952, 50, 265.
[2] Fulton, F., Armitage, P. *Ibid*, 1951, 49, 247.
[3] Hoyle, L. *Ibid*, 1952, 50, 229.

AS A PATIENT SAW IT

WHEN patients speak their minds of the nursing they receive in hospital they generally complain of lack of sympathy. That this is a judgment made partly at an emotional level is suggested by the criticisms offered by Mrs. Freda Naish at last week's conference at the Royal College of Nursing. She went into a paying ward of a large London hospital for an operation—a paying ward, as she explained, because otherwise she would have had to wait a long time for a bed, and she feared that in the interval she would develop the unpleasant symptoms so mysteriously absent in her case. No advocate of home nursing, she prefers the ministrations of professionals; but she dreaded the thought of hospital, and especially the thought of a ward full of people. She came to reverse this opinion completely, finding that she welcomed the help of the other patients. When her voice became a whisper a neighbour called a nurse for her, and in the self-pity of the days after the operation it was a good thing to see that there were others who were worse.

Unlike many another patient she did not particularly want a nurse to herself; for, as she said "how distressing it would be to find yourself allotted to the one nurse you didn't fancy." She liked the large numbers of ever-changing nurses, and when they discussed the latest hospital dance over her dressing she was reassured to feel that hers was not an interesting case. She was also unusual in liking a good deal of traffic and activity in the ward, finding it comforting, especially at night; and she even enjoyed the early start of the day. "To me the twenty-four hours seemed much the same in hospital, and it was no special hardship to go to sleep, and wake up, relatively earlier than at home."

What did try her was the ill-informed medical gossip of the other patients, and the behaviour of the ward nuisance. This lady was not nearly ill enough; she was far too mobile. Mrs. Naish awoke from sleep soon after her operation to find the nuisance holding her hand and saying: "I know just how you feel, dear. I *started* with your operation fifteen years ago." In fact the patient needs the nurse's protection, not only from other patients of this kind, but also from enthusiastic visitors. Hospital visiting hours were generous—every afternoon and evening—and relatives were allowed to see visitors in non-visiting hours. We all know that our nearest are not necessarily our dearest, and as Mrs. Naish pointed out, relations have more power to upset us than anyone else. Even visitors who are less emotionally loaded can be very tiring. She felt she was allowed far too many: "the effort of entertaining them left me quite exhausted." If she had mentioned this to the sister she would have been spared the undue strain; but with considerable insight she notes that a change came over her character in hospital: she childishly accepted everything as it came without question, and even had a childish tantrum when she was told she was well enough to wash herself.

However, as she gradually recovered her adult outlook and status she began to resent the scanty information she was given about what was after all her own body. Though the operation had been gynæcological, she had been left with a brachial palsy in her right hand, which troubled her, since dexterity is necessary to her in her profession. It was not reassuring to be told: "Yours is not nearly so bad as Mrs. X's. *She* can't even hold a cup." It is hard, however, to see what other comfort a loyal sister could offer; she was not responsible for the palsy, and could hardly criticise those who were. Mrs. Naish would also have liked more advice about how to manage her life when she left hospital, and more warning of how she would feel and what things would tire her. Oddly enough, the hospital staff would probably have been at a loss here: the proper person to help her was her family doctor. Yet the doctor received no notification from the hospital of her return home until several days later, and she herself did not know whether to report her return to her doctor or not. Something better in the way of liaison is badly needed here.

Her most important criticism, from a medical point of view, had to do with sterile technique: a young nurse, unfamiliar with a treatment, used on her a piece of apparatus which was not sterile; and she wondered, as we have often done, whether bacteriology is being taught to nurses in a way that allows them to use their imagination and fit their knowledge to circumstances as they arise. She mentioned the experience of a friend in another hospital that aseptic technique was something the nurse didn't bother about if sister wasn't looking. Such an irresponsible attitude can only be the outcome of thinking in terms of rules rather than germs. Nevertheless, one piece of laxity had her whole-hearted support. Each day, as her drainage tube was shortened, the safety-pin which prevented it from slipping into the wound had to be inserted afresh through the rubber. Under the sister's eye the nurse achieved this almost impossible feat with forceps; which meant ten agonising minutes for the patient. In the sister's absence it was done in a moment with the fingers. Surely, she says, something easier could be found? The answer, of course, is a clip properly designed to be manipulated with forceps: our surgeons and manufacturers must surely have invented one. Why is it not in use?

CARDIAC ARREST

DEATH on the operating-table is by no means rare, even in this country where the general standard of anæsthesia is as high as anywhere in the world. It has long been realised that prompt restoration of the circulation by cardiac massage may offer a chance of recovery; but reluctance to publish details of these tragedies, and the difficulty of carrying out the prompt and courageous measures that are necessary, have militated against the accumulation of much precise knowledge about the best measures in these circumstances.

Within the last few years, however, great interest has been taken in the treatment of cardiac arrest, particularly in the United States, where the standards of anæsthesia are perhaps a little more patchy than in this country; and a certain amount of exact knowledge has been gained. Experimentally Kay[1] made a study in dogs in which either ventricular standstill was produced by deep anæsthesia with chloroform or ether, or ventricular fibrillation was evoked by passing a 30-volt 60-cycle alternating current directly through the heart. In both instances cardiac massage was the most important procedure for restoring normal activity, although with ventricular fibrillation preliminary electric defibrillation proved the most successful measure, the resulting ventricular standstill being remedied fairly easily by massage and drugs. Of these drugs isopropyl adrenaline and barium chloride were the two valuable ones. Procaine proved unsatisfactory in fibrillation.

Dale,[2] reporting 12 cases of cardiac arrest, underlines once again the need for speed in treatment (although Carter[3] has lately described a case in which cardiac massage was continued for 15 minutes before the first heart-beat was felt, and was continued for altogether 25 minutes, and yet the patient recovered completely). Certain important practical clinical points are brought out by Dale. He advises that cardiac massage be proceeded with immediately the patient is pulseless and no heart-beats are heard on auscultation. An incision through the chest wall is always preferable to one through the abdomen and the diaphragm. Massage through the diaphragm he regards as inefficient and a waste of time. Dale advises incision at the 4th left interspace; the ribs spread easily if the costal cartilages

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1. Kay, H. J. *Surg. Gynec. Obstet.* 1951, 93, 682.
2. Dale, W. A. *Ann. Surg.* 1952, 135, 376.
3. Carter, M. G. *J. Amer. med. Ass.* 1951, 147, 1347.

are cut above and below the interspace. No bone instruments are needed. Dale remarks that "a poorly done incision with immediate massage is better than a skilful approach if brain damage has occurred." Once the heart has responded, the operation is better deferred, or at any rate carried on only so far as is necessary to safeguard the patient's life. On the question of using adrenaline Dale points out that this, by itself, rarely restores cardiac action, and he suggests that it should be reserved until massage has been started. In the 300 reported cases found by him the mortality was 69%.

While the frequency of cardiac arrest through physiological neglect or mishandling during anæsthesia is likely to decrease with improving standards of anæsthesia, the extension of surgery, particularly of the thorax, will probably produce a continuing number of such cases. Courageous measures then lose nothing and may save a life.

NUTRITIONAL DEFICIENCIES IN NIGERIA

THE basic agriculture varies widely in different parts of Nigeria. In the north the staple food is usually guinea-corn (*Sorghum vulgare*), but in some districts large amounts of the bulrush millet (*Penisetum typhoideum*) and sweet potato are cultivated; in the south, yams and cassava are the principal food-crops. A little maize is grown, and in the small towns some white bread and milled rice are to be had. In some districts there is a plentiful supply of red palm oil, rich in carotene, whereas in others there is no oil or fat containing vitamins. Usually beef, pork, mutton, and dairy products are scarce. In a few areas fish provides a liberal quantity of animal protein. But commonly the only source of this nutrient is dried monkey, rat meat, snake meat, snails, frogs' legs, porcupine, and African weevils; and even these unusual delicacies are only to be had in very limited amounts. A wide variety of native beers and spirits are consumed. Thus the diet varies greatly from district to district. The over-all calorie content is usually adequate, but there are areas with apparent deficiencies in vitamin A, aneurine, riboflavine, nicotinic acid, calcium, and animal protein. Nicol[1] has recorded the results of six separate diet surveys in different parts of the country. In each survey the composition of the diet was determined by weighing for a week all the food consumed by the adults in the families; and in each some 80 persons were investigated.

The special interest of these surveys lies in the associations between deficiency of the various nutrients and prevalence of the various clinical stigmata of deficiency diseases. Thus in areas devoid of the red palm oil, the mean vitamin-A activity of the diets was below 750 international units (I.U.) daily. Here there was a high prevalence of corneal opacity associated with dryness of the conjunctiva, staring hair, and hypochromotrichia, general xerosis and follicular hyperkeratosis, "elephant skin," "crackled" skin, and night blindness. In the red palm oil district the average vitamin-A activity of the diets was over 5000 I.U. daily, and here the prevalence of these conditions was low. Nicol concludes that vitamin-A deficiency is an important factor in the production of these conditions. In the north one group with a high intake of sorghum consumed appreciably more riboflavine than the remainder. In this group there was less nasolabial seborrhœa, permanent gooseflesh, injection of the conjunctiva, and angular stomatitis. This suggests that riboflavine deficiency partly accounts for these signs. In two groups in the south, where little or no cereal was eaten, levels of aneurine and nicotinic acid were low and there was a high prevalence of calf tenderness (aneurine deficiency) and magenta and lilac tongues and, in one group, enlargement of the filiform papillæ of the tongue. These two changes in the tongue are attributed to nicotinic-acid deficiency. In all the peasants there was a high prevalence of folliculosis, atrophic skin, ulcers and scars of ulcers, thickened conjunctiva, and photophobia. These are probably not due directly to dietary causes, but deficiencies of the B complex of vitamins may act by exaggerating the effects of minor trauma.

Heights and weights at different age-levels were determined in four groups. In two of these with a good supply of fish, growth was appreciably faster than in the other two; and in one of these groups the final levels of height and weight were well above the remainder. This is suggestive evidence of a growth-promoting "animal protein factor."

These findings are important to the health and agricultural authorities in Nigeria. Shaw and Colville[2] have lately reported on the livestock situation in this colony. Animal husbandry is still very backward, and there is much undeveloped, potentially good stock land. They point the way to greatly increased local supplies of both beef and dairy products, which would undoubtedly raise the levels of health of Nigerian peasants. These problems must be tackled urgently if Nigerians are to take their full share in the development of Africa.

DEATH DURING ANTABUS TESTS

AN account by Becker and Sugarman[3] brings up to three the number of reported deaths due to an 'Antabus'-alcohol test reaction. Considering the widespread use of antabus, the mortality has apparently been very low. Nevertheless this new report must be taken as a serious warning to all who are using the drug. The patient was examined most carefully before being subjected to the test; the examination included routine electrocardiography, exercise-tolerance test, kidney and liver function tests, and blood chemistry studies. The clinical report gave no inkling that a severe reaction was to be expected. The patient, after receiving antabus for four days, was given 1 oz. of whisky. His reaction was very severe, and he was resuscitated with oxygen, adrenaline, and intravenous glucose-saline. Two hours later his condition seemed satisfactory; but two and a half hours after this he suddenly collapsed and died. Necropsy gave no clue to the cause of death. This case corresponds closely to that reported by Jones.[4]

Becker and Sugarman state that the dose of antabus was "that usually recommended" and that the test dose of alcohol was "well within the limits recommended in the literature." These doses were, however, larger than those recently advised by Moore and Drury,[5] who recommended a "loading dose" of 3 g. of antabus, and emphasised that a glass of beer should be used for the initial test, and spirits given only if beer produced an unimpressive reaction. Becker and Sugarman state that "it is necessary to obtain a strong test-reaction in order to teach the alcoholic patient aversion." Moore and Drury found that a "safe reaction" was quite strong enough for this purpose; and that vomiting, dyspnœa, and a fall in blood-pressure were to be avoided. Becker and Sugarman conclude: "This is not a drug to be used in general practice and dispensed in maintenance doses like digitalis. At most it may be another tool, still unproved, for the psychiatrist or those willing to devote time to the cause of the patient with chronic alcoholism."

THE 13th British Congress of Obstetrics and Gynæcology has been held this week in Leeds. On Wednesday the University of Leeds was to confer the honorary degree of doctor of laws on Dr. Albert Aldridge (New York), Prof. M. A. van Bouwdijk Bastiaanse (Amsterdam), and Sir Eardley Holland.

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1. Nicol, B. M. *Brit. J. Nutrit.* 1949, 3, 25; *Ibid*, 1952, 6, 34.
2. Shaw, T., Colville, G. Report of Nigerian Livestock Mission. H.M. Stationery Office, 1950. Pp. 175. 5s.
3. Becker, M. C., Sugarman, G. *J. Amer. med. Ass.* 1952, 149, 568.
4. Jones, R. O. *Canad. med. Ass. J.* 1949, 60, 609.
5. Moore, J. M. P., Drury, M. O'C. *Lancet*, 1951, ii, 1059.

BRITISH MEDICAL ASSOCIATION

FOR the fourth time in its history the British Medical Association chose Dublin for its annual meeting, but this year was the first in which the meeting had been held ointly with the Irish Medical Association. The annual representative meeting was held from July 3 to 7, followed by the scientific sessions from July 8 to 11. The meeting ncluded three plenary scientific sessions—a popular nnovation—and a scientific exhibition was arranged in University College.

It was announced that H.M. the Queen has consented to become Patron of the association.

The president of the B.M.A. for 1952–53 is Dr. P. T. J. O'FARRELL, senior physician to St. Vincent's Hospital, Dublin, and consulting cardiologist to St. Kevin's Hospital, who was president of the I.M.A. for 1950–51. In his address to this 120th annual meeting he recalled that at the Dublin meeting of 1867, when scientific sessions were first held, Joseph Lister spoke momentously on the Antiseptic Principles of the Practice of Surgery. Discussing the impact of a National Health Service on both doctor and patient, Dr. O'Farrell said:

> "Although much has been written about the plight of the general practitioner, too little has been said about the reactions of the patient under the influence of State-organised medicine. Of recent years broad changes have taken place in the attitude of patients towards their illnesses. They now often welcome, and indeed demand, full-scale methods of investigation and do not mind running the gauntlet of men and gadgets. While, up to a point, this outlook is desirable, it can be abused when patients avail themselves of a service which gives them the right to consult their doctors and consultants on the slightest provocation. There is also a fear that under a so-called free service some patients may become too introspective about minor ailments and that the trammels of imaginary ills and anxieties may become self-nurtured to an unreasonable degree. No-one would decry the importance of minor disturbances of either the body or the mind, but factors which might tend to initiate, aggravate, or perpetuate them should be discouraged. The unnecessary direction of patients from doctor to doctor in a roundabout fashion may appeal to some of them, but others will be dissatisfied and lose confidence in the competency of their own medical attendant."

Dr. A. W. S. SICHEL, the retiring president for 1951–52, was present in Dublin, having made the journey from Cape Town for the second time in his year of office. Mr. J. W. TUDOR THOMAS, ophthalmic surgeon to the Royal Infirmary, Cardiff, was named president-elect of the association for 1953–54.

Representative Meeting

The representatives gathered in the Round Room of the Mansion House, close by St. Stephen's Green. They were officially welcomed to the city by Senator ANDREW CLARKIN, lord mayor of Dublin.

Dr. S. WAND (Birmingham) was in the chair. Dr. E. A. GREGG (chairman of council), in a preliminary examination of some of the events of the past year, congratulated the General Medical Services Committee, and particularly its late chairman, Dr. Wand, on the "magnificent work, splendidly done" which had led to the Danckwerts award.

REMUNERATION

Dr. WAND told the story of the Danckwerts award and of the Working Party set up to advise on the distribution of the central pool. The vindication of the profession's claim in open court would, he said, ensure a fair reward for the past four years of underpayment. There were good grounds for claiming that the betterment factor of 100%, applied in the award to the year 1951, was too low. The committee inferred from the terms of the award that a variable betterment factor should be applied in future years, but the Government did not agree. However, the committee thought that, as a contribution to national economy, higher figures should not be urged. Dr. Wand told the meeting that the question of income-tax on arrears had been settled. The arrears will be treated for tax purposes as four separate annual sums and not as a single sum taxable in the year of payment. Any additional payments to assistants made for services in the past four years as a result of the award would be allowed as expenses in assessing tax, and Dr. Wand hoped that principals would consider making such payments. He thought that the Commissioners of Inland Revenue had been very fair. The increase in the central pool for 1952–53 should be reflected in payments to practitioners in September next, when the increase due for the first quarter of the current financial year will be made. The second quarter's increase will come with the December payment, and the other two quarters will be covered in March of next year.

Turning to the proposals of the Working Party, Dr. Wand said that they had tried to encourage the entry of the young doctor into general practice by the Initial Practice Allowance. Moreover the loaded capitation fee would make established practitioners look more readily for partners. He thought that the decision to fix the loaded capitation fee on patients from 500 to 1500 was the right one; for below 500 the new doctor had the Initial Practice Allowance to help him. Some doctors' lists remained around 1200 from their own choosing; perhaps they had other sources of income or felt that they could provide a better service for fewer patients. But if most doctors decided to do a first-class job for 1200 patients, there would be a lot of work for the others.

The council recommended the meeting to endorse the resolutions on the Working Party's report adopted by the special conference of representatives of local medical committees on June 26.[1]

Dr. A. C. E. BREACH (Orpington) feared that the Working Party's report brought nearer the danger of a whole-time salaried service. Some doctors would be worse off, and he foresaw a new depressed class of doctors. Dr. WAND replied that nothing would be accepted that might lead headlong to a salaried service. Summing up, he thought that every practitioner depending mainly on N.H.S. practice for his living would be looked after by the Working Party's arrangements. The recommendations of the council were carried.

DISCIPLINARY ACTION

Representatives were concerned at the possibility of a doctor's name being removed from an executive council's list for an offence against the so-called spirit of the N.H.S. Act, an offence which did not involve any breach of his terms of contract. A motion by Dr. W. O'CALLAGHAN (Manchester) opposing such an action was carried, but only after Dr. F. GRAY (London) had warned the meeting that by doing so it would be enlarging the penalty for such offences, not diminishing it. Did representatives want all disciplinary cases that did not involve a formal breach of contract to be referred to the General Medical Council? It seemed from the mood of the meeting that they did. Dr. H. GUY DAIN (Birmingham) declared that it was quite improper that a doctor could be penalised in this way for other than a technical breach of contract. Dr. A. Talbot Rogers (Bromley), the new chairman of the General Medical Services Committee, said that counsel's advice was being taken on this point, and that when their case was ready the committee would speak to the Minister.

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[1] See *Lancet*, July 5, 1952, p. 27.

PATIENTS' COMPLAINTS

Dr. J. W. McCarthy (Hendon) moved that every patient who complained against a doctor to an executive council should be required to deposit £2 with the clerk of the council as a token of good faith, and that should he fail to establish his complaint, or should it prove to be frivolous or vexatious, then the money could be made forfeit. He thought that a deterrent of this kind was badly needed. An amendment by the East Kent division sought to impose forfeiture only if the complaint was ruled to be "frivolous or vexatious." The meeting was not altogether happy about this idea, and a second amendment by Dr. Breach found support. He proposed that the patient should make a statutory declaration of the substance of his complaint, and that no disciplinary action of any kind should be started until such a declaration had been received by the executive council. Dr. Talbot Rogers thought that the type of patient most likely to make complaints of this kind would not be deterred by a statutory declaration. The East Kent amendment was agreed to, and the amended motion, together with Dr. Breach's amendment, was passed back to the council for consideration by their subcommittee, which, under the chairmanship of Dr. Dain, is already preparing a report on the working of the Tribunal and the medical service committees.

PREREGISTRATION YEAR

Referring to the terms of the Medical Act, 1950, Dr. J. A. Gorsky (Westminster) proposed that a period of six months in general practice should be accepted as one of the appointments qualifying for full registration. The matter was eventually referred to the council.

SPECIAL OBSTETRICAL LIST

An abrupt motion, brought from Gateshead by Dr. J. C. Arthur, asked that the special obstetrical list be abolished; and it was as abruptly and rather surprisingly carried. Opinion was evenly balanced: there were those who felt with Dr. Arthur that the list should go, in acknowledgment of the right and competence of all practitioners to do obstetrics; and there were others who agreed with Dr. F. Gray that its abolition would encourage further intervention by those who sought to take midwifery out of the practitioners' hands altogether. Dr. Talbot Rogers favoured its retention, for the signs as he read them suggested that a modus vivendi between the obstetricians and the practitioners would soon be reached.

EVIDENCE ON MARRIAGE AND DIVORCE

The agenda contained 21 amendments to the motion by the chairman of council to approve the memorandum, prepared by a special committee set up by the council, which was submitted in evidence to the Royal Commission on Marriage and Divorce. Most of these amendments criticised the council's action in submitting the memorandum without first referring it to the divisions and branches of the association. Dr. Gregg announced that the council had decided to ask permission to withdraw the motion, and that it would ask to have the memorandum removed from the evidence before the Royal Commission.

FILLING OF PRACTICE VACANCIES

There was much dissatisfaction with the present method of filling a vacant practice. Dr. W. M. C. Hallinan (Lewisham) pointed out how a small-list practice could dwindle alarmingly while the executive council's machinery was trying to get into top gear, which it seldom reached. He suggested that a register be kept of the names of doctors in a council's area who were prepared to fill vacancies; by this means the usual delay of many weeks could be reduced. This suggestion was generally popular, though Mr. J. E. Purves (Bromley) feared that it might give the executive council another chain with which to bind the doctor. The matter was referred for the attention of the council. The General Medical Services Committee will soon be able to give the results of its inquiries on this subject.

PRESCRIPTION CHARGES

The debate on the 1*s.* charge suddenly collapsed when the meeting unexpectedly decided that it would pass to the next business. But Dr. W. N. Leak (mid-Cheshire) did have time to say that he thought the charge would do little to discourage the scrounger, who still appreciated the bargain of getting 5*s.* worth of goods for 1*s.* However, representatives later considered that they had been too hasty, and decided to give the rural practitioners a hearing. Dr. H. H. Goodman (Newcastle upon Tyne) declared that the collection of the shillings by the country doctors was impracticable and iniquitous, and that it should not be asked of them. There were inevitable losses to the doctor, and it was a laborious business making sure that patients paid. Dr. Talbot Rogers observed that the method of collection by stamps had been the idea of a rural practitioner; it was certainly a big improvement, he said, on the Ministry's first proposals, which would have meant collecting cash and accepting a reduced dispensing capitation fee. He thought the scheme worked as well as could be expected, and a number of rural practitioners later agreed with him. Dr. Talbot Rogers told how, with representatives of the Rural Practitioners' Committee, Dr. Wand and he had vigorously opposed the charge before the Minister. It had become clear to them that an inflexible decision had been taken by high Government authority, and they were obliged to accept such concessions as they could get. The Newcastle motion to stop the collection of the charge by rural doctors was defeated.

VACCINATION

The meeting deplored the complacent attitude of the Ministry towards its inadequate propaganda about infectious diseases and especially about vaccination. Dr. N. J. Cochran (Burton on Trent) foresaw a panic over smallpox in another 20 years if the present tendency continued.

TRAINEE ASSISTANTS

Dr. Barbara Woodhouse (Harrow) thought that the trainee-assistant scheme was open to abuse in two ways: the trainee might desert general practice after his period of training; and the training doctor might use it to get a cheap assistant. Moreover the scheme was a waste of public money, for surely any principal who wanted a good assistant should be prepared to teach him without payment. The six months in general practice suggested for the preregistration year might make a more acceptable alternative to the scheme. Dr. H. S. Howie Wood (Isle of Wight) disagreed; he had found that a young doctor in the practice gave a stimulus to the work of the older man, a stimulus that many established practitioners would not receive but for the trainee scheme. Mr. E. E. T. Taylor (Northamptonshire) criticised the scheme for subsidising the teacher. An assistant is an asset, not a liability. The intelligence of young doctors was underestimated; they were quite capable of making sound practitioners without the formal instruction required by the scheme. Dr. R. M. S. McConaghey (Torquay) counted the scheme as one of the few really statesmanlike features of the health service. It did not really matter if the trainee left general practice in the end; he could not fail to be a better doctor in any branch of medicine after his year as an assistant. The Harrow motion that the scheme be abolished was defeated.

REGISTRARS

A general practitioner, Dr. J. L. McCallum (Westminster), pleaded the case of the senior registrars who may shortly lose their posts. They feel, he said, that few are interested in their grave difficulties, and that they would be better off under a full-time salaried service. The numbers involved are not so great as was at first feared, for some concessions have been gained; but perhaps 300 men, most of them between 35 and 45, are faced with the prospect of having to find work outside the hospital service. He asked the meeting to say that it considered that the Ministry of Health was responsible for finding them other employment. Dr. T. Rowland Hill (London), chairman of the Central Consultants and Specialists Committee, said that they had been fighting a continuous battle for the registrars, and though the position for many was still anxious the acute crisis had been relieved. Dr. Gorsky thought the battle had not been waged hard enough and he asked for an immediate increase in the registrar establishment. Mr. H. H. Langston (Winchester) could only see a solution to the problem if the consultant establishment was raised as well. At the division Dr. McCallum won his point.

S.H.M.O.S

Many representatives thought poorly of the Ministry's attitude towards the senior hospital medical officers. The Ministry had carried out its promise to review the status of all S.H.M.O.s in the latter half of 1951, but Dr. J. C. McMaster (West Somerset) knew that the S.H.M.O. group still included men with higher qualifications and years of experience who were being paid at a parsimonious rate. He thought that the grading committees should contain more general practitioners—not less than 20%. Dr. K. C. Bailey (West Somerset) condemned the S.H.M.O. idea as a mistake from the start; and the meeting went with him as far as to agree that all such posts in hospital establishments should be reviewed as a matter of urgency. Another source of annoyance was the way in which some newly graded consultants found their salaries unchanged because they were occupying posts graded as S.H.M.O. The Central Consultants and Specialists Committee did not feel that this circumstance could be challenged, provided the post was correctly graded. The meeting did not think that a grading committee should be influenced by whether or not the person under review was in general practice.

THE G.P. AND THE HOSPITAL

Mr. A. Staveley Gough (Watford) introduced his committee's report on the association of the general practitioner with hospital work. He hoped that it would help to reunite the practitioner with the hospital, from which the N.H.S. Act had divorced him. The meeting accepted the council's recommendations based on the report. The gist of these was:

(1) That the smaller cottage and G.P. hospitals be returned to the practitioner, and that certain wards in all other general hospitals be set aside for the treatment of patients by G.P.s.

(2) That part-time clinical assistantships be set up. Firstly, honorary clinical assistants could spend short periods in two or more special departments to widen their knowledge generally. Secondly, clinical assistants should be appointed for two years or so in a particular special department to enable the practitioner to gain some part of the experience necessary to become recognised in that specialty. These posts would be part of the hospital establishment, they would have definite responsibilities, and they would be paid. Thirdly, senior clinical assistantships should be offered to G.P.s who have adequate experience in a particular specialty, and who preferably have a higher qualification. They would help the consultant by doing work of a non-consultant nature. These appointments should be for regular weekly sessions and should be paid on this basis.

(3) That, particularly in rural areas, the appointment of part-time G.P.-consultants be continued.

(4) That G.P.s be given the opportunity for consultation on their own patients in hospital, and the right to attend ward-rounds and clinical and scientific meetings.

RETIRING AGE FOR CONSULTANTS

An amendment was passed calling for the compulsory retirement of consultants at 65 to be abandoned, and saying that this retirement was contrary to national policy in the economic crisis.

REGIONAL HOSPITAL BOARDS

Dr. J. E. Thomas (North Glamorgan) proposed the abolition of the regional hospital boards, and the vesting of their power in the local hospital management committees. The lack of interest shown by the boards and their annoying interference were, he said, a constant source of irritation. Dr. Rowland Hill was sure that the motion would defeat its own ends and increase the danger of stricter Ministerial control. They all wanted more freedom but this was not the way to get it. The motion was heavily defeated.

PROFESSIONAL SECRECY

The meeting disagreed with a recommendation of the council which would have modified the association's policy of absolute professional secrecy by allowing a doctor to speak when it became his moral or social duty to do so for the protection of innocent persons, and when the patient refused to act himself on the proper advice of the doctor. Dr. Robert Forbes, moving the adoption of this recommendation, emphasised that it did not seek in any way to weaken the bond of professional secrecy, but to provide for those cases in which the silence of absolute secrecy might bring harm to doctor, patient, or an innocent third party. Dr. Ffrangcon Roberts (Cambridge) regretted that as society advanced it became more and more menaced by the individual, and he deplored any move to change the attitude of the profession towards secrecy. Dr. Howie Wood thought that the recommendation would certainly be misinterpreted by the public and that it would lower the profession in public esteem. Dr. Gorsky saw no harm in the suggestion; for there were already lawful excuses which freed a doctor from his legal bond of secrecy, and there had been no public objection to such excuses. An amendment was passed removing the modifying words from the recommendation.

CIVIL SERVICE MEDICAL OFFICERS

Dr. Gregg announced that the Treasury had declined arbitration on the pay of doctors in the Civil Service. The association's request to reopen discussions in the light of the Danckwerts award had been unsatisfactorily answered. The Treasury had undertaken to review the new scale of salaries after a trial period. What this meant, said Dr. Gregg, was that the Treasury sought an opportunity to engage doctors on their own terms. The council had decided not to accept further advertisements of Civil Service medical posts for the *British Medical Journal* until a more satisfactory answer was given. The meeting unanimously approved this action.

JOINT MEETING OF ORTHOPÆDIC ASSOCIATIONS

A JOINT meeting of the orthopædic associations of the English-speaking world was held in London from June 30 to July 4. This congress was opened by H.M. Queen ELIZABETH the Queen Mother, who presented jewels of office, the gift of the British Orthopædic Association, to the presidents of the visiting associations from the United States, Canada, Australia, New Zealand, and South Africa. During the week there were demonstrations at London hospitals and many social events; and at the close visitors dispersed to visit provincial orthopædic centres.

At the congress dinner on July 3, attended by some 800 people, Sir HARRY PLATT, speaking of The Guests, welcomed particularly the representatives of the Brazilian, Dutch, Swedish, Portuguese, and other orthopædic associations, which if not English-speaking were English-reading and English-writing. Mr. IAIN MACLEOD, the Minister of Health, who responded, said that the link between so many participants of different country, politics, colour, and religion was that they really cared that there are sick and broken people. Dr. FREMONT CHANDLER, in proposing the toast of Orthopædic Surgery, spoke of the practical usefulness of the conference, and Sir REGINALD WATSON-JONES, the chairman, described it as a great event in the history of orthopædics. He hoped, incidentally, that on their visits to other parts of England, and to Scotland, Ireland, and Wales, the guests from abroad would take the opportunity of seeing to what extent the medical profession has become regimented. "We may not think much of our head gardeners," he remarked, "but at least they have not pulled up the unofficial English rose and planted rows of tulips." The conference had, he believed, shown that what holds together the Commonwealth and the United States is the pursuit of truth with no political bias.

The final toast, The English Language, was proposed by the MARQUESS OF READING, who quoted Bismarck's saying that the most important thing in the world is that the people of America speak English. Today Bismarck might say that the most important thing is that the English peoples speak American; but, after all, language was a living growth, and even the well of English undefiled might be the purer for a few tablets of American chlorine. We might be a poor country but we had a rich language: indeed, he regarded the 13 volumes of the *Oxford Dictionary* as a sort of linguistic Fort Knox in which is stored away—unseen, unused—the wealth of the English-speaking world. Basic, or debased, English might help the foreigner; but English without effort would never do for Englishmen. We had a language rich and subtle, resonant and strong: let us not condemn it to anæmia. Lord Justice BIRKETT, responding, said that English, with its flexibility and its words from every language under the sun, can deal with every situation. He agreed that it should not be afraid of importations, and he acknowledged our debt to America for such expressive inventions as sobstuff, sky pilot, highbrow, tenderfoot, and lounge lizard. But with the vitality of living speech we must seek also lucidity and grace—the one to make our thoughts plain, the other to make them memorable. Illustrating from Shakespeare what C. E. Montague called the "glamorous prestige of words in high company," he described it as our duty to welcome every importation that will live by its vitality, but also to regard ourselves as trustees. The English tongue was one of the bonds between the nations that use it; and in such bonds, he felt, lies the chief hope of the world.

Some of the papers read at the congress are summarised below.

Traumatic Dislocation of the Hip

Mr. E. A. NICOLL (Mansfield) said that in 144 cases of traumatic dislocation of the hip the incidence of aseptic necrosis of the femoral head was 10%. If the incidence reported from other sources varied, this was because necrosis was often confused with traumatic arthritis. The two conditions were very different. Necrosis was a vicious process; radiographic evidence, always present within two years of injury, preceded clinical features. Traumatic arthritis was a common, relatively benign complication of later development and slower course. Necrosis was commoner in children than in adults because there was absolutely no anastomosis across the epiphyseal cartilage-plate to make up for the interference with the blood-supply to the femoral head caused by retinacular damage. It might therefore be reasonable to carry out prophylactic drilling of the cartilage-plate after dislocation in childhood, but if so there was no point in blocking the new channels with bone grafts. Half the cases of necrosis were associated with delayed reduction or repeated attempts at reduction, so early recognition and gentle management were obviously essential. Premature weight-bearing was also dangerous; 20% of patients allowed to take weight within a month of injury developed necrosis, whereas the incidence was only $7^{1}/_{2}$% when walking was delayed. But even prolonged abstention from weight-bearing would not facilitate reconstruction of a normal head, once necrosis was established, by creeping substitution; the revivification process was too slow to prevent cartilage degeneration and massive collapse. The over-all incidence of necrosis was not high enough to justify routine prohibition of weight-bearing for more than eight weeks; but every case must be examined radiographically every three months for two years. If radiographic evidence were seen management was a difficult problem, for disability might be trivial despite the most alarming appearances. Of 15 cases of necrosis only 6 required operation (2 arthrodeses and 4 displacement osteotomies); the remaining patients had trivial symptoms and were all working.

Dr. MARCUS J. STEWART (Memphis), from an experience of 128 cases of dislocation and fracture-dislocation of the hip, did not believe that age, method of fixation, or time of weight-bearing had any influence on the outcome. The important factors were the severity of the initial trauma and delay in reduction. Because the urgency of reduction in determining the quality of the result was to be reckoned in hours, dislocation was more of an emergency than many a compound fracture or abdominal condition. But, quite apart from vascular disturbance, an important cause of necrosis was the molecular change in structure of the head produced by the impact; the fact that the time of onset of necrosis was exactly the same—17 months—whether open or closed methods of reduction were employed suggested that the die was cast for or against necrosis at the time of injury. When there was coincident sciatic nerve injury and the radiograph showed large separated bone fragments exploration should be done; for the nerve might be transfixed.

In the discussion of these two papers Dr. PAUL B. MAGNUSON (Washington) confirmed that minimal clinical features might accompany severe radiographic changes of necrosis; the plane of flexion-extension at the hip habitually used by the patient could be smooth and painless, though the surgeon was able to demonstrate that other ranges were blocked and painful. Revascularisation of a dead head could be accelerated by partial resection of the subjacent neck, bringing up the shaft and transplanting the great trochanter downwards.

Mr. JAMES PATRICK (Lanarkshire) thought a clear distinction between necrosis and arthritis was not made sufficiently often. The stigma of necrosis was collapse of the head, and this might occur abruptly after months of apparent radiographic normality.

Dr. J. M. EDELSTEIN (Johannesburg) agreed that the initial damage to the head was often concealed and therefore an unfavourable prognosis could sometimes be made, but never a favourable one. The only conceivable short cut to good function in severe established necrosis might be the use of a prosthesis for the femoral head.

Mr. K. H. Pridie (Bristol) admitted no essential distinction between necrosis and arthritis. Massive necrosis was recognisable as such; but minor focal necrosis invisible in the radiograph could initiate spreading reactive changes and degeneration of the overlying cartilage which was in fact post-traumatic arthritis.

The Arthritic Hip

Dr. Frank Stinchfield (New York) opened a discussion on the indications for the various operations for osteo-arthritis of the hip. Sound arthrodesis was painless and satisfactory; and he aimed to obtain it by combining joint erasion, metallic internal fixation, and an ilio-trochanteric bone graft: some 20% of cases developed pseudarthrosis, but half of these were satisfactorily fused at a second operation. Arthrodesis was preferable in young patients, in manual labourers, in unilateral disease, in old septic hips, and when patients were uncoöperative. Cup arthroplasty had not given dependably good results; some limp was universal, and the range of movement tended to diminish after the fourth year. It was more suitable for the middle-aged sedentary person with bilateral disease who could be relied on to work almost religiously at postoperative exercises. Coxa valga and a shallow acetabulum were also points in favour of arthroplasty—an operation which did not preclude subsequent revision or arthrodesis. Old patients did not stand cup arthroplasty well, and here the use of the Judet prosthesis was better. This procedure was easier and less shocking, with rapid reablement, and was valuable for aseptic necrosis; but it had no place with young patients and the late results were unknown.

In discussion, Mr. Alexander Law (London) thought that the high incidence of pseudarthrosis and backache after fusion favoured arthroplasty, which was no more likely than arthrodesis to cause old sepsis to flare up. His impression was that the Judet operation gave a very mobile hip initially which subsequently tightened up, and he questioned the durability of the prosthesis if used for young patients. Follow-up of a series of bilateral cases treated by insertion of a cup on one side and an acrylic head on the other would be very instructive.

Mr. John Charnley (Manchester) described his technique for arthrodesis of the hip, in which a central dislocation was produced, the femoral head entering the pelvis. The resulting bone block made rotation and late adduction deformity impossible, so there was no need to fix the knee postoperatively. Even a fibrous ankylosis was sound under these circumstances, but he now made bony fusion certain by applying spring compression via a transfixing screw. All his patients had clinical fusion at six weeks and were back at work in three to four months—a remarkable record. The balance of opinion against fusion was due only to the irregularity of its success in the past; when bony ankylosis could be routinely produced within a few months without secondary back or knee strain the indications for arthroplasty would be fewer.

Dr. Arthur Steindler (Iowa) was opposed to any irreversible operation on the hip-joint unless the compelling symptom of pain had been carefully analysed as to its source. Pain of purely synovial origin could clear up if the synovial pathology were reversible, as it often was.

Treatment of Tuberculous Hip

Mr. Thomas King (Melbourne) described the advantages of allowing adduction deformity to occur during conservative treatment of tuberculous hips in adults, and then performing Brittain's ischiofemoral arthrodesis. The operation was much easier with a short ischiofemoral interval, and a stout graft (he preferred the fibula) could be used without fear of breakage; he added an arthrodesis nail fixed to a plate on the outer aspect of the femur so as to dispense with plaster fixation.

In a written comment Mr. H. A. Brittain (Norwich) said that he disliked the use of metal in tuberculous joints, could see no need for a nail and plate when the essence of his operation was osteotomy-displacement without fixation, found his original tibial graft more easily vascularised than a portion of fibula, and noted that extreme adduction was usually associated with enough flexion to bring the sciatic nerve dangerously forward into the operation field.

Dr. D. M. Bosworth (New York) did an arthrodesis as soon as he made the diagnosis, so there was no time for adduction to develop; nail fixation could carry tuberculosis into the pelvis. Late adduction was only compatible with ischiofemoral fusion when the head and neck had not been destroyed.

Mr. G. Parker (Middlesbrough) had for several years been allowing adduction to occur and performing Brittain's operation in those tuberculous hips in children likely to require fusion, with excellent results. But Mr. Michael Wilkinson (Black Notley) deplored any routine adoption of such a programme; for, in his hands, chemotherapy combined with subtotal synovectomy in early cases gave mobile hips with good function; and the opportunity to do this, once lost, was irretrievable.

Osteoid Osteoma

Mr. John Golding (London) reviewed the characteristic features of osteoid osteoma. Continuous boring pain might be accompanied by local swelling, and operation revealed the cherry-red, highly vascular tumour lying within sclerosed bone. The tibia was the commonest site, but obscure lesions in the spine or hip made diagnosis difficult and radiographic evidence was not always available. The typical widespread regional sclerosis was a reaction to the vascularity of the tumour of the kind often seen in relation to angiomata of bone. The disease was self-limiting after a course of several years; so, while easily accessible lesions should be removed, radiotherapy should be employed for other sites rather than attempted radical extirpation.

Dr. H. H. Young (Rochester, Minnesota) said that femoral lesions could cause sciatica simulating disc prolapse. Pain was too severe to justify waiting for spontaneous regression. Dr. J. R. Moore (Philadelphia) classified the disease into cortical, cancellous, and subperiosteal varieties; juxta-articular lesions could mimic acute arthritis.

Mechanism of Gait

Prof. John Saunders (San Francisco) gave an account of an investigation into the mechanics of normal gait. Human locomotion was an exceedingly complex process to analyse; Nature's object was the translation of the body through space with the least expenditure of energy, its centre of gravity describing a sinusoidal pathway of low amplitude with a horizontal as well as a vertical excursion, and making a figure of eight in two dimensions and a spiral curve in three. The major determinants of normal gait could be deduced by comparing human progression with that of a simple compass model. The centre of gravity of such a model passed through a series of high arcs with sharp deflections and extravagant energy expenditure. The body modified this by means of pelvic rotation, which reduced the required range of flexion and extension at the hip; by pelvic tilt; by knee flexion on the weight-bearing side between the extension which began and ended the stance phase of gait; by providing subsidiary arcs at forefoot, heel, and knee; and, finally, in the horizontal plane, it limited the wide sweep of the compass model by means of normal femorotibial angulation. All these devices combined to make the legs $2^1/_2$ times longer functionally than they were in reality, and to limit the excursion of the centre of gravity to the confines of a 2-in. cube.

Dr. VERNE T. INMAN (San Francisco), collaborator in this research, had studied the energy expended in raising and lowering the centre of gravity during locomotion by means of force plates—horizontal platforms supported on bronze pillars—the deformation of which was electrically recorded. The resulting oscillograms were obtainable from one or both legs and recorded both vertical stress and lateral shear. Force-plate studies confirmed the sinusoidal path of the centre of gravity and demonstrated the extra expenditure of energy necessitated by pathological conditions. High heels, like fused ankles, caused little change, though accompanied by increased knee flexion and pelvic roll; but the fixed knee required more energy output. The below-knee amputee was relatively normal from this point of view, but a thigh amputation required 27% greater energy expenditure; such a patient in effect walked 5 yards to another man's 4, and this must be considered in supplying an artificial limb to a cardiovascular invalid after amputation. Energy was also expended in walking in producing oscillation of the legs, two-thirds deriving from the foot and ankle and one-third from the hip mechanism; the knee merely absorbed and dissipated energy, and patients with a fixed knee or long leg plaster had a greater hip excursion than normal.

In discussion, Mr. PHILIP WILES (London) said that such fundamental studies might help in assessing the value of a proposed operation such as arthrodesis. Dr. BECKETT HOWORTH (Connecticut) said that the higher the heel the nearer was the functional approximation to the Symes amputation because of obliteration of ankle function and shortening of forefoot leverage. The quadriceps mechanism was the first to fail in leg strain.

Traumatic Paraplegia

Mr. F. HOLDSWORTH (Sheffield) described his management of traumatic paraplegia, based on experience with 68 patients with lumbodorsal fracture-dislocation. There had been too much pessimism about prognosis in these cases. The dictum that complete motor and sensory loss for forty-eight hours indicated irreversible damage applied only to the cord; but at the common level of injury around the lumbodorsal junction the cord contained only sacral segments and the lumbar elements were present as roots, which could recover. Here any retained power in the legs was an index, not of a spared cord, but of root escape; and it was vital to encourage root recovery by reducing and fixing the spine lesion. Return of control of the hips would allow relatively normal walking compared with the tripod gait of the complete paraplegic. Treatment of the fracture was also essential, because angulation interfered with balance when reablement began. Radiography was not always helpful in assessing the displacement obtaining at the time of injury, or the potential instability during nursing. Gross crush of a vertebral body with facets intact was a stable lesion and no operation was indicated, even for partial cord damage unless this was progressive. The common cause of unstable fracture-dislocation with paraplegia was torsion plus flexion, which disrupted the facets, produced a horizontal slice fracture of the lower vertebral body, and was recognisable clinically by a gap between the spinous processes and a local hæmatoma. This lesion was so unstable that open operation and internal fixation by two long plates screwed to the spinous processes was required as an emergency. It was then possible to turn the patient two-hourly; plaster beds were unnecessary, and there were no bedsores, myositis ossificans, or stiff joints. In 47 patients treated from the outset there had been not one bedsore; and these patients walked at six months and left hospital in ten months, 30 having been operated on. But not 1 of 21 patients admitted late was out of hospital in under two years, and these suffered the complications of classical management. An indwelling catheter was far better than suprapubic drainage.

Mr. NICOLL said that Mr. Holdsworth's policy offered the only hope to these patients, though the operation was not always simple. Colonel A. W. SPITTLER (Washington) used the Stryker frame and Foster bed to facilitate turning: if operation were done he obtained fusion by bone grafting.

Dr. LUDWIG GUTTMANN's experience with 800 paraplegics at the Ministry of Pensions Hospital, Stoke Mandeville, had led him also to abandon the plaster bed and suprapubic drainage; but he did not feel that early operation necessarily guaranteed any recovery of function. Reablement began when the patient was first seen; even a patient completely paraplegic from waist down should be at work in seven to twelve months. Dr. PHILIP WILSON (New York) doubted the security of metal-plate fixation and preferred bone grafting; but Sir REGINALD WATSON-JONES (London) accepted Holdsworth's thesis because fixation for nursing purposes was required only for the few weeks before the spine acquired its own stability.

Fractures of Cervical Spine

Dr. WILLIAM ROGERS (Boston) described his experience with 77 cases of cervical fracture-dislocation. Of the 15 deaths, 12 were associated with cord injury and 3 were due to pulmonary embolism. Anterior dislocation was the usual cause of quadriplegia, but the severity of the cord injury was not commensurate with the degree of displacement. The most dangerous group were the old people with stiff arthritic necks, and there were some cases of hyperextension injury; paralysis without radiographic evidence of fracture-dislocation was due to disc retropulsion or to hyperextension with infolding of a ligamentum flavum. Hyperflexion dislocation could occur with complete rupture of all ligaments and yet undergo complete spontaneous reduction. Only a minority of cervical fracture-dislocations escaped cord injury; but in 10% of cases this was acquired *after* injury during transit to hospital, or actually in hospital from careless handling or such manœuvres as halter traction or laryngoscopic intubation. When cord damage came on immediately, death was inevitable. For the emergency nothing was better than the simple turnbuckle distraction brace, based on shoulders, neck, and occiput; later, skull traction produced complete reduction in most cases without any hazard to the cord. Most of the failures with skull traction were in cases of posterior displacement and unilateral rotary dislocation.

Mr. V. H. ELLIS (London) agreed that patients who had succeeded in breaking their necks without cord damage ran a grave risk of acquiring the latter during treatment. Once skull traction was in place the patient was safe; and because the spine remained unstable he wired the spinous processes and performed bone grafting at the same time. Dr. T. C. THOMPSON (New York) applied skull traction by means of malar fish-hooks, and such traction could be weighted unequally to correct lateral shift.

Adrenocortical Function

Dr. PHILIP WILSON (New York) described a study of adrenocortical response in orthopædic patients, as shown by eosinophil-counts. Adrenocortical function must affect the outcome of many procedures, and good results were often attributed to technique which were really the outcome of the non-specific stimulus to the pituitary-adrenal axis. Stress eosinopenia was common in patients admitted with injuries, infections, and acute low-back strain; it was also seen with bone tumours. It was not seen in patients admitted for elective surgery. Post-operatively, there was immediate profound eosinopenia (which did not occur during the anæsthesia) followed by a rebound, sometimes above normal, on the second to fourth day; failure of this response indicated a dangerous lack of adrenocortical reserve. Protracted eosinopenia was associated with complications in recovery and was of some prognostic value.

Prof. J. Trueta (Oxford) welcomed this work as a corrective to the mechanical-mindedness of orthopædists; but eosinophil-counts were so variable that care was needed in their interpretation. Dr. Beverly Raney (North Carolina) wondered if the mechanism of eosinopenia was always the same, for there was some evidence that it could occur in adrenalectomised animals.

Changes in Lumbosacral Region

Dr. Ian MacNab (Toronto) gave an account of an investigation into the structural changes seen in a large number of lumbar spines post mortem. The intervertebral discs were maximally developed by the end of the second decade and thereafter aged and degenerated by inspissation and transformation of the ground substance into formed elements. The rate of senescence varied, and degeneration differed from normal ageing only in its prematurity and its possible association with trauma. The changes included radial posterior or posterolateral annulus tears; nuclear extrusion; multiple hæmorrhages giving a brown siderotic disc; or a massive single hæmorrhage into the nucleus. The entire disc might become soft and putty-like and extruded beyond the rim of the vertebral bodies by body-weight. Disc degeneration made segmental intervertebral movement lose its smoothness, and the axis of flexion-extension passed backwards to the small articulations, which suffered considerably, tending to subluxate in flexion and with an overriding of the facets which might allow the inferior articular process of one vertebra to wear a hole in the lamina below. Such overriding could also be associated with reversed spondylolisthesis of the upper centrum and with nerve-root pressure. The capsules of these small joints became fibrosed, chondrified, or ossified, and loose bodies in the joint cavities could lock the back in acute lumbago. The radiographic signs of late disc degeneration were obvious; at an earlier stage it was necessary to demonstrate abnormal mobility of the upper vertebral body in flexion and extension films. Disc degeneration was not necessarily accompanied by disc prolapse, though prolapse was always an incident in a degenerate disc. Degeneration was universal and gave rise to radiographic signs; prolapse was an accident in a few individuals and might have no radiographic features.

Mr. E. F. West (Adelaide) discussed the origin and treatment of spondylolisthesis. Trauma seemed a more likely cause than congenital ossification defects; and progressive displacement was probably rare because limited by ossification in the anterior bulge of the associated disc.

Discussing these two papers, Dr. J. A. Freiberg (Cincinnati) advised excision of thickened zygapophyseal joint-capsules at operation for sciatica, for they might be the sole cause of root pressure. It was difficult to reconcile the bulging disc of senile vertebral osteoporosis with the progressive inelasticity of disc degeneration. Mr. A. D. Eyre-Brook (Bristol) doubted the practical value of the numerous radiographic abnormalities of the lumbosacral region; clinical evidence should be the basis for operation for sciatica, and if no disc prolapse were found the intervertebral foramen must be explored.

Dr. Donald King (San Francisco) found anterior fusion with a tibial bone graft through an abdominal approach unsatisfactory in spondylolisthesis; the graft fractured where it traversed the avascular disc. But Prof. Merle d'Aubigné (Paris) was very happy with the abdominal operation; he replaced the disc with an iliac graft, transfixed the lumbosacral joint with a large screw, and allowed his patients up in two weeks without immobilisation. Mr. Norman Capener (Exeter) thought that spondylolisthesis might be sometimes due to stress fracture of the neural arch. Reduction of displacement was possible but this always recurred, even after grafting. Prof. Sten Friberg (Stockholm) said that the condition could be due to congenital deficiency, chronic strain, or acute trauma. Congenital causes certainly existed. The other two types were associated with an elongated or a ruptured isthmus respectively. Loss of elasticity was the essence of disc degeneration, and discography with opaque media showed this could begin in the 'teens.

The Ischæmic Hand

Dr. Sterling Bunnell (San Francisco) described the entity of local ischæmic contracture of the intrinsic muscles of the hand, due to swelling within tight plaster or vascular injury in the forearm. The intrinsic minus position of ordinary claw-hand was well known; but here there was an intrinsic plus position due to spasm or fibrosis of the small muscles, with metacarpophalangeal flexion and interphalangeal extension in the fingers and fixed adduction of the thumb. It might accompany Volkmann's contracture or occur independently, and when the metacarpophalangeal joints were fully extended passively the interphalangeal joints could not be flexed. The hand could not be opened for grasping. Prophylaxis consisted in avoiding further embarrassment of the circulation in the hand after injury. Treatment of the established condition was by forward stripping of the interossei along the metacarpals when the muscles had any residual function, so allowing them to lengthen; or, when they were fibrosed, tenotomising the lateral bands of the finger-joints. The thumb was dealt with by complete incision of the first cleft, stripping or excising contracted muscle and opening the first carpometacarpal joint; the functional position of opposition was maintained with an intermetacarpal bone graft threaded with a wire and the raw cleft lined with a free or pedicled skin graft.

Mr. Guy Pulvertaft (Derby) spoke of the need for prolonged after-treatment with this procedure, for there was a tendency to relapse and re-formation of the lateral bands. Splintage and elastic traction were essential.

Arthroplasty for Congenital Dislocation

Dr. Paul Colonna (Philadelphia) described the good results obtained over twenty years with his operation of capsular arthroplasty for congenital dislocation of the hip. His age-limits were 3–6 years for bilateral, and 3–8 years for single, cases. The femoral head must be brought right down by preliminary traction, a deep cup-(not saucer-)shaped acetabulum made at the original site, and the head placed therein with capsular interposition. For marked anteversion a supracondylar femoral osteotomy could be done subsequently. The false acetabulum was left alone and no shelf made; it filled in spontaneously over the years. Very occasionally a shelf was needed years later for instability.

Dr. Alexander Gibson (Winnipeg) discussed open reduction of congenitally dislocated hips via the posterolateral approach. Closed reduction was often satisfactory to patient and parents for some years, though the radiographs gave the surgeon little cause for complacency. His operation was less damaging than manipulation and so simple as to be the method of choice. The superior part of the capsule was incised transversely and the medial flap stripped with a thin layer of bone off the dorsum ilii down to the level of the true acetabulum. The femoral head was gently replaced and the medial capsular layer overlapped above the lateral layer, so obliterating the entry of the head into the joint diverticulum above; the osteogenic capsular flap contributed to the formation of a good roof without any necessity for a shelf.

In discussion, Sir **Harry Platt** (Manchester) said that open reduction could be used as an alternative to closed methods when concentric reduction was made difficult by soft-tissue anomalies or an over-large femoral head; but no reconstruction of the acetabulum was needed for these young children except the occasional making of a shelf. He was not convinced that operation should routinely replace closed reduction.

Mr. H. J. **Seddon** (London) wondered whether Dr. Colonna was using his procedure where other surgeons might perform simple open reduction, with or without acetabuloplasty. What was to be done with patients too old for capsular arthroplasty and too young for an adult type of procedure? Could a cup or prosthesis be seriously considered? He did Colonna's operation in this difficult age-group of 8–14 years, but with less satisfactory results; the hips were often very stiff but were at least in good position for subsequent arthrodesis or arthroplasty. Mr. J. B. **Colquhoun** (Melbourne) said that those who believed that a high proportion of cases could be reduced by manipulation reserved Colonna's operation for their failures, and it was not surprising that their results were worse than those of Colonna himself, with his more liberal indications.

Scoliosis

Dr. **John Cobb** (New York) discussed the selection of the fusion area in scoliosis. A mature massive fusion would maintain the stability of a corrected curve, but the operation was necessary in less than 5% of idiopathic scolioses. The ideal case was a single stable non-paralytic non-progressive curve in a patient over 15, in whom correction was desirable and possible. There was some confusion as to the meaning of correction, which applied to the angular deformity and did not mean straightening the whole curve. If, as was usual, the compensatory curves could not be corrected completely correction of the primary curve must not be complete and the accepted principle of always fusing between parallel lines was wrong. This was indicated when side-bending away from the primary convexity did not obliterate the secondary curves, and the area of fusion must be balanced against the residual uncorrectable angular deformity. When, on the other hand, maximum permissible correction of the primary curve was not obtainable, the fusion area might be extended beyond the parallel lines into the secondary curves themselves.

Mr. J. I. P. **James** (London) discussed prognosis in idiopathic scoliosis in relation to curve patterns and age of onset. Onset could be infantile, juvenile, or adolescent; and prognosis was worse the higher the apex of the curve.

The most benign pattern was *lumbar idiopathic scoliosis*, mainly of adolescent origin in girls. Severe angular deformity was seen in only 9%; and the clinical appearance was better than the radiograph suggested, the shoulders remaining level and the ribs unrotated. But late lumbar osteo-arthritis was the rule, all patients over 35 suffering pain.

The *primary thoracolumbar curve*, again mostly in adolescent girls, had its apex around T11–12. Severe deformity was now seen in a third of the cases and most patients had pain in adult life.

Thoracic idiopathic scoliosis was usually a right convexity with a variable apex between T6 and T10; two-thirds of the cases were severe, with marked rib rotation and shoulder asymmetry. The clinical appearance was worse than the radiograph, and an ugly deformity developed when the curve angle reached 70°. In this group the minimum final angulation was 50° and the maximum 150°. Half the cases of adolescent onset and 90% of those of juvenile onset developed severe curves.

Infantile idiopathic thoracic scoliosis was exceptional in being mostly in males and usually left-sided. It invariably became severe with growth and little could be done to prevent this.

Combined lumbar and thoracic scoliosis comprised two primary and two secondary curves—the only pattern with four instead of three curves in all. It was almost as benign as lumbar idiopathic scoliosis.

In treatment, operation was rarely required for lumbar and combined curves, but fusion was necessary for severe pain and deformity in thoracic cases. Mr. James had not operated on children under 10, but this might prove desirable in some cases.

In discussion, Dr. **Claude Lambert** (Chicago) said that such a classification was not always helpful in deciding treatment. He did not agree that lumbar curves never needed fusing, and operation would be indicated for severe progressive deformity even in children under 10. Mr. H. **Osmond-Clarke** (London) spoke of the possibility of dealing with scoliosis by controlling vertebral epiphyseal growth.

Sympathectomy for Causalgia

Mr. **Roland Barnes** (Glasgow) spoke on causalgia after injury to major peripheral nerves. The spontaneous severe persistent burning pain spread beyond the anatomical territory of the nerve concerned, was exacerbated by physical and emotional stimuli, and was accompanied by trophic changes. There were good reasons for not believing it to be mediated by afferent sympathetic pathways despite the relief afforded by sympathectomy; nor was there such persistent peripheral vasoconstriction as to support Lewis's suggestion that sympathectomy afforded relief by securing vasodilatation. Benefit must be due to interruption of efferent sympathetic fibres which stimulated the nerve-trunk through an artificial synapse or short-circuit at the site of injury, centrifugal impulses causing the peripheral vascular disturbance and centripetal ones the pain. Only this view explained the relief which might follow nerve-block distal to the lesion, and the rarity of causalgia after complete nerve section. In the arm, preganglionic section was effective and postganglionic operation the usual cause of relapse; lumbar sympathectomy was necessarily mainly preganglionic and the results satisfactory.

Mr. D. **Lloyd Griffiths** (Manchester) commented that causalgia did, rarely, occur after complete nerve section and in the phantom limb after amputation. Peripheral short-circuits must not be confused with true synapses. If sympathectomy did not relieve causalgia it was because the operation had not been adequate. But Dr. I. W. **Nachlas** (Baltimore) had found that the most extensive sympathectomy might fail to relieve. Not all cases were the same; the skin might be warm or cold, the bone texture normal or porotic.

Skeletal Tuberculosis Treated by Isoniazid

Dr. **David Bosworth** (New York) gave a breath-taking account of his experience in treating skeletal tuberculosis with *isoniazid (isonicotinic acid hydrazide* and its isopropyl derivative). It was premature to speak with assurance after only eight months' acquaintance with these substances; but it was already clear that they could produce remarkable subsidence of fever, and also euphoria, weight gain, and relief of pain (the last often independently of any improvement in the local condition). Sinuses of long duration which had resisted streptomycin might heal in a couple of weeks, sometimes even while the patient was dying of tuberculosis. Though the drugs were certainly bacteriostatic, these rapid results suggested a possible action on mesodermal tissue, as distinct from a suppression of infection; and this was borne out by the benefit they gave in collagen diseases like lupus erythematosus. But there was no evidence that they had a cortisone-like action; eosinophil and ketosteroid studies did not support this view, nor indeed the remarkable tendency to wound healing. Meningeal and cutaneous tuberculosis responded favourably; and a non-specific improvement in pain and function was even seen with rapidly growing malignant tumours. Toxic manifestations with the isopropyl derivative included hepatitis and central-nervous system disturbance ushered in by clonus. The margin of safety in dosage was small; it was best to begin with a dose of 4 mg. per kg. body-weight, increase this until clonus developed, and then come down to a safe level.

In the discussion of this paper there was a general feeling that these drugs supplemented, but did not replace, surgery. Dr. Bosworth had made it clear, however, that patients could be made safe for surgery at a much earlier date than hitherto.

Orthopædic Manifestations of Leukæmia

Mr. D. LLOYD GRIFFITHS (Manchester) gave an account of the orthopædic manifestations of leukæmia, which seemed to be on the increase in childhood, where it was now the sixth commonest cause of death. When the early stages were aleukæmic, and when the presenting lesion was osseous, diagnosis was difficult without sternal puncture. The leading symptom might be backache, sciatica, limp, or paraplegia; so cases might be treated for months as tuberculous spines or instances of Perthes's disease before the situation became clear. Destructive (not osteolytic) changes were seen as translucent metaphyseal zones, as focal erosions, or as diffuse painful infiltrations; these changes might reflect an attempt at compensatory extension of red marrow. Extensive bone infarction could occur and would not necessarily show in the radiographs, since the disease inhibited the healing processes which demarcated infarcted areas. Other changes included sheath-like subperiosteal ossification and, usually in the vertebral bodies, massive sclerosis. Apparent remissions with anti-folic-acid drugs or A.C.T.H. were only temporary.

Mr. JACKSON BURROWS (London) remarked that the disease was sometimes confused with senile osteoporosis when it affected the spines of old people; but osteoporosis did not involve the hands or pelvis, and such odd points should arouse enough suspicion to justify sternal puncture.

Special Articles

COST OF A RADIOLOGICAL SERVICE

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THE National Health Service has removed the patient's concern about the cost of his treatment. Indeed, as a contributor intent on getting his money's worth, he may take a pride in the number and variety of tests and examinations carried out upon him, and he is often more impressed by the complexities of his investigation and treatment than by the result achieved. He may retain for years a feeling of satisfaction and self-importance arising from a complete overhaul, during which hardly any avenue has been left unexplored by "scope" or contrast medium. We have reached the stage when the good specialist may be defined as the doctor who knows when to stop. Investigations are not only unnecessarily wasteful but (even more important) they use materials which in these days are hard to obtain, such as chemicals, X-ray film, drugs, and dressings.

Radiological investigations are the most expensive commonly carried out in hospitals, and it seemed to us that all who ask for a radiological examination to be made ought to know what it costs in money and materials. Accordingly we surveyed the expenditure in our department for the year, April 1, 1950, to March 31, 1951. We did not include the costs of buildings, heating, lighting, water-supply, painting, and other expenses directly concerned with the structure of the department. Expenditure on these items is of course essential, but it was difficult for us to estimate the sums involved, especially in a department that had undergone only minor structural changes for many years.

TABLE I—EXAMINATIONS MADE IN 1950

Examinations		*Special examinations*	
Chest	8911	Barium meals..	2545
Skeletal (general) ..	8148	„ enemas	479
Cranial	1432	„ swallows	127
Biliary tract	631	Cholecystograms	568
Alimentary tract ..	3760	Intravenous pyelograms ..	863
Urinary tract ..	1319	Retrograde „ ..	59
Female generative ..	805	Encephalograms and ventriculograms	127
Dental	927	Arteriograms	70
Miscellaneous ..	168	Contrast examinations of lungs, sinuses, and spine ..	87
	26,101	Miscellaneous	17
		Tomograms	175
			5117

THE WORK DONE

The department is a closed one, dealing only with patients from the different sections of an 800-bed regional hospital. In 1950, 25,000 patients were examined and the general scope of the work is set out in table I.

WHAT IT COST

Staff

The staff consists of a whole-time consultant radiologist, a senior registrar, and a registrar on the medical side; a superintendent radiographer, a senior radiographer, four junior radiographers, and a dark-room technician on the radiographic side; a clerical staff of four; two assistant nurses; two porters; and a cleaner. The pay-roll of these nineteen people comes to £11,760 (including superannuation and national insurance). About £100 was spent in arranging transport for radiographers on call after normal working hours.

Materials

During the year, approximately 58,000 films of various sizes were used, costing £6200. The cost of chemicals used in the dark-rooms was £373 for the year.

Contrast media were a fairly heavy item. Barium sulphate preparations for gastro-intestinal examinations cost £285. Diodone compound for pyelography, intracavitary radiography, salpingography, and arteriography cost £291. Iodised oil preparations, used almost entirely for bronchography, cost only £60. Pheniodol compounds for cholecystography cost £61. Smaller amounts of contrast media for other examinations cost £12.

Breakdowns

So far the expenditure was foreseeable. But in any radiological department mechanical breakdown of plant is fairly common.

Though the modern rotating anode tube may survive 30,000–40,000 exposures or even more, a breakdown, which means an expensive renewal, may be expected at any time after the lower figure has been passed, and there is always the possibility of it happening before. The makers usually guarantee a minimum of 20,000 exposures and will generally bear a proportion of the cost of replacement below this number.

X-ray rectifying valves are also expensive to renew, and in our experience valve failure in the four-valve X-ray set is 2–3 times more common than tube failure on the same set.

Mechanical breakdown is also not unusual. It can be reduced by regular inspection and overhaul but it cannot be avoided.

The cost of replacement and maintenance for the year, together with an additional rotating anode tube, was £1250.

Cassettes and intensifying screens in continuous use must be replaced, and additions are necessary where the work is increasing. These items accounted for £269 in the year. The cost of sundry items, including replacements of lead protective gloves, aprons, and film-markers, was £36.

Clerical and Nursing Section

Expenditure on the clerical side of the department was considerable. Additional filing accommodation for films cost £227, record-card filing accommodation £48, a lantern-slide cabinet £12 10*s*., and sundry other items, including viewing-boxes, brought the total cost of equipment in the offices to £392. Stationery, including record books and film envelopes, cost £413.

Syringes, instruments and similar expenses on the nursing side were estimated at £200.

Depreciation

X-ray equipment, like all complex electrical devices, has a comparatively short life. This can be prolonged by maintenance up to a point, but after some years it becomes increasingly unserviceable and progressively outdated in design and capacity. For the purposes of depreciation an arbitrary life of ten years was allowed to the X-ray sets themselves, and yearly depreciation calculated on the basis of a tenth of the estimated value. The figure arrived at was £1750 for the whole department.

The Total

The total cost of £23,453 incurred by the department in the year is summarised in table II.

TABLE II—ANALYSIS OF COST OF DEPARTMENT

Salaries and wages	£11,760
Transport cost	100
Cost of films	6200
„ „ chemicals	373
„ „ contrast media	709
Maintenance	1250
Cost of cassettes and screens	269
Sundry protective items	36
Clerical section	806
Nursing	200
Depreciation	1750
	£23,453

The department did bring a little revenue to the hospital. Old X-ray films sold at £61. The silver-recovery plant in the fixing tank brought in £26. The credit total was £87.

WHAT EACH EXAMINATION COSTS

The net cost of the department was thus about £23,400 for the year, and this did not include any allowance for essential services or structure.

If the cost of films, chemicals, and drugs (£7282) is deducted from the total, the remainder (£16,118) represents the basic cost of the department, an average of 13*s*. per patient. To obtain the cost of an examination, we have added to this basic cost the cost of the average amount of material used in the examination. Thus, a barium-meal examination that may need 3 sq. ft. of film costs 6*s*. 6*d*. for film, 2*s*. for contrast media, and a few pence for chemicals, plus the basic cost of 13*s*.—in all about 22*s*. On similar accounting a barium enema costs about 23*s*. 6*d*. An intravenous pyelogram costs 12*s*. for film, 4*s*. for an ampoule of contrast, a few pence for chemicals and the basic cost of 13*s*. making a total of about 29*s*. 6*d*. A chest film or a plain film of the abdomen costs 17*s*., a bronchogram about 30*s*., and a cerebral arteriogram (where perhaps six films of each side may be necessary and four ampoules of contrast media) about 50*s*. The cost of various examinations is given in table III.

TABLE III—COST OF VARIOUS EXAMINATIONS

Examination	*Cost*
Plain X ray of chest or abdomen	17*s*.
Postero-anterior and lateral chest	21*s*.
Bronchogram of both lungs	30*s*.
Intravenous pyelogram	29*s*. 6*d*.
Retrograde pyelogram	24*s*.
Barium meal	22*s*.
Barium enema	23*s*. 6*d*.
[illegible]	24*s*. 6*d*.
[illegible]	50*s*.
[illegible] spine and pelvis	21*s*.
„ „ whole spine	25*s*.
Dental radiograph	14*s*. 6*d*.

CONCLUSION

We have not tried to do more than get an idea of the expense of the investigations ordered so often in hospital. This will clearly vary a good deal from hospital to hospital. All that we can claim is that our estimates are those of a department where economy is practised as far as is consistent with a satisfactory standard of work. We do not suggest that the cost of an examination should deter a clinician from requesting it. But he ought always to consider whether it is reasonably likely to give him information which is of value and which cannot be obtained by less expensive means.

We wish to thank Mr. J. Collins, assistant secretary, The Central Middlesex Hospital, for making the necessary accounts readily available to us, and Dr. Horace Joules, the medical director, for his criticism and advice.

COST OF AMBULANCE SERVICES

THE cost of running ambulance services under the National Health Service in the year ended March 31, 1951, is shown in a return [1] published last week.

Over the whole of England and Wales the average cost per vehicle mile was 1*s*. 8*d*., covering direct, agency, and supplementary services but not rail; and the cost per 1000 population was £169. The ambulance services of local authorities and their agents comprised, at the end of the twelve months, 4149 ambulances and cars and 10,986 operational staff. In addition, a large number of private cars were providing voluntary reinforcements through the hospital car service, and a number of patients travelled by rail under arrangements made by local health authorities. During the year the ambulance services ran more than 89 million miles and carried more than 9 million patients, compared with 79 million miles and 7 million patients in 1949.

The total cost of the ambulance services in the year was £7,411,502, of which £5,849,995 was the cost of directly provided services and £781,425 that of agency services. Other services, such as the hospital car service, cost £762,865, and rail journeys £17,217. An analysis of the expenditure on the directly provided services shows that of the total cost 59·7% represented operational staff, 19·5% fuelling and maintenance of vehicles, 5·6% provision of vehicles, 2·9% maintenance of buildings, furniture, &c., 1·2% provision of land and buildings, and 11·1% other expenditure, including administrative expenses.

PROTECTION OF THE WORKER

THE International Labour Conference, representing the governments, employers, and workers of some sixty countries, decided at its meeting in Geneva last month to pave the way for the possible adoption next year of international regulations to protect the health of workers in places of employment. The decision entails chiefly measures for combating occupational diseases, by early notification to labour or factory inspectors and by various preventive methods. Among other things, it was suggested that medical examination of workers employed in occupations involving special risks to

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1. National Health Service: Ambulance Services Costing Return 1950–51. H.M. Stationery Office. Pp. 47. 4*s*.

health—either examinations carried out before or shortly after entry into employment, or periodical examinations, or both—should have a place in the proposed international regulations, but it should be left to national laws to define the classes of workers to be medically examined.

Meanwhile, the conference substituted a revised Maternity Protection Convention for that which it adopted in 1919. The new convention is substantially on the lines of the old, in that it maintains the right of working women to twelve weeks' leave before and after childbirth, to the receipt of cash and medical benefits during that period, and to immunity from dismissal from employment while on maternity leave. The main changes from the 1919 convention are: (1) the inclusion of agricultural and domestic workers; (2) the requirement that the cash benefit shall be not less than two-thirds of the woman's previous earnings; and (3) the relaxing of the previous stipulation that six weeks of the leave should be taken before confinement and six weeks after. The antenatal leave may now be as short or as long as necessary, provided that at least six weeks' postnatal leave is allowed.

The convention is supplemented by a recommendation proposing that the total leave period should be fourteen weeks, and containing a number of suggestions relating to facilities for nursing mothers and infants and to the protection of employed women during the maternity period against overstrain or work that might be harmful to their health or that of their children. The recommendation also amplifies the provisions of the convention concerning benefits. It proposes that these should include wherever practicable: general-practitioner and specialist outpatient and inpatient care, including domiciliary visiting; dental care; care given by qualified midwives and other maternity services at home or in hospital; nursing care at home or in hospitals or other medical institutions; and maintenance in hospitals or other medical institutions.

The British Government delegates did not vote either for or against the convention, taking the view that in this country the protection it embodies is already well provided under arrangements based partly on law and partly on practice, and that there would be serious disadvantages in substituting rigid legislation on the lines of the convention for the present elastic but adequate system of protection.

ESTIMATES FOR GENERAL PRACTITIONERS' REMUNERATION

THE Supplementary Estimates include an additional £35,456,000 for the remuneration of general practitioners under the terms of the Danckwerts award; and in a memorandum[1] the Government says that this total is compounded as follows:

Year	*£000*
1948–49 (arrears)	4275
1949–50 (arrears)	4805
1950–51 (arrears)	9359
1951–52 (arrears)	9963
1952–53	10,743
Gross total	39,145
Less estimated saving* on estimates for 1952–53.. ..	457
Less appropriations in aid (employers' and employees' superannuation contributions)	3232
Net total	35,456

*Provision made in current year's estimates for certain payments from the Inducement Fund which will not now be made.

The central pool has been calculated on the basis of a betterment factor of 85% in the years 1948–50, and of 100% in the years 1951–53; and allowance has been made for practice expenses by applying to gross remuneration a percentage of 36·5% in the years 1948–50, and of 38·7% in the years 1951–53.

The memorandum also includes the following table showing estimates, in the light of the figures accepted by Mr. Justice Danckwerts, of the total gross receipts of general practitioners in the National Health Service (estimates of net receipts in parentheses):

Year	1948–49 (from July 5, 1948)	1949–50	1950–51	1951–52	1952–53
Number of doctors*	18,812	18,969	19,227	19,565	19,850 (estimated)
	£000	*£000*	*£000*	*£000*	*£000*
Central Pool	30,396	41,268	41,533	41,433	53,482
Other receipts under Part IV of the National Health Service Act, 1946, and the National Health Service (Scotland) Act, 1947	2317	4920	5158	5384	
Receipts under Part II of the Acts	1009	1364	1100	1100	
Receipts under Part III of the Acts	268	362	400	400	
Receipts from other Government Departments	487	659	700	800	
Receipts from private practice	1479	2000	2000	2000	
Exchequer superannuation contributions ..	1609	2224	2357	2365	
Total amount under pre-award arrangements. (Net income, after deduction of practice expenses, in parentheses)	37,565 (24,441)	52,797 (34,338)	53,248 (33,553)	53,482 (33,700)	53,482 (33,700)
Additional amount due under award.. ..	4275	4805	9359	9963	10,743
Grand Total† (Net income, after deduction of practice expenses, in parentheses)	41,840 (28,716)	57,602 (39,143)	62,607 (42,912)	63,445 (43,663)	64,225 (44,443)

*Does not include 850 to 1000 doctors providing only limited services.
†Includes £120,000 to £200,000 for doctors providing only limited services.

Part IV receipts include: training of assistants, maternity medical service, ophthalmic medical practitioner fees, dispensing fees, inducement payments, and mileage (part).
Part II receipts include: part-time posts in hospitals, and payments to general practitioners in cottage or general-practitioner hospitals.
Part III receipts include: sessions at local-authority clinics, midwife aid calls, and vaccination and immunisation payments.
Receipts from other Government Departments cover fees for serving on medical boards.

A.C.T.H. AND CORTISONE IN RHEUMATIC FEVER

LAST year the American Heart Association and the Medical Research Council began a joint investigation into the relative value of A.C.T.H., cortisone, and aspirin in the treatment of rheumatic fever; 13 centres in the U.S.A., Canada, and Great Britain are participating. Prof. A. Bradford Hill and Dr. E. G. L. Bywaters represented the British centres at a meeting in Chicago last month of a panel of investigators engaged on this work. Dr. David D. Rutstein (Boston), moderator of the panel, later summarised the preliminary findings in the following statement:

> "A group of investigators in the United Kingdom, Canada, and the United States initiated in January, 1951, a coöperative study on the relative value of A.C.T.H., cortisone, and salicylates in the treatment of rheumatic fever and the prevention of rheumatic heart-disease. The

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[1] Memorandum on the Supplementary Estimates for the additional sums to be provided for the remuneration of general medical practitioners in the National Health Service. Cmd. 8599. H.M. Stationery Office. Pp. 6. 4d.

plan of study provides for uniform criteria for the diagnosis of rheumatic fever and for the degree of rheumatic activity required for the admission to the study, the random allocation of patients to the three treatment groups, a defined dosage schedule of the drugs for a fixed period of time, a specified period of observation following treatment, and a long-term follow-up schedule. It also lays down precisely the frequency and type of clinical and laboratory observations to be carried out on each patient.

"To date, in all three countries, 658 cases have been admitted to the study and the analysis of rather less than half of these is the basis of the preliminary report. These cases were analysed for changes in those symptoms, signs, and laboratory observations usually considered important in evaluating the course of acute rheumatic fever. In the type of cases admitted to the trial and with the régime of treatment laid down, it appears that individual symptoms, signs, or laboratory observations may have been affected more favourably by one or another of these three drugs, but no consistent pattern is evident. In short, no firm conclusions can at present be drawn concerning the drug most effective in the control of the acute illness. The cases have not been under observation sufficiently long to provide data on the prevention of rheumatic heart-disease.

"Admission of new cases to the study will be brought to an end later this year. It is anticipated that a total of 750 cases will be available in all three countries for complete and detailed analysis of the effects of the drugs on the acute course of the disease and later, after adequate follow up, on the prevention of rheumatic heart-disease."

Parliament

Charges in the Health Service

IN the House of Commons on July 2, a general debate took place on the new regulations under the National Health Service Acts imposing or increasing charges for dental treatment, drugs and appliances, pay-bed accommodation in hospital, and hospital drugs and appliances.

Mr. HECTOR MCNEIL thought that the practitioner, to save his patient from being charged, would sometimes put more than one item on the prescription form and prescribe quantities larger than previously. Thus there might be no appreciable net saving. He was told that some outpatient departments were already not very zealous about the collection of the shillings. If such departments were concerned solely with their legitimate task of diagnosing, prescribing, advising, and dispensing, there would not be any time for this nonsense. Mr. ARTHUR BLENKINSOP said it was a tragedy that so many professional men today, particularly dispensing doctors, were obliged to spend so much more time on administrative tasks. Through these regulations they were being made into tax-gatherers.

Mr. H. N. LINSTEAD was surprised that this quite substantial administrative provision had been brought in with so much smoothness. Speaking as one who had daily contact with pharmacists, he believed that the new arrangements would soon settle down into a normal part of the health service.

Mr. JOHN BAIRD spoke of ill-feeling between the patient and the practitioner caused by the charges. According to the Minister's estimates the prescription charges were to bring in £13,000,000 while the dental charges might bring in only £7,000,000. But Mr. Baird forecast that less would be received from the prescription charges and more from the dental charges. Because of the dental charges people were not receiving treatment, and there was a great deterioration in the dental health of the nation.

Mr. IAIN MACLEOD, Minister of Health, said that from information received about the first month's working of the scheme five general conclusions had been reached about the hospital charges for drugs and appliances: (1) there had been no noticeable decline in the number of prescriptions dispensed; (2) there had been no variation in the quantities of drugs in prescriptions or in repeat prescriptions; (3) there had been no falling off in the number of outpatients; (4) there had been no noticeable increase in queueing in outpatient departments; and (5) generally no difficulties had been caused by the introduction of charges. There had been an extremely substantial fall in the estimates for dental treatment; a substantial proportion had been for people who could claim exemption. As there were not enough resources or dentists to meet all requirements, it followed that those most in need were getting treatment. The number of dentists in the school dental service had increased in the past six months from 716 to 793 and the trend was continuing. This meant that the priority classes would be better looked after than ever. In general practice during the first month—admittedly a month of fine weather with many people on holiday—there had been a 15% drop in prescriptions. Replies from ten regions showed that there had been no substantial change in the quantities of drugs prescribed on each prescription.

Mr. HILARY MARQUAND said that the Minister should not persuade himself that all was going well. The charges were felt severely in working-class areas, and the number of complaints would increase with the onset of winter.

The motion to annul the regulations relating to charges for drugs and appliances in England and Wales was negatived by 254 votes to 235.

QUESTION TIME

Limitations of the Danckwerts Award

Replying to Mr. J. S-W. ARBUTHNOT, Mr. R. A. BUTLER, Chancellor of the Exchequer, said that he wished to make it clear that the terms of reference of Mr. Justice Danckwerts's award were confined to the remuneration of general practitioners in the National Health Service and his award had no wider application. In accepting the results of the adjudication, which was of an exceptional nature, the Government had by no means adopted the view that similar adjustments in other fields should follow. In their view there was no justification for any assumption that the appropriate standard of remuneration for the professional classes was a rate of 100% above that in force in 1939. They considered that remuneration should be determined in the light of all relevant circumstances.

Industrial Reablement Units

Mr. HECTOR HUGHES asked the Minister of Labour if he was aware that the existing provision for the industrial rehabilitation and training of injured and handicapped persons was insufficient; that this was unjust to those persons and an economic loss to the community; and if he would set up a committee or commission to inquire into the subject.—Sir WALTER MONCKTON replied: There are now fourteen industrial rehabilitation units administered by my Department, including the residential centre at Egham. Over 30,000 people have attended them and 1373 are at present undergoing courses. As to training, the Government training centres are all open to disabled persons, and half of the courses are provided wholly or mainly for them. More than half those in training are disabled, and waiting-lists are now very short.

Dispensing Doctors and Prescription Charge

Replying to Dr. A. D. D. BROUGHTON, Mr. MACLEOD said that at the request of the British Medical Association it had been arranged that in the case of dispensing doctors, at the option of the patient, the prescription charge might be paid by postage stamp. The practitioner would convert any other payments to stamps and surrender them monthly to the executive council. The value of the stamps would be transferred from Post Office funds to Ministry of Health vote.

Crimes of Violence

In answer to a question Sir DAVID MAXWELL FYFFE, the Home Secretary, said that the numbers of persons found guilty in England and Wales of robbery, rape, and such offences of violence against the person as murder, attempted murder, manslaughter, wounding, and indictable assaults were 2717 in 1947 and 4274 in 1951.

Home Help Service

In answer to a question Mr. MACLEOD said that during 1951 166,759 people were assisted by the Home Help Service. He did not think that local health authorities required any special financial inducement to develop this service to the maximum extent practicable.

In England Now

A Running Commentary by Peripatetic Correspondents

GOING back to school after 30 years of general practice is an astonishing, stimulating, and humiliating experience. To many good G.P.s who have "kept up with the journals" it would be, no doubt, merely a matter of refreshing the memory; but to those of us who have lost touch with the hospital outlook a refresher course is something quite different. It is true that we can take up the story of, say, acute rheumatism or chronic nephritis and follow, with reasonable understanding, what has been happening in the meantime: but when it comes to electrocardiography, radiology, and biochemistry we are apt to find ourselves floundering in a strange, new world. Even the medical jargon of our youth has changed almost beyond recognition, and there has been an intense proliferation of syndromes. Morale is a little restored in the post-mortem room, but perhaps more so at the bedside, where, despite an abysmal ignorance of academic medicine, we have at least learnt by experience that common things are common. Here we contrive to keep our ends up with our bright young classmates and even to some extent with our brilliant and polite young tutors. Here also we sometimes make the right diagnosis, albeit for quite the wrong reasons, not scientifically but by employing that more or less inspired guesswork which we learnt from our pastors and masters in the 1920s—and nowadays this simply will not do.

* * *

"What's Australia like?" we asked our new orthopædic resident. He looked up from his macaroni cheese: his eye fell on the semolina pudding waiting on the hotplate. "A lot of protein," he said wistfully.

Only a few days later I came across him on the balcony dilating on the hard lot of our feathered friends to a couple of soft-hearted female patients. "A long winter," he said, "A late spring." Tears filled their eyes; they promised regular donations of crusts and crumbs to the absurdly plump birds that flock round their beds at mealtimes.

I wish he'd never let me share his guilty secret. How can I face the good ladies, or the old men on the balcony below, also pledged to sacrifice the last morsels of their every meal? Replete with roast pigeon, tortured by remorse, I follow him from bed to bed, urging them to keep up the good work: and I find it as much as I can do not to glance up to the roof to see if the traps we set each night are keeping up the good work too. "The trouble with you English," declares my resourceful Australian colleague, "is that you don't exploit your natural resources. There's a lot of protein here, too."

* * *

In the recently published work of Rhine of Duke University on parapsychological phenomena there is a notable omission which has not escaped the attention of Continental workers in the same field. Bumpf (*Med. Z. Kotentleer.*) describes the phenomenon of the psychological induction of electric currents by apparently unrelated and non-psychological stimuli. He takes as the field for his observations the house telephone, and his first note is that the best results are achieved within narrow time-limits—in this series of observations between 8.30 and 9 in the morning. Greips, in a short but brilliant essay entitled Hindernisse beim Durchfall (*Klin. Wschr. Stuhlsitzens*) comes to almost identical conclusions.

Put simply, the gist of the observations made by these and other workers is that the induced currents in the telephone circuit are *directly proportional* to the intensity of the psychosomatic stimulus. Thus if on the one hand the psychical urge (*Drang*) of the Stimulus Supplying Subject (S.S.S.) is feeble or lacking, results will be poor. And if, on the other hand, the somatic desiderata—which form a group including posture, clothing, &c.—are not complied with, success need not be looked for. The standard of success as accepted by all workers is the induction of a current of such strength as to result in prolonged ringing of the bell. A notable observation is that a feigned *Drang* and simulated physical dispositions of posture, clothing, &c., such as are liable to occur in laboratory experiments, inevitably fail. This leads to the conclusion that all work must as it were be in vivo, and not in vitro.

Some observers lay stress on the posture of the S.S.S., who they insist must be seated. No induction takes place while the standing position is maintained. For the disposition of the clothing which he describes as necessary, Bumpf has coined the rather clumsy term *Hosenuntergang*, which perhaps unnecessarily complicates the terminology, since the quite satisfactory description of the French workers *culotte en bas* could scarcely be bettered. Be that as it may, to Bumpf is due the credit for the primary observation that under the above conditions current induction invariably follows of such strength that the telephone bell rings continuously, ceasing only when the S.S.S. disrupts the conditions—i.e., changes the sitting posture for another, and alters the clothing disposition.

Two further observations also lie to his credit. The first is that current induction is stronger, and bell-ringing louder, if at the same time there is an *added auditory stimulus*, which he this time appropriately names *Wassersplusch und Papiergeräusch*. The second is that the approach of the S.S.S. to the bell breaks the circuit and the bell stops ringing, starting again however as soon as the other conditions—distance, posture, clothing, &c.—are reimposed.

These observations are challenged by several French workers who have been unable to get parallel results, and maintain that the German observations are vitiated by a factor which they term *blague*. The Germans retort that the French failure to obtain results is simply due to the fact that the necessary stimuli, especially *Wassersplusch und Papiergeräusch*, are rarely to be found in France.

Research continues and new discoveries are claimed from many quarters, but up to the present there is no doubt that Bumpf has written the most.

* * *

Unrecorded Minute from Dublin

Mover of Motion: I ask the chairman's advice. May I divide this motion into two parts?

Chairman (looking at clock): I think the two parts could reasonably be taken as a reference to council.

M. of M. (dourly): I did not ask that. May I move it in two parts?

C. (cautiously now): Well, I think it would be best taken as a whole.

M. of M. (triumphantly): If you had said that it could be divided, I would have asked permission to withdraw the first part.

C. (quickly to meeting): Is permission given to withdraw the first part.

M. of M. (even more quickly): But I have not asked permission because you would not let me divide it.

C. (desperately and dimly through the laughter): Do you ask permission to withdraw the first part?

M. of M.: I cannot because I have not been allowed to divide it.

C. (seeing the end in sight): Do you ask permission to divide the motion?

M. of M. (quietly): No.

Motion hastily carried unanimously in toto.

* * *

Agricultural scientists in Ohio have discovered that poultry and pigs gain weight more rapidly on feeding-stuffs enlivened with a small amount of a detergent akin to those soapless soaps that precipitate a latent exophthalmos in the housewives on our hoardings. The mode of action of the detergent, when given by mouth, is not clear: it may inhibit the growth of harmful bacteria in the gut, or, by ensuring a thorough "wetting" of the food by the digestive juices, it may promote absorption. The amount used is apparently not enough to whip the food-trough into a lather; nor does it make the animals foam at the mouth; so this discovery seems to have nothing to do with Inner Cleanliness.

Letters to the Editor

SPORT AND MEDICINE

SIR,—A British Association of Medicine and Sport has recently been formed. Its aims are to promote the study and investigation of the medical and scientific aspects of sport in all its branches. Membership will be open to medical representatives nominated by all national sporting bodies and to any interested medical men and women with a qualification registrable in the United Kingdom. It is hoped that this association will attract a large membership of doctors. Those who are interested are invited to write for particulars to the Hon. Secretary, British Association of Medicine and Sport, c/o British Olympic Association, 71, St. George's Square, London, S.W.1.

ADOLPHE ABRAHAMS
President.
ARTHUR PORRITT
Chairman.

TREATMENT OF URÆMIA IN CHOLERA

SIR,—It is well known that anuria and azotæmia are constant accompaniments of the cholera syndrome. Next only to circulatory failure, uræmia is the most important fatal complication of cholera. In the series described by Rogers,[1] uræmia was responsible for death in 3·5% of all cases (20% of all deaths), even after he had instituted the standard treatment by transfusion of alkalis.

In Lahiri's[2] series the proportion of deaths from uræmia varied from 22·7 to 50% of the fatalities, according to whether sulpha drugs had been withheld or used in treatment; these drugs definitely aggravated kidney failure in his series.

The causes of uræmia in cholera are partly prerenal and partly renal. The underlying causative factors of prerenal uræmia are shock and the great loss of chlorides, the former resulting in the pronounced diminution of blood-flow and filtration pressure through the kidney. The important thing to be noted is that, in cholera, the suppression of urine continues despite the restoration of the blood-volume and blood-pressure, and of the specific gravity of the blood by means of transfusions.

Besides these circulatory factors, the other underlying causes of this somewhat specific type of kidney failure peculiar to cholera must be sought in the changes in the structure and function of the nephron. Some of these changes have been described in detail, or are suggested as the causative factor, by Chatterjee.[3] Most of those changes are reversible; so if the patient survives the uræmia, he makes a complete recovery and never suffers from subsequent kidney failure or its sequelæ.

The structural changes in the nephron consist mainly in a peculiar swelling and "fibrillation" of the basement membrane of the malpighian corpuscle and of the tubular epithelium. There is also acute capillary dilatation of the medullary region.

This reversible acute kidney failure of cholera is non-inflammatory and non-degenerative. There is little evidence of any toxic degeneration of the tubules, or for the matter of that of any so-called "cholera toxin." The kidney lesions heal spontaneously, and chronic nephritis or nephrosis never ensues.

This extremely acute but completely reversible kidney failure led me in last year's cholera epidemic to use antihistamine drugs and ascorbic acid in those cases where restoration of the specific gravity of the blood was not followed by urination. By this means the proportion of deaths from uræmia in cholera was reduced to less than half the lowest figure of Rogers[1] and Lahiri.[2] A very large number of last year's patients were admitted more or less moribund, as a large proportion were refugees from Pakistan; yet uræmic deaths amounted to 9%, in contrast to the 20% reported by Rogers and the 22·7–50% described by Lahiri.

Encouraged by these results we have repeated and modified this treatment in the 1952 epidemic, and to our surprise there has not been a single uræmic death in our cholera cases this year, during which we have so far treated 740 cases. In every case of suppression of urine we give intravenous injections of ascorbic acid 500 mg. twice daily. This starts urination in 70% of cases. In those cases where urination is not initiated by this treatment we inject an anti-histamine compound ('Antistin' 0·1 g. in 2 ml.) intramuscularly in the kidney region. We have found that injection in this way is more efficacious than administration intravenously or by any other method. We are unable to explain this difference. It is rather a surprise to see the onset of urination in cases which we would formerly have regarded as hopeless.

The treatment of circulatory shock and collapse in cholera is purposely not considered here; nor are the great advances in our knowledge of the electrolytic changes in the plasma and body-fluids in shock due to various causes, including cholera.[4] The treatment of the kidney disorder is supplemental to the treatment of circulatory shock and collapse.

I would again repeat that the administration of ascorbic acid in rather large doses, along with an antihistamine compound in the more difficult cases, after restoration of blood-volume, has eliminated anuria and uræmia in cases admitted to our cholera ward in this year's epidemic.

HEMENDRA NATH CHATTERJEE.

Chittaranjan Hospital,
Calcutta National Medical Institute,
Entally, Calcutta, India.

PERIODIC DISORDERS OF CHILDREN

SIR,—There is a great deal to delight the psychiatrist in Dr. Franklin's wise and admirable paper (June 28).

There is a tendency to diagnose a neurotic disturbance in the child by negative physical, rather than by positive psychiatric, findings. It is evident that far too much emphasis is placed on the presenting physical symptom. A careful psychiatric history will always reveal other positive symptoms of a psychiatric disturbance, often masked by the parents' over-concern with the alarming and often socially inconvenient presenting symptom. Furthermore, one cannot relate the severity of the psychiatric disturbance to that of the physical symptoms. Acute, dramatic, physical symptoms are often the most modifiable. A diagnosis of a psychiatric disturbance can be made at an early stage, but the mechanisms of the psychopathology will usually only be evident after an exhaustive examination of the parents, child, and environment. A neurotic child invariably denotes a neurotic parent.

Dr. Franklin makes it plain that bad social conditions result from faulty emotional attitudes and that the social conditions do not in themselves make for emotional problems in the child, as these are dependent on the same faulty emotional attitudes. But I do not agree that explanation is important in treatment. My experience is that explanation is futile, because the faulty parental emotional state does not allow of its acceptance. Furthermore, experience shows how disappointing is the response of the child's condition to mere instruction of the parents in the daily management of the child. The basic faulty emotional attitude, responsible for the bad management, remains untouched by a mechanical change of technique. The preoccupation with the presenting physical symptoms inevitably leads to the offering of symptomatic relief and the use of suggestion. No doubt it is this that leads Dr. Franklin to suggest magic and ritual as the best line of treatment. The clearing up of a symptom by suggestion merely leads to the substitution of another; and, if the new symptom is socially less undesirable, this carries the danger of the discontinuance of the parents' attendance and the ignoring of the underlying neurosis, both in the child and the parents. One should, correctly, ask why a parent's neurosis becomes canalised in the child and why the parent is neurotic at all. These problems are indivisible; for removing the child from the parent, whilst it may cure the child, invites the parent to exhibit the neurosis in another channel—perhaps in another child.

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[1] Rogers, L. Bowel Diseases in the Tropics. London, 1921; p. 117.

[2] Lahiri, S. *Brit. med. J.* 1951, i, 500.

[3] Chatterjee, H. N. *Trans. R. Soc. trop. Med. Hyg.* 1941, 34, 337.

[4] Chatterjee, H. N. *Ibid*, p. 379; *Ibid*, 1946, 39, 321.

It matters little who takes the psychiatric history, or who assesses the psychiatric symptoms; but it is clear that the child psychiatrist, or, better, family psychiatrist, should explore the psychopathology and apply the psychotherapy. The greater part of his time will be spent with the parents.

Department of Child Psychiatry,
Ipswich General Hospital.
J. G. HOWELLS.

"ISONIAZID"

SIR,—Anyone who in the last few months has had anything to do with the new drugs isonicotinic acid hydrazide and its derivatives would welcome a word which did not take quite so long to say or write. A portmanteau word such as isoniazid, used in the June number of the *American Review of Tuberculosis* and in your excellent article of June 28, is at first sight attractive. But if we attempt to cram a portmanteau too full it may burst; and when we coin new words we should see that, like portmanteaux, they perform the function for which they were designed and do not become nuisances instead. I suggest that the use of isoniazid (or isoniazide) as a *generic* name may be not only confusing but dangerous too. We know already of several other related substances of similar activity against tubercle bacilli, and no doubt we shall hear of many more. The ones already known differ widely in toxicity and in effective dose. If we are to use abbreviations we must know precisely which drug we are abbreviating, and we should be quite clear whether the word isoniazid (if that is to be the word) refers to isonicotinic acid hydrazide (isonicotinyl hydrazine, I.N.H., I.N.A.H.) itself or is intended to cover the whole group of related hydrazides.

Department of Bacteriology,
Medical School,
Guy's Hospital, London, S.E.1.
ROBERT KNOX.

HOSPITAL ADMINISTRATION

SIR,—It surprises me that Dr. Stephen Taylor (July 5) finds administration "often tedious, repetitive, and dull." It is hard work, often difficult, and sometimes exasperating; but tedium is the child of idleness, not of work. It is only superficially repetitive. Just as no two cases of pneumonia are exactly alike, no two administrative situations are exactly alike, and it is in the adjustment of action to unique cases that the art of administration resides. And any job that deals with people is never dull, but lively, varied, and fascinating as humanity itself. Such at least is my own experience.

It surprises me even more that he prefers lay to medical administrators. When I first undertook administration I was impressed by the number of medical decisions I had to take, and at the range of medical knowledge I needed to help me to make them wisely. The lay administrator can get medical advice if he asks for it, but he may not always recognise the medical nature of his problem. He may, for example, decide about flooring for wards without realising that he is influencing the problem of cross-infection. One cannot have too much medical knowledge if one is to administer a hospital. As for personal relations, if my colleagues think meanly of my clinical skill I can bear it cheerfully (always reserving my own opinion on that question) provided they realise that I am trying as hard as they are to do my best for the patients. In my experience the only doctors who resent medical knowledge in an administrator are those who like him to accept a view simply because they have pronounced it, and are unprepared to support it with reasons; but there are not many like that.

Giggleswick, Settle, Yorks.
D. P. LAMBERT.

CORTISONE IN ADRENAL VIRILISM

SIR,—The valuable preliminary communication of Dr. Bishop and his colleagues in your issue of June 28 is obviously of great interest. As the reported demonstration of the inhibition of pituitary-adrenocortical activity is limited to one patient, you may consider it worth while to add this brief record of another case of adrenogenital syndrome, commencing at puberty, under my care some months ago, in which there was a similar response to cortisone.

The patient was a female of 18 years who, at the age of 14, began to menstruate scantily and at long and irregular intervals, and developed hair on the face and acne on the face and back. She weighed 112 lb. and was 60 in. in height. On examination she had a narrow pelvis, small flat breasts with small nipples, and hair on the sides of the face, upper lip, and cheeks, on the buttocks, in the anal and vulval regions, and on the arms and legs. Her back was covered with severe and extensive acne. The clitoris was grossly enlarged. She had been treated with ethinyl œstradiol without obvious effect. The 24-hourly urinary values for 17-ketosteroids at intervals of about 3 days before the administration of cortisone were 35, 32, 22, 35 and 23 mg.; and corresponding values during the injection of 100 mg. of cortisone were 7·6, 5·4, 6·4, and 5·3 mg.—a clear-cut and persistent reduction.

The patient was unwilling to remain in hospital to permit the study of 17-ketosteroids after leaving off the cortisone. A return to pre-cortisone values after some weeks might be anticipated. There was no obvious effect on the hirsutism during the three weeks of administration, but the patient was delighted with the almost complete disappearance of the generalised acne, which had previously been refractory to all forms of therapy. The effects of longer-term therapy will await larger supplies of cortisone for such kind of work. Enlargement of the breasts, more regular menstruation, and some amelioration of the hirsutism would not be improbable.

The history and investigations are in keeping with adrenal hyperplasia and not neoplasm. There would seem little doubt that cortisone is effective in inhibiting pituitary-adrenocortical activity in some patients.

The hormone assays were carried out by Dr. E. Kawerau at St. Mary's Hospital and by Mrs. A. M. Robinson at St. Bartholomew's Hospital. The cortisone was allocated by the Medical Research Council.

London, W.1.
S. LEONARD SIMPSON.

BRITISH STUDENT TUBERCULOSIS FOUNDATION

SIR,—This foundation was formed last year with the aim of opening in this country a 100-bedded rehabilitation centre, where students convalescing from tuberculosis can be fitted for return to college by courses of study including lectures, set reading and essay writing, and tutorials. In a little over eighteen months British students have collected some £20,000 towards this.

This April the North-West Metropolitan Regional Hospital Board agreed to open a small experimental unit for men at Pinewood Hospital in Berkshire.

This centre is expected to be ready in September; it has accommodation for 16 student patients in one self-contained ward. This is to be divided into three parts: a dining-room where all meals will be taken, a lounge, and a bed-ward where students can read in silence during rest periods. The medical care and supervision of the patients will be the responsibility of the physician superintending the hospital. The academic side will be the responsibility of the foundation. Those admitted will have to be recovering satisfactorily; they must be sputum-negative. As only a minimum of nursing staff will be available, students must be fit enough to do a few light duties for themselves, such as making their beds. They must be able to take all meals up and stay up and dressed for some four hours a day at least. Patients will be expected to abide by the rules of the sanatorium during their three or four months' stay there.

The foundation is to be responsible for occupational treatment and is now making arrangements for university teachers, principally from the University of London, to visit the centre regularly to give lectures and supervise individual courses of study.

Entry is open to all full-time male students from any part of Great Britain, whatever their race, colour, or creed. It is expected that applications will greatly exceed the number of places available, and it is to be understood that selection of medically suitable candidates rests finally with the regional hospital board; however, the board has agreed to accept the advice of the foundation as to academically suitable applicants as far as possible. The foundation will be pleased to receive, at the earliest opportunity, applications from any full-time student who would like to come to Pinewood and who expects to be fit to do so by the autumn, or at any time throughout the coming year. Applicants need consider themselves under no obligation to come if or when they are offered a place. It is important that application should be made early—any time up to six months ahead of the expected date of fitness—so that delays in admission and empty places can be avoided. The foundation will keep in touch with applicants to confirm their medical progress.

Such is our scheme. I would be grateful if any doctor in touch with, or in charge of, a tuberculous student who might wish to avail himself of these facilities, would either give the student the address of this foundation or communicate with us. Application forms and detailed information may be obtained from this office on request.

British Student Tuberculosis Foundation, 6, Gordon Square, London, W.C.1.

NICOLAS MALLESON
Hon. Secretary.

PROVISION FOR THE MENTALLY DEFECTIVE

SIR,—I am disturbed by certain statements in your annotation of June 14. There appears to be confusion between the terms "mental defective" and "educationally subnormal." In connection with mental defectives, for example, you mention that in Sheffield there are 360 places in day special schools, but in actual fact under the Education Act mentally defective children are not eligible for admission to school at all. The schools to which you refer are for children who are educationally subnormal, and the mention of them in an article on mental defectives is therefore incorrect. Incidentally, the number of places should read 395 not 360.

You will excuse me for feeling hot on this subject; but school doctors, who ascertain all children who need special educational treatment, are with some success endeavouring to dissipate the stigma formerly attached to schools for educationally subnormals. In doing so they quite rightly assure the parents that the schools have no connection with mental deficiency, and that the children are admitted purely on educational grounds. Children who are found by the doctor, on examination for admission to the special school, to be mentally defective are, of course, reported to the local health authority as ineducable in a school sense, though they may profit by the practical type of education given at an occupation centre.

Furthermore, the mention in your article of the three special classes for dull children in Sheffield is, if I may say so, even more out of place. These classes are remedial in nature; and once the child is fulfilling his potentialities—that is his attainments matching his mental age—he passes into the ordinary school stream. The intelligence of these children, therefore, may be of any grade within the normal, though, in the main, it is the lower normal who need such help. The classes are under the direct supervision of the child-guidance centre. Sheffield has many other classes for dull children which are of a different nature.

It is disappointing to parents to find that a child of theirs is of the educationally subnormal standard, and they need from the school medical officer assistance in facing the fact and realising the importance of accepting a place offered in a special school. The removal of the stigma is therefore of supreme importance to them. It is also of equal importance to the child, who is already aware that he is less clever than his contemporaries and should not have to refute the unfair suggestion that he is also mentally defective.

Sheffield.

M. C. TAYLOR
School Medical Officer.

BUTAZOLIDINE

SIR,—In six months I have used 'Butazolidine' in the treatment of some fifty patients. Of these, some old, some young, 37 were suffering from rheumatoid arthritis in an active phase, 6 from osteo-arthritis, 2 from spondylitis, the rest from gout, Paget's disease, "periarthritis" of the shoulder, "sciatica" and non-articular rheumatism following a "chill." They were given 1 g. of butazolidine as a 5 ml. intramuscular injection daily for eight days, then on alternate days, and later every third day, usually for a period of four weeks, sometimes longer.

The relief of pain and stiffness that followed was almost constant and in some instances dramatic. Apart from the improvement of function with increase in range of joint movement there was no constant objective change. The blood picture remained unaltered. Complications have not been serious. The drug was stopped in 2 patients because of a complaint of nausea and sleepiness (unaccompanied by alteration in the white blood-cell count). In 1 there was a sudden onset of auricular fibrillation; after administration of gr. 6 of digitalis the rhythm reverted to normal. In another there was an abscess at the site of injection in the buttock.

This drug is not "curative," but I believe that it can play a useful rôle in clinical practice. Already I have found it of value as the first step in the management of a patient with active rheumatoid arthritis who is put on the waiting-list for admission to hospital, or who is starting a course of gold, or is about to have physical treatment, manipulation, or the application of plasters. If given in conjunction with cortisone, by relieving the pain due to permanent joint changes it may enable us to cut down the dose of cortisone necessary to "control the activity" of the disease.

Some twenty years ago, while on a visit with my then chief, the late Dr. Matthew Ray, to Aachen, Professor Krebs showed us the value of amidopyrine in the treatment of spondylitis. On our return we used it with success but gave it up because of the repeated warnings of the complications that might follow. Last week Professor Lucherini, the eminent Roman rheumatologist, while going round my wards told us that he gave his rheumatic patients 3 g. of amidopyrine daily with great success. In thousands of cases he had noted no complications. He urged me to adopt his method. This I am not ready to do, but I am using butazolidine (Geigy) and strongly recommend other people to try it.

London, W.1.

FRANCIS BACH.

OSLER MEMORIAL TABLET

SIR,—After attending the summer meeting in Oxford, on June 28, of the pædiatric section of the Royal Society of Medicine, held at the Radcliffe Infirmary, with cases and demonstrations in the Osler lecture-theatre and tea in the garden of Osler House, one naturally visited the Oslers' old home, "The Open Arms," at 13, Norham Gardens, to pay tribute to the memory of one of the greatest clinicians of all time, whose genuine love for children has been so graphically described in Harvey Cushing's *The Life of Sir William Osler* and Edith Gittings Reid's *The Great Physician*.

Sir, imagine one's surprise to find, pinned to the front door, a notice: "The Bureau of Statistics has moved to other premises." The spacious and once beautiful house was empty and in disrepair, and the huge garden a wilderness, overrun with weeds.

It may not be generally known that this house received its name from the unbounded hospitality that the late Sir William and Lady Osler, during their years in Oxford, showered on literally hundreds of medical men and their wives from Canada, the United States of America, Great Britain, and Europe, as well as undergraduates at Oxford. Sir William lived there from 1905 till his death on Dec. 29, 1919, while occupying the chair of regius professor of medicine at the university. Lady Osler continued to live in the house until her death on Aug. 31, 1928.

It makes one sad to think that this once famous house bears no tablet commemorating the fact that this outstanding personality—"The Shakespeare of Medicine"—once lived there and, in his will, bequeathed it to his own beloved college, Christ Church, as a suggested home for future regius professors of medicine at Oxford.

May I, Sir, suggest that a fund be opened at once to erect such a tablet, the balance of the proceeds from which to go towards some worthy cause such as the committee responsible for its distribution might think fit?

The council of the Osler Club of London, jointly with the council of the Osler Society of Oxford, would seem to me to be the appropriate body to put this suggestion into effect; and I appeal to the profession in Great Britain, the United States of America, and Canada to give it their wholehearted support.

This seems to me a singularly opportune moment to bring this matter to the attention of our profession, as on Saturday, July 12, the Osler Club of London is holding its annual dinner to celebrate the 103rd anniversary of Osler's birth.

42, Corringway,
London, W.5.

L. CARLYLE LYON
Assistant Hon. Secretary,
Osler Club of London.

COMPLICATIONS OF CONTROLLED HYPOTENSION

SIR,—Your leading article last week contains a very reasonable call for caution against the indiscriminate use of methonium compounds for the control of bleeding in surgery, but some of the evidence put forward is irrelevant.

The decrease in the renal blood-flow which follows the administration of pentamethonium iodide (C5) in *conscious* subjects[1] is, of course, no indication of what may occur under general anæsthesia. In fact, we have shown that under cyclopropane and ether anæsthesia the renal blood-flow is unaffected by C5 despite a marked drop in the systolic pressure to 50–80 mm. Hg for periods of up to half an hour.[2] Whatever the dangers of this technique—and they are very real—there is no evidence that it impairs the renal circulation.

St. Thomas's Hospital,
London, S.E.1.

H. E. DE WARDENER
B. E. MILES
W. D. WYLIE
H. C. CHURCHILL-DAVIDSON.

BENEMID IN THE TREATMENT OF STREPTOCOCCAL ENDOCARDITIS

SIR,—Last week's article by Dr. Baker and Dr. Pilkington on this subject is of great importance in drawing attention to the existence of a drug which by its power of restricting tubular secretion of penicillin can be life-saving. I have recently treated successfully one case of staphylococcal septicæmia with 'Benemid' and penicillin after heroic doses of the latter had failed, and after failure with full doses of aureomycin and the other more recent antibiotics. Similarly, complete success attributable to the combination of benemid and penicillin has been seen in two cases of infective endocarditis due to *Streptococcus viridans* of unusual resistance.

It should be emphasised that tubular "blockage" is useless unless the therapeutic agent with which it is employed is known to be excreted largely or in part through the tubular epithelium. Self-evident as this may seem, I have observed on more than one occasion that it is not so.

London, W.1.

A. H. DOUTHWAITE.

PREVENTION OF SEASICKNESS

SIR,—The investigation by Dr. Glaser and Dr. Hervey[1] into the prevention of seasickness with hyoscine, 'Benadryl,' and 'Phenergan,' was well planned from a statistical point of view, but their article contains fallacies that should be corrected.

Discussing dimenhydrinate ('Dramamine'), they infer that the 8-chlorotheophyllinate portion of its molecule is unnecessary to its action against motion sickness, and suggest that diphenhydramine (benadryl) without this portion of the molecule might control motion sickness. Therefore, they dismiss dimenhydrinate without further comment.

It is not known what influence 8-chlorotheophylline exerts to control motion sickness, but the drug is *not* inert. Although it has been shown to have no effect on the vomiting produced by apomorphine, the conclusion that it cannot have any effect on motion sickness is fallacious.

Haley and Harris[2] demonstrated that the action of dimenhydrinate was contrary to that of diphenhydramine and many other anti-histamine agents. They concluded that dimenhydrinate caused *dilatation* of the arterioles of the frog's mesentery; the other anti-histamines tested (including diphenhydramine) caused *constriction* of capillaries.

The more recent work of De Jongh et al.[3] is of great importance; their experiments show that 8-chlorotheophylline has the same effect on the frog's isolated heart and on the circulation in the perfused isolated hindquarters of the rat and frog as has theophylline—another proof that 8-chlorotheophylline is not inert. Further, they show that 8-chlorotheophylline enhances the narcotic action of sodium pentobarbitone in mice. The dual action cited above makes it improbable that the presence of 8-chlorotheophylline in the molecule of dimenhydrinate has no bearing on the action of the drug, even though its exact function remains undetermined.

The investigations of Gutner et al.[4] establish additional evidence that the 8-chlorotheophylline portion of dimenhydrinate gives rise to pharmacological action different from that of diphenhydramine.

Glaser and Hervey state that Chinn et al.[5] have given doses of hyoscine amounting to 2·25 mg. daily with no side-effects other than dryness of the mouth in most subjects and blurred vision in some. But they omit Chinn's comment that, because of the "high incidence of side effects" in a number of subjects, the drug could not be administered continuously over several days. Gay and Carliner[6] in their original study of dimenhydrinate gave many soldiers 300–400 mg. daily for as long as 11 days with no side-effects except drowsiness in an occasional subject. In a much larger number of subjects than either Chinn et al. or Gay and Carliner studied, Wright[7] found that by the end of 2 hours the army motion sickness preventive (M.S.P.) "cured" 50% of the sick patients, whereas diphenhydramine and dimenhydrinate "cured" 88% and 98% respectively.

Lastly, Glaser and Hervey prescribed the maximum dose of hyoscine (1 mg.) to the subjects of their experiment, but they prescribed 25 mg. of diphenhydramine and 25 mg. of promethazine hydrochloride (phenergan). In their trials Gay and Carliner, Chinn et al., and Wright

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[1] Mackinnon, J. *Lancet*, July 5, 1952, p. 12.
[2] Miles, B. E., de Wardener, H. E., Churchill-Davidson, H. C., Wylie, W. D. *Clin. Sci.* 1952, 11, 73.

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[1] Glaser, E. M., Hervey, G. R. *Lancet*, 1951, ii, 749.
[2] Haley, T. J., Harris, D. H. *J. Pharmacol.* 1949, 95, 3.
[3] De Jongh, D. K., Van Proosdij-Hartzema, E. G., Knoppers, A. T. *Acta physiol. pharmacol. neerland.* 1951, 2, 63.
[4] Gutner, L. B., Gould, W. J., Batterman, R. C. *Fed. Proc.* 1950, 9, 280.
[5] Chinn, H. I., Noell, W. K., Smith, P. K. *Arch. intern. Med.* 1950, 86, 6.
[6] Gay, L. N., Carliner, P. E. *Bull. Johns Hopk. Hosp.* 1949, 84, no. 5.
[7] Wright, W. L. *U.S. Armed Forces med. J.* 1950, 1, 570.

prescribed 50–100 mg. as often as every 4–6 hours. The efficacy of the drugs prescribed by Glaser and Hervey, therefore, cannot be evaluated on an equal or a comparable therapeutic basis. There *is no doubt that* the dose of diphenhydramine was too small. Further, the drug was given too long before the start of their experiment. Rough sea was encountered $1^1/_2$–2 hours after intake of the drug and the soldiers were exposed to seasickness for 2 *additional* hours. Therefore diphenhydramine was expected to be effective for 4 hours. The experimental reports of Landau and Gay [8] and Landau et al.[9] had long since established that diphenhydramine is one of the short-acting anti-histamine drugs in contrast to promethazine hydrochloride.

In conclusion the single-dose trials of Glaser and Hervey are quite inadequate to prove which of the anti-seasickness drugs are comparably effective. Further, their failure to make use of reported experimental facts diminishes the usefulness of their studies and militates against the validity of their conclusions. I trust that in their next trials they will use dimenhydrinate, diphenhydramine, promethazine hydrochloride, and hyoscine in comparable and adequate dosage in a *much* larger number of subjects; and I suggest that they should not be satisfied with a sea trip of less than 8 days, on which they are present as actual observers.

In your issue of March 8 Dr. Glaser and Dr. Hervey describe a motion sickness in which the volunteers were subjected to artificially induced turbulent water. I do not believe that the motion of a ship on the high sea during the winter months can be reproduced in this way.

Johns Hopkins University
School of Medicine,
Baltimore, Maryland, U.S.A.
LESLIE N. GAY.

*** We have shown Dr. Gay's letter to Professor Glaser and Dr. Hervey, whose replies follow.—ED. L.

SIR,—Please permit me to reply to Dr. Gay's complaints about publications by Dr. Hervey and myself.

Dr. Gay states that it is not known what influence 8-chlorotheophylline exerts on motion sickness. This is incorrect. In fact, Dr. Hervey and I have quoted the evidence which suggests that 8-chlorotheophylline exerts no influence on motion sickness. Dr. Gay's references to other actions of 8-chlorotheophylline and of certain histamine antagonists are irrelevant to the problem of motion sickness.

Dr. Gay criticises us for quoting Chinn et al.'s [10] findings rather than their comments. I respect Dr. Chinn's opinions, but I think he would be the first to agree that observations mean more than comments. Chinn and his colleagues did record auditory hallucinations in 1 of 88 men who were given 3·25 mg. of hyoscine in 36 hours; but a single case does not prove anything.

I do not know why Dr. Gay quotes observations about M.S.P. This preparation contains a trifling amount of hyoscine, and Dr. Hervey and I were not concerned with it.

Dr. Gay blames us for giving comparatively small doses of one drug. He may be right, but we based our dosage on the available data and gave the reasons for our choice.

Dr. Gay states that we gave the maximum dose of hyoscine. This is incorrect. Holling et al.[11] gave 20% more hyoscine than we did, and Chinn et al. gave larger total quantities.

Dr. Gay states that the effects of one of the drugs *may* have worn off before some of our tests were completed. This may be true; but any drug which ceased to have effect after less than 4 hours was useless under the conditions with which we were concerned, and we did not claim or imply that our results were valid beyond those conditions.

Dr. Gay believes that the motion of a ship on the high seas cannot be reproduced by artificial waves and he is free to do so, but Dr. Hervey and I accepted the advice of an Admiralty expert on wave motion who took painstaking records and whose data were given in our publications.

Since we quoted 27 references in one paper it seems odd that we should be blamed for failing to make use of reported experimental facts, but it is true that we did not include some of Dr. Gay's own claims. Rather than say more, I will refer to opinions held by distinguished American scientists [12–14] and one of your contemporaries.[15]

Department of Physiology,
University of Malaya, Singapore.
E. M. GLASER.

SIR,—I should like to endorse Dr. Glaser's reply to Dr. Gay.

The 25 mg. of benadryl given by us was not such a very small dose. It contained as much diphenhydramine as 46 mg. of dramamine; and we have referred to two reports showing no statistically significant difference between the effectiveness of benadryl and dramamine, given in doses in the ratio of 1 : 2, in preventing motion sickness. We did give phenergan, which appeared to be more effective, in a larger dose during the later series of experiments, with little difference in the results.

It is, of course, only claimed that our results were valid for the conditions under which they were obtained, and "a sea trip of not less than eight days" would obviously have been better in some ways. None the less, protection for a short time is sometimes required in practice (e.g., in assault craft). Our experiments were designed to investigate protection for short periods, to give statistically valid results and to avoid any possible effects of bias on the part of the observers or subjects.

Department of Experimental Medicine,
Cambridge.
G. R. HERVEY.

Medicine and the Law

A Question of Fees

A REPORT by its ophthalmic services committee that was approved by the London Executive Council when it met on June 26 draws attention to a course which, without specifically violating the terms of service, is regarded as "clearly an undesirable and unworthy practice."

The patients' version of the facts appears to have been accepted. Mrs. A had her sight tested under Supplementary Ophthalmic Services arrangements by Mr. X, an ophthalmic medical practitioner on the London Ophthalmic List. Forms O.S.C. 1 and 2 were completed and no charge was made. Mrs. A was accompanied by Mrs. B (her mother), who asked to have her own sight tested. Mr. X fixed an appointment for this purpose and later Mrs. A arranged with him by telephone that on the same occasion he would also test Miss C (her aunt). When Mrs. B and Miss C attended at his consulting-room, he asked them for "a small fee of £1 1s. each." This surprised them because they supposed they were being treated (like Mrs. A) under the National Health Service; but they paid the fee and were, they said, assured by Mr. X that they would obtain their glasses free under the scheme on his prescription. He advised them to go to a named firm of dispensing opticians, and he telephoned details to the firm. When they visited the firm to get their glasses, they were told that they could not have them until the duly

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8. Landau, S. W., Gay, L. N. *Bull. Johns Hopk. Hosp.* 1948, 83, 330.
9. Landau, S. W., Marriott, I [illegible] p. 343.
10. Chinn, H. I., Noell, W. K., [illegible] *Med.* 1950, 86, 810.
11. Holling, H. E., McArdle, B., Trotter, W. R. *Lancet*, 1944, i, 127.
12. Nickerson, M. *Science*, 1950, 111, 312.
13. Tyler, D. B. *Ibid*, 1949, 110, 170.
14. Tyler, D. B., Bard, P. *Physiol. Rev.* 1949, 29, 311.
15. *Brit. med. J.* 1949, i, 855.

authorised forms O.S.C.2 were handed over. Mrs. A thereupon reported the matter to the committee.

Mr. X told the committee that he had regarded the ladies as private patients. He said he had been advised by a legal organisation specialising in medical matters that there was nothing to prevent his seeing a patient privately one day and their returning to him another day to obtain a copy of the prescription on O.S.C.2. The organisation denied having so advised. The committee pointed out that such a course would result in the practitioner receiving two fees for the one service—viz., a fee from the patient for the "private" consultation and, after the prescription had been copied on to form O.S.C.2, a sight-test fee under National Health Service arrangements. The committee conceded that a practitioner practising under the National Health Service is not thereby debarred from accepting private patients. As no National Health Service form was initiated by Mr. X for Mrs. B and Miss C, the committee could not definitely decide that he had accepted them as N.H.S. patients. The committee, however, were satisfied of his awareness that the two patients wished their sight to be tested under the N.H.S. and of his having deliberately diverted them into "private" channels. It was this practice which, as already stated, the committee stigmatised as undesirable and unworthy. If persisted in, it might furnish grounds for representations to the tribunal that the continued inclusion of Mr. X in the Ophthalmic List would be prejudicial to the interests of the service. In view of his statements the committee found themselves inclined to conclude that he sought to induce the patients to come back to him for a further consultation for which a sight-testing fee could be claimed from public funds.

In formulating their recommendations the committee announced that they found no failure by Mr. X to comply with the Terms of Service. They thought, nevertheless, that he should be warned that persistence might lead to the removal of his name from the Ophthalmic List, and they recommended that the special attention of the Minister of Health be directed to the acts disclosed in the case.

Employee's Duty to Disclose Disability

The Court of Appeal has modified the award of damages to the widow in the case of Cork *v.* Kirby Maclean Ltd.,[1] where the husband who suffered from epilepsy had a fatal fall from the platform on which he was working. His employers had been at fault inasmuch as the platform was not of the width and was not equipped with the guard-rails required by the Building (Safety, Health and Welfare) Regulations. The defendant employers contended that the deceased had been subject to epileptic fits for 10 years and had been under treatment for epilepsy only 10 days before his death; his doctor had warned him that he must not work above ground level and he had promised to obey; he had not, they said, disclosed these facts to them. Mr. Justice Donovan held that the fatality must be deemed due to the employers' breach of their statutory duty unless they proved the contrary. He was following, it seems, a dictum of Lord Justice Scott in Vyner *v.* Waldenberg Bros. (1945)—a case of injury by a circular saw where the protective guards required by the Woodworking Machinery Regulations had not been provided.

Lord Justice Singleton[2] expressed the view that Lord Justice Scott's opinion went too far. Mr. Cork's fatal injury had two causes. One was the employers' breach of the regulations; the other was the workman's failure (a breach of his duty towards his employers and his fellow-workmen) to disclose his disability. Both sides were at fault, and the Court of Appeal was unable to decide that one party was more negligent than the other. Applying the Law Reform (Contributory Negligence) Act of 1945, it ruled that each side was responsible for half the damage. Accordingly Mr. Justice Donovan's award to the widow is reduced by one-half.

Obituary

PERCIVAL HORTON-SMITH-HARTLEY

Kt., C.V.O., M.A., M.D. Camb., F.R.C.P.

Sir Percival Horton-Smith-Hartley, consulting physican to St. Bartholomew's Hospital, who died on June 30 at the age of 84, came of a family eminent in the legal profession. Perhaps it was the influence of this inheritance that made him unique among the physicians of his time.

The eldest son of Mr. R. H. Horton-Smith, K.C., he was educated at Marlborough and St. John's College, Cambridge. After taking a double first in the natural sciences tripos he continued his medical studies at St. Bartholomew's Hospital, where he qualified in 1893. After holding house-appointments at Barts and a fellowship at St. John's College, he spent some years of postgraduate study in Paris and Vienna. Soon after his return to London he joined the staff of the Metropolitan and Brompton Hospitals. In 1899 he was elected F.R.C.P., and the following year he delivered the Goulstonian lectures on typhoid. In 1906 he became assistant physician to Barts.

He was appointed C.V.O. in 1912 and created a knight bachelor in 1921. For many years he was a member of the court of the Company of Ironmongers and in 1942 he was elected master.

[Vandyk

"Despite an orthodox medical education," writes F. R. F., "Sir Percival was an individualist and he differed in many ways from his contemporaries, for his interests and abilities led him along original paths in his professional as well as his private life. His wide culture enabled him to enjoy his life to the full, and the many fields into which his trained intelligence attracted him were a constant surprise to his acquaintances. His kindliness, his sympathy, and his interest in human beings had a therapeutic value for his patients, perhaps of even greater importance than his knowledge of scientific medicine, and the example he gave by his care for his patients was of greater educational value than his formal instruction. He would have made a wonderful family doctor, but his erudition and his mental abilities marked him out for a career in academic surroundings where his educational value had a wider scope. The scientific age and the rapid advances in medical science that occurred during his time had little influence on his professional life and he remained essentially a humanitarian scholar and a wise physician. As the wife of a colleague once said 'Sir Percival is a dear.'

"To the younger generation he is best known as the author with Sir Richard Douglas Powell of the later editions of the textbook on *Diseases of the Lungs and Pleuræ*, and the versatility of his interests is seen in the book which he wrote with Mr. H. R. Aldridge of the British Museum on *Johannes de Mirfield of St. Bartholomew's, Smithfield* and his article in the *British Medical Journal* (1939) on the Longevity of Oarsmen. He would surprise his friends by offering them seats at Lord's for a test match. In preparing his lectures he took great pains, and his fluency and correct use of words were a delight and a lasting example. He will be greatly missed by his students and colleagues, and his gentle influence on their way of life, their ideals, and their sense of values will never die."

Sir Percival married in 1895 Miss Josephine Hartley, of Hartley, Kent, and in 1904 he assumed the additional surname of Hartley. She survives him with a daughter and a son who is a master at Eton College.

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[1] See *Lancet*, 1952, i, 824.

[2] *Times*, July 1.

Notes and News

SECURITY MEASURES AT BROADMOOR

THE last escape from Broadmoor had such dreadful consequences that the Minister of Health appointed a committee to inquire into the security arrangements. The members were Mr. J. Scott Henderson, Q.C. (chairman), Dr. P. K. McCowan, Captain C. Waterhouse, M.P., and Mr. K. G. Younger, M.P. They have reported promptly, and all their recommendations have been accepted in principle by the Government.

Broadmoor receives those ordered to be kept in safe custody during Her Majesty's pleasure (which includes people found insane on arraignment for a criminal offence, or criminals found guilty but insane), those whom the Home Secretary may order to be removed to a mental hospital, and those prisoners certified before or after trial to be insane. Formerly it was managed by a council of supervision appointed by the Home Secretary, but under the Criminal Justice Act, 1948, it was transferred to the Minister of Health and put under the management of the Board of Control. The nursing staff have Civil Servant status and are members of the Prison Officers' Association, though they are regarded as part of the National Health Service.

On June 1 this year there were 891 patients in Broadmoor—701 men and 190 women. The medical staff consisted of the medical superintendent and his deputy, and two other doctors. The post of a fifth medical officer is at present vacant.

The patients live in a series of blocks, each with three wards, and are allotted to different blocks according to their mental condition and behaviour. The block for refractory patients consists of single rooms, while other blocks have dormitories; and in the wards for the best patients single rooms may be awarded as a privilege. The most dependable patients are allowed to go into the terrace gardens and canteen, or visit other blocks to see friends among the patients.

In 1932–40 there were no escapes from Broadmoor; but since 1950 there have been 6, of which the last was in April of this year. The full staff of attendants authorised is 279, but on June 1 there were only 260—193 men and 67 women. Moreover, though the pensionable age is fifty-five, 14 of the male staff were over sixty, and 5 of these were over sixty-five. The wage now payable to a male nurse recruit is £5 4*s.* a week; and though this amounts to £40 a year more than the wage paid to students in ordinary mental hospitals (who in turn receive £30 a year more than students in general hospitals), it does not compare as favourably with the wages of other—and possibly more congenial—local employments as did the wage of 1938. Hence young entrants to the staff are few, and the average age of the male staff has risen, since 1938, from forty to forty-five, and of the female staff from thirty-one to forty. The committee recommend that sufficient increases in pay should be made to attract suitable applicants for training; and that the pay and conditions of service of the nursing staff should not be automatically linked with those of the National Health Service.

The escapes in recent years have been due, the committee find, to carelessness on the part of the staff; and this in turn has been due to lack of adequate numbers of staff of the right quality. Some added difficulties in maintaining supervision have arisen because of building work in progress, and some of the workmen employed by the Ministry of Works maintenance staff have pass keys to move about inside the institution, though only the resident engineer and foreman of the works have keys to get in and out. The committee suggest that much of the traffic by maintenance personnel inside the institution could be reduced by putting the works yard outside the security wall; and they point out that as few keys as possible should be in the hands of workmen. In 2 cases patients have escaped by making keys, and modern locks are now being fitted throughout the building.

Patients wear ordinary clothing except when at work, when their clothing is distinctive. The committee propose that in blocks where it seems desirable the patients' ordinary clothes should be in a locked cupboard, and no patient should have access to them without the knowledge of a nurse.

They insist that, in the event of an escape, the public are entitled to an effective warning. A distinctive siren or other audible alarm should be put into action by the officer on duty as soon as an escape is discovered; and this should be electrically coupled to an alarm at Wokingham police-station. They also suggest that the Chief Constable of Berkshire should consult the Post Office authorities about the best way o warning schools of any escape which takes place during school hours; and that he should work out, with the medica superintendent of Broadmoor, a plan of coöperation between the staff of the institution and the police. In proper cases the committee think, the British Broadcasting Corporation should be asked to give priority to an announcement of an escape.

POSSIBLE RISK FROM CHLORAMPHENICOL

IN the U.S.A. the Food and Drug Administration has initiated a nation-wide survey after receiving reports o many cases of aplastic anæmia following treatment with chloramphenicol. The *New York Times* (July 5) says that doctors are being warned to make precautionary blood studies when administering this drug. It has been emphasised, however, that there is still no definite proof that chloramphenico is unsafe, since in many of the cases sulphonamide compounds and other antibiotics had been administered.

HOSPITAL PATIENTS AND INSURANCE BENEFITS

THE National Insurance Advisory Committee have recommended [1] that when insurance benefits are increased [2] patients who have been in hospital for a year should keep more of their benefit. The committee reaffirm the principle that there should not be double provision under the public social services for the same need. Since a patient while in hospital receives free maintenance in addition to treatment, his National Insurance benefit, which also includes provisions for maintenance, is therefore reduced. The committee recommends that the reduction for hospital maintenance should be increased broadly in proportion to the increases in benefit. The following regulations have been drawn up to implement the committee's recommendations:

After 8 Weeks in Hospital

The reduction after eight weeks for patients without dependants (now 10*s.*) will be increased to 12*s.* 6*d.* weekly. The reduction after eight weeks for patients with dependants (now 5*s.*) will be increased to 6*s.* 6*d.* weekly. Together with the increased rates of benefit these increases mean that single people on sickness benefit will receive during the rest of their first year in hospital about 4*s.* more than now, and the married patient about 10*s.* 6*d.* more. Single retirement pensioners who received the full 4*s.* increase last year will receive the same amount as now and married pensioners 2*s.* 6*d.* more.

After 12 Months in Hospital

The pocket-money allowed to long-term patients, with or without dependants, after they have been in hospital for a year (now 5*s.*) will be increased to 6*s.* 6*d.* weekly. The pocket-money allowed to patients suffering from respiratory tuberculosis, after they have been in hospital a year (now 10*s.*), will be increased to 11*s.* 6*d.* weekly.

Resettlement Benefit

In future the usual weekly instalment by which resettlement benefit is paid out (now £2) will be increased to £2 10*s.*

The committee will consider any objections to these regulations which are sent before Aug. 5 to the secretary, National Insurance Advisory Committee, 30, Euston Square, London, N.W.1.

ADVENTURES IN TWO WORLDS

Dr. A. J. Cronin has had an eventful life and his telling of it [3] makes an engaging if at times irritating book; engaging for its flow of anecdotes, irritating for its too-vivid medical drama. For instance, the story of the girl dying in a lonely house on a Welsh hillside because her father obstinately refused to call a doctor is a good one, but it is marred by the "not a second to lose" Hollywood version of the mastoid operation that saved her. But, as Dr. Cronin could justifiably retort, he is not writing for medical readers, whose delicate sensibilities are certainly not those of the reading public in general. *Hatter's Castle*, consigned in manuscript to the dustbin by the disconsolate author, has since gone through 29 impressions, and *Adventures in Two Worlds* may well do the same. A sister whom he came to know in a convent, herself a raconteuse specialising in tales of 15th-century Italy, had, he says, "a vivid imagination which, I assure you, did not diminish the interest of her stories." Nor does Dr. Cronin's verve detract from his story as a story, but it introduces colours too glaring to fall pleasingly on the eye of another doctor.

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1. Cmd. 8600. H.M. Stationery Office. 1952. 6*d.*
2. See *Lancet*, July 5, 1952, p. 47.
3. Adventures in Two Worlds. By A. J. CRONIN. London: Gollancz. 1952. Pp. 288. 16*s.*

University of Oxford

In a congregation on June 26 the degree of D.M. was conferred on the following:

R. H. Cowdell, H. J. F. Cairns (in absence).

The university has accepted from the Nuffield Foundation a grant of £2500 a year for two years towards the cost of research on the synthesis of cortisone.

University of London

Dr. A. W. Woodruff has been appointed to the Wellcome chair of clinical tropical medicine tenable at the London School of Hygiene and Tropical Medicine.

Dr. Woodruff graduated M.B. at the University of Durham in 1939. After holding resident appointments at the Royal Victoria Infirmary, Newcastle upon Tyne, he joined the medical branch of the Royal Air Force in 1940, serving later as a medical specialist. In 1941 he took his M.D., in 1944 the M.R.C.P., and in 1946 the D.T.M.&H. The same year he was demobilised from the R.A.F., and later he worked in the department of medicine at Ibadan Medical College, being also attached to the London School of Hygiene and Tropical Medicine. At present he holds the appointments of senior lecturer in clinical tropical medicine at the school and of first assistant at the Hospital for Tropical Diseases. Last year he was awarded the Katherine Bishop Harman prize. He has published papers on anæmia of pregnancy among Africans in Nigeria, on tropical sprue, and on the absorption of folic acid.

Mr. F. L. Warren, D.SC., reader in biochemistry at University College, has been appointed to the chair of biochemistry at London Hospital Medical College.

Dr. Eric Neil, senior lecturer in physiology at Middlesex Hospital Medical School, has been appointed to the readership in physiology at the school.

University of Manchester

The following have been successful in recent examinations:

M.D.—J. L. Braithwaite (commendation), P. R. Duncan (commendation), E. G. Wade (commendation), Roger Warwick (gold medal), J. L. Wilkinson (commendation), R. M. Winston.

M.B., Ch.B.—I. S. Bailey (honours), W. M. C. Allen, S. B. de C. Baker, J. G. Bancroft, Margaret E. Bennett, Barbara M. Benson, A. D. Bostock, Carl Burns, L. J. Chadwick, Don Clynes, J. R. Coope, A. B. Cooper, D. R. Dodsley, H. J. Done, Bernard Dudley, F. B. Eyres, Joyce A. Fiddick, P. V. Fitton, J. D. Fletcher, Peter Griffiths, Linton Grimshaw, J. A. M. Henderson, R. F. Heys, Joyce Hougie, Edmund Howarth, Helena E. Hughes, Mary I. J. Hughes, G. C. Jackson, J. B. Jacovelli, C. H. St. J. James, H. B. Kedward, J. H. Kemp, I. M. Kendal, B. W. Laithwaite, A. B. Lishman, Jean M. Lumb, Dorothy J. Marsden, C. N. Matthews, Peter Mawdsley, Douglas Millington, R. G. Mitchell, Marjorie Naylor, Joyce Newman, J. T. Newton, D. P. Oakley, T. E. Ormerod, J. F. Patrick, J. R. Raby, Derek Robinson, Audrey Ross, J. G. Searle, J. J. Shepherd, Geoffrey Taylor, G. W. Taylor, Sheila A. S. Thompson, Leslie Turner, E. G. O'H. Warburton, Robert Welton, Roger Whitaker, John White, J. A. Wright, Joan P. Wright.

University of St. Andrews

At recent examinations the following were successful:

M.D.—D. G. Adamson and J. M. Johnstone (with commendation).

Final Examination for M.B., Ch.B.—W. N. Laing, I. R. McLellan, J. H. Margerison, A. J. Mutch, G. M. Ross, R. B. Skeoch, G. C. Winch (with commendation); J. T. Allardice, John Anderson, Bryan Ashworth, C. E. Ballance, D. A. Barbour, Ralph Bibby, J. M. C. Bisset, Jack Boswell, Elizabeth H. Brown, J. R. W. Bryce, Ronald Cable, E. A. Cameron, A. A. Campbell, James Carnegie, Elizabeth F. H. Clarke, Helen P. Cochrane, F. C. Crowe, W. S. Cunningham, W. J. Dally, Joan C. Davey, J. D. Denison, Anne C. Donald, F. H. Doyle, Audrey V. E. Duthie, J. M. Eaton-Turner, D. R. Edmiston, T. R. Elder, Flora M. L. Emery, J. S. Garrow, J. L. Graham, R. W. Henderson, G. W. Johnston, Clarence King, Anne G. Lacey, I. G. D. Laing, J. M. Langlands, D. M. Lindsay, R. W. D. Low, Rosaleen Lynch, Lena M. MacBean, H. W. McFarlane, J. B. MacGillivray, Norman McLeod, J. R. Marshall, Helen Menzies, Grizel M. B. Patrick, P. J. Pearce, N. T. Piercy, Fay M. Rennie, Robert Robertson, H. H. Robinson, H. S. Ross, Marion M. T. Roy, James Sinclair, R. F. Stark, W. B. Steel, Michael Steele, Marjory Stewart, M. K. Thompson, William Turner, G. M. J. White, D. L. Whitton, R. W. Wright.

University of Aberdeen

On July 4 the honorary degree of LL.D. was conferred on Colonel H. E. Shortt, F.R.S., professor of medical protozoology in the University of London and head of the department of parasitology in the London School of Hygiene, and on Mr. D. Landsborough Thomson, PH.D., professor of biochemistry in McGill University, Montreal.

On July 3 the following degrees were conferred:

M.D.—Robert Semple (with commendation); Bessie C. Laing, Jean M. Sheach.

Ph.D.—P. G. Walker.

M.B., Ch.B.—I. H. Anderson, A. D. Calder, George Cassie, A. G. Chisholm, T. J. Crowley, A. R. Dow, Alison H. Edwards, Peter Harvey, A. H. Innes, N. D. Innes, T. I. Kemp, J. H. Lewis, K. L. Lipp, G. B. McCutcheon, A. M. Macleod, Archibald Morrison, David Ruddiman, A. R. L. Russell, R. A. W. C. Smith, W. J. M. Stewart, D. J. W. Sutherland, I. R. Swanson, J. G. Weir.

University of Dublin

On July 3 the following degrees were conferred:

M.D.—G. L. Daly, P. G. Daly, D. F. Doherty, J. R. Hassard, T. B. Madden, J. S. Ruddell, S. B. Sachs.

M.Ch.—W. G. Fegan.

M.B., B.Ch., B.A.O.—E. T. Baldwin, Colette A. Barouch, E. G. Bennet, Mary E. Bewley, G. J. Bigley, R. C. P. Bradley, Fodla B. K. Burnell, G. A. H. Cookson, Lois R. Davidson, R. J. Draper, I. A. Eppel, Noreen M. H. Evans, S. S. Faloon, B. W. Fisher, Peter Froggatt, J. H. van R. Hofmeyr, James Hunter, Eunice Hurworth, H. Q. Hutchings, R. F. Hutchings, Janet B. Hyde, W. T. Irwin, H. R. B. Jack, Christopher Kennedy, Gordon King, H. G. Knox, B. F. St. L. Liddy, G. S. McCarthy, Elisabeth M. McNab, R. W. Mitchell, Oluyinka Olumide, Freda M. E. Parker, Barbara W. M. Partridge, W. J. C. Pearson, A. F. C. Scott, J. A. Scully, R. B. S. Smith, A. A. Sugerman, T. E. W. Winckworth, Mary V. Young.

Royal College of Surgeons of England

On July 3 Sir Clement Price Thomas, Mr. C. Naunton Morgan, and Mr. Hedley Atkins were elected members of the council. The result of the poll was as follows:

	Votes
SIR CLEMENT PRICE THOMAS (Westminster Hospital)	826
C. NAUNTON MORGAN (St. Bartholomew's Hospital)	770
H. J. B. ATKINS (Guy's Hospital)	727
R. Milnes Walker (Royal Infirmary, Bristol)	588
Ian Aird (Postgraduate Medical School of London)	576
V. W. Dix (London Hospital)	479
H. C. Edwards (King's College Hospital)	471
R. H. O. B. Robinson (St. Thomas's Hospital)	416
M. F. Nicholls (St. George's Hospital)	247
H. W. S. Wright (Queen Mary's Hospital for the East End) ..	242

In all 1988 fellows voted; and in addition 25 votes were found to be invalid.

British Association of Urological Surgeons

The eighth annual meeting of this association was held in London from June 26 to 29 under the presidency of Mr. E. W. Riches. The following were elected officers for 1952–53:

President, Mr. E. W. Riches; vice-president, Mr. T. J. Millin; hon. secretary, Mr. A. W. Badenoch; hon. treasurer, Mr. R. H. O. B. Robinson; hon. editorial secretary, Mr. J. D. Fergusson; council, Mr. J. C. Anderson, Mr. David Band, Mr. J. G. Yates Bell, Mr. T. L. Chapman, Prof. V. W. Dix, Mr. W. H. Graham, Mr. J. G. Sandrey, Mr. H. Hamilton Stewart.

American Research Grants

The American Embassy and the United States Educational Commission in the United Kingdom offer grants to assist senior British scholars to lecture or carry out research in the universities of the United States during 1953–54.

The minimum period of grant assistance for which application will be accepted will be three months; the maximum will be ten months. The monthly stipend will not be more than $270. No living allowances will be provided for the dependants of grantees. Candidates who receive these grants will be expected to attend American universities as visiting scholars, and, therefore, no provision will be made for the payment of tuition fees. To attend an American university as a visiting scholar, applicants should be able to show considerable professional or academic attainment. Candidates may receive a grant to cover expenses of travel to and from the United Kingdom and the university which is their destination in the United States.

Application forms may be obtained from the Assistant Cultural Relations Officer, Room 302, 41, Grosvenor Square, London, W.1, after Aug. 1.

International Congress of Internal Medicine

The second congress of the International Society of Internal Medicine will be held in London from Sept. 15 to 18. Mr. Iain Macleod, the Minister of Health, will attend the opening by Sir Russell Brain, P.R.C.P., on Monday, the 15th, at 11 A.M. The scientific programme is to consist solely of symposia, and the subjects have been chosen from a wide field in the hope that as many members as possible will join in the discussions.

The opening speakers and subjects are as follows:

Dr. C. D. de Langen (Utrecht), Dr. A. L. Froehlich (Antwerp), Prof. A. C. Frazer (Birmingham), and Dr. Chester M. Jones (Boston), Sprue Syndrome—Idiopathic steatorrhœa and Cœliac Disease; Prof. J. G. G. Borst (Amsterdam), Dr. F. T. G. Prunty (London), Prof. R. Platt (Manchester), Dr. R. S. Mach (Geneva), Prof. R. A. McCance, F.R.S., Miss E. M. Widdowson, D.SC. (Cambridge), Prof. J. Hamburger (Paris), Dr. O. J. Broch (Oslo), and Mr. A. W. Wilkinson (Edinburgh), the Clinical Importance of Disturbances of Fluid and Electrolyte Balance; Dr. J. R. Paul (Yale), Dr. Herdis von Magnus (Copenhagen), and Dr. W. Ritchie Russell (Oxford), Neurotropic Virus Disease; Sir Alexander Fleming, F.R.S. (London), Dr. F. Magrassi (Naples), Prof. A. Kekwick (London), and Prof. C. Jimenez Diaz (Madrid), Antibiotics in Man.

A limited number of non-members may attend the congress on payment of a fee; only members of the International Society may take part in the discussions. Further particulars may be had from the secretary of the congress, Sir Harold Boldero, Royal College of Physicians, Pall Mall East, London, S.W.1.

Mass Radiography in the Birmingham Region

The mass-radiography service in the Birmingham region has been augmented by the formation of two new units. The Stoke unit (Dr. E. Posner) will serve the Potteries and the north of the region, whilst the *Birmingham mobile unit* (Dr. W. M. Dixon) will operate in and around Birmingham.

Faculty of Radiologists

The following officers were elected at the annual general meeting on June 20: president, Dr. Peter Kerley; vice-*presidents, Prof. A. S. Johnstone and* Mr. C. J. L. Thurgar; hon. treasurer, Dr. J. W. McLaren; hon. secretary, Dr. Rohan Williams; hon. editor, Miss Margaret Tod.

Hospital Dental Service

The Minister of Health (R.H.B.[52]75) has suggested that a grade of whole-time general dental surgeon should be introduced in hospitals. The day-to-day work of this officer would include the conservation of teeth by means of routine fillings, scaling *and treatment of the gums, the extraction of teeth* for the removal of oral sepsis or the relief of pain, and the supply of dentures. He might serve two or more hospitals *within a group. The grade would, in the Minister's view,* be of particular value in long-stay hospitals where general dental work is often undertaken for inpatients. There may also be *scope for general dental surgeons in other hospitals, but it is* not intended at this stage to offer short-stay patients dental treatment beyond what is needed as part of their medical care or for relief of pain. The Minister hopes that the introduction of this grade will attract to the hospital service those who wish to make a career there without aspiring to senior staff status; in particular he thinks that some dental registrars who do not obtain senior registrar appointments may welcome the opportunity which it affords. The salary scale for the new grade is to be £900 × £30 to £960 × £40 to £1200 × £50 to £1500.

The Minister of Pensions has appointed Prof. Walter Mercer chairman of the Standing Advisory Committee on Artificial Limbs in succession to Mr. St. John Dudley Buxton.

Sir Harold Gillies has been appointed emeritus consultant plastic surgeon at Rooksdown House, Basingstoke, on his retirement from active work at this hospital.

In an advertisement by Boots Pure Drug Co. Ltd., which appeared in our advertisement columns last week the quotation from the *Archives of Dermatology and* [illegible] *“... therapeutic results confi* [illegible] *in placing undecylenic acid—* [illegible] *studied.”*

Diary of the Week

JULY 13 TO 19

Monday, 14th

GUY'S HOSPITAL MEDICAL SCHOOL, London Bridge, S.E.1
5 P.M. Prof. H. Sicher (Chicago): Functional Anatomy of the Temporomandibular Articulation.
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5 P.M. Prof. Lorimer Dods (Sydney): Some Aspects of Pædiatric Endocrinology.

Tuesday, 15th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Mrs. Margaret Hill: Dangers of Chronic Inactivity in Old Age. (F. E. Williams lecture.)

Wednesday, 16th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Prof. Urpo Siirala (Turku, Finland): Frequency of Ear Diseases and the Prevention of Deafness.

Thursday, 17th

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
7.30 P.M. (26, Portland Place, W.1) Brigadier J. S. K. Boyd, F.R.S., Dr. G. H. Hitchings, Mr. I. M. Rollo, and Dr. L. G. Goodwin: Symposium on the New Anti-malaria Drug—Daraprim.

Friday, 18th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. V. Zachary Cope: Sir John Tomes—A Great Dental Pioneer. (Charles Tomes lecture.)

Appointments

CLARK, J. S., M.B. Durh.: M.O., Nyasaland, in the Colonial Medic Service.
GOULD, L. N., M.R.C.S., D.P.H.: M.O.H. for the Haltemprice U.D. and divisional M.O. for the East Riding of Yorkshire.
KENNY, SHEILA, M.D. Dubl., D.M.R.D.: consultant radiologis South Down and South Armagh hospital group, Norther Ireland.
LECKIE, F. H., M.C., L.R.C.P.E., M.R.C.O.G.: asst. obstetrician an gynæcologist, East District Hospital and Glasgow Roy Infirmary.
O'HANLON, R. H., M.R.C.P.I., M.R.C.O.G.: honorary asst. gynæcologist, Dr. Steeven's Hospital, Dublin.
O'TOOLE, P. M., M.B. N.U.I., D.A.: anæsthetist, Dublin Corporatio
ROBERTSON, DANIEL, M.B. Glasg.: appointed factory docto Lincoln district.
SIMM, FRANCIS, M.R.C.S.: asst. M.O.H., Warrington, Lancashire.
STEVENSON, D. K., M.B. St. And., M.R.C.P.: consultant che physician, Bradford.
STRACHAN, A. B., M.B. Aberd.: appointed factory doctor, Goo district, Yorkshire.
TAYLOR, ROBERT, M.B. Edin., D.P.H.: deputy M.O.H. and depu school M.O., Middlesbrough.
WILLCOX, D. R. C., M.B. Lond.: S.H.M.O. in clinical patholog Bethlem Royal Hospital and Maudsley Hospital, London.

Manchester Regional Hospital Board:

BEETLES, E. A., M.S. Madras, D.M.R.D.: asst. radiologist, Macclefield and South Cheshire Hospitals and Parkside Hospita Macclesfield.
HADELMAYR, ILSE, M.D. Vienna, D.A.: asst. anæsthetist, Oldha hospitals.
POLLOCK, MARGERY, M.B. Dubl., D.A.: asst. anæsthetist, We Manchester hospitals.

North-East Metropolitan Regional Hospital Board:

BATES, MICHAEL, F.R.C.S.: *maximum part-time* regional thorac surgeon (consultant).
[illegible] M.R.C.S., D.A.: full-time or maximu [illegible] (consultant), Oldchurch Hospital.
LUNN, G. M., M.B. Camb., F.R.C.S.: part-time surgeon (consultant), Metropolitan Hospital.
MONRO, J. W., M.B. Camb., D.A.: part-time anæsthetist (consultant), Whipps Cross Hospital.
PHILIPP, E. E., F.R.C.S., M.R.C.O.G.: maximum part-tim obstetrician and gynæcologist (consultant), Oldchur Hospital.
SAVAGE, C. S., F.R.C.S.: part-time E.N.T. surgeon (consultant Rush Green Hospital.
STRIDE, S. D. K., M.R.C.S., D.A.: part-time anæsthetist (consultant), Broomfield Hospital.

Sheffield Regional Hospital Board:

BAUER, JACOB, M.D. Warsaw: *director, Lincolnshire* mas radiography unit.
FORBES, D. E. P., M.D. Edin.: deputy physician-superintenden Leicester Isolation Hospital, and Chest Unit, Groby Roa Leicester.
TEWFIK, G. I., M.D. Lond., D.P.M.: asst. psychiatrist, Middlewoo Hospital, Sheffield.

Welsh Regional Hospital Board:

BECKETT, H. DALE, M.R.C.S.: asst. psychiatrist (S.H.M.O. Morgannwg H.M.C.
DAVIES, WILLIAM, M.R.C.S., D.C.H.: asst. pædiatrician (S.H.M.O. East Glamorgan area.
HUGHES, ANEURIN, M.B. Lond., M.R.C.P.E.: consultant physicia North Monmouthshire, Newport, and East Monmouthshi H.M.C. groups.

The Terms and Conditions of Servic[illegible] *Dental Staff apply to all N.H.S. hospit*[illegible] *otherwise stated. Canvassing disqualifies,* [illegible] *visit the hospital by appointment.*

Births, Marriages, and Deaths

BIRTHS

CAMPBELL.—On June 25, at St. Brenda's Nursing Home, Clifto to Mary (née Clarke), wife of Dr. A. M. G. Campbell—a daught (Fiona Mary).
NAISH.—On June 21, at Bristol, to Nora, wife of Dr. John Nais —a son.
TANNER.—On June 21, to Mary, wife of Mr. Clive H. Tanner, F.R.C.S., of 61, Walter Road, Swansea, Glam—a daughter.

MARRIAGES

PIRRIE—HAMILTON.—On July 1, at Glasgow, Robert Pirrie, M.B., to May Hamilton, S.R.N.
REY—WOOD.—On June 21, in London, C. Humphrey J. Rey, M.R.C.S., to Thelma M. Wood.

DEATHS

DAVID.—On July 5, at Fyfield, Essex, Archibald Sinclair David, M.R.C.S., D.P.H.
HARE.—On July 2, at Birkdale, Lancs, Alfred William Hare, M.B. Aberd.
HARTLEY.—On June 30, 1952, in London, Sir Percival Horton-Smith-Hartley, KT., C.V.O., M.D. Camb., F.R.C.P., of Adkins, Ingatestone, Essex, aged 84.
MACLEOD.—On July 3, at St. Thomas's Hospital, London, Henrietta Mary Macleod, M.R.C.S.
RAYMOND.—On July 2, in Colchester Hospital, George Raymond, M.R.C.S.

FEEDING DISORDERS IN INFANTS
THEIR INTERPRETATION

C. WILFRED VINING
M.D. Lond., F.R.C.P., D.P.H.
VISITING PÆDIATRICIAN TO THE DEWSBURY HOSPITALS;
EMERITUS PROFESSOR OF CHILDREN'S DISEASES IN THE UNIVERSITY OF LEEDS

THE term "feeding disorders" is now in general use as a description of the group of symptoms, common in the early weeks and months of life, which includes vomiting, posseting, screaming, "colic," "wind," abnormal stools, and failure to gain weight satisfactorily. Formerly these symptoms were ascribed to "infantile dyspepsia," which seems to imply an inability to digest food or some part of the food, or that the food itself is proving harmful to the child; and there is still, I think, a considerable body of opinion that supports this idea. But the truth, I believe, is that these symptoms are chiefly due to hunger, the result of underfeeding. The feeds may be too small or too dilute, or, because of wrong feeding technique, the infant may be unable to obtain enough.

It will be appreciated that I bear in mind that vomiting and/or loose stools may be associated with congenital obstruction of the œsophagus, pylorus, duodenum, or beyond; or with some bacterial infection, especially gastro-enteritis. Gastro-enteritis and "infantile dyspepsia" are very often confused; and, because the treatment of the one is the exact opposite of the treatment of the other, care must be taken in diagnosis. Gastro-enteritis starts suddenly, and the quick change in the frequency and appearance of the stools is distinctive. Listlessness, refusal of food, and some degree of toxæmia are usual.

THE PAST FIFTY YEARS

Half a century ago, when I was a medical student at St. Mary's Hospital, the infant-mortality rate of the Borough of Paddington was 155, and I well remember the large number of marasmic babies which were brought to the medical casualty department and the clinics of that hospital. Gastro-enteritis was then prevalent, and I bring to mind the queues of mothers with extremely ill babies in their arms. Voluntary welfare centres came into being, frequent discussions took place at medical societies, and infant feeding and infantile dyspepsia became major problems. The press were asking why medical students were not taught about infant ailments, and why these matters were not referred to at the final examinations. The reason no doubt was that consultants and the medical profession generally knew little about them. Dr. Ralph Vincent put forward his system of "percentage feeding," and Dr. Truby King produced handbooks offering fantastic formulæ for artificial infant feeding. The dangers of overfeeding were emphasised by all, and fat dyspepsia, curd and protein dyspepsia, sugar dyspepsia, and even salt dyspepsia were described and added to the increasing worries of medical students.

The vomiting of curds, or their passage in the stools, was considered sufficient evidence that the fault lay in the protein content of the milk, but we students sometimes wondered what else a baby was expected to vomit when fed with milk! Nor was it explained to us that most stool curds were not protein curds at all. For some years so-called curd dyspepsia held the field as the main cause of the infant feeding disorders. Citration and prolonged boiling of milk were recommended to overcome this difficulty, but the commonest recommendation was modification of cow's milk ("humanisation") by dilution with water and the addition of cream and sugar. Very soon this supposedly ideal artificial method of infant feeding deteriorated into feeding the baby with overdiluted milk, and sugar. I once possessed a treasured poster, issued some forty years ago by a medical officer of health of one of the largest cities in the north, which advised mothers, if they could not breast-feed their babies, to use a half-and-half mixture of milk and water. And we still wondered why marasmus was so common among infants.

Marasmic infants succumb readily to infection, and their proportion of the infant population at that time was undoubtedly a grave potential danger and an important cause of the high mortality-rate. Dirty feeding-appliances were blamed and the importance of germ infection emphasised, but there were many who believed that "infantile dyspepsia" was due to the milk itself.

Why is the marasmic infant now rarely seen? Certainly no one factor can be claimed to have wrought the change; but the marketing of dried milk, first introduced about thirty years ago, almost certainly did more than anything else to reduce infant mortality. Some ascribed this improvement to the absence of bacteria in the dried-milk feed; but, looking back, it seems to me more likely that the real reason was that for the first time the artificially fed baby was presented with a square meal and a square deal. When a measureful of milk powder is added to an ounce of water, the baby is given the equivalent of whole cow's milk.

The baby, however, continued to experience disappointments. Some makers of dried milk did not supply a metal measure, and teaspoons were recommended; but, because milk powder is very light in weight, a flat large teaspoonful of powder added to an ounce of water provided the baby with only the equivalent of approximately a half-and-half milk and water mixture. Even when metal measures for milk powder were available, the baby was still denied a well-concentrated feed, because mothers were (and still are) told to measure the water with tablespoons, and this means an overdiluted mixture because most tablespoons measure a good deal more than half an ounce. Unfortunately, few at that time realised that good nutrition is Nature's chief protection against infection.

Some may feel that I am flogging a dead horse. I agree that the present state of affairs is quite different from what it was fifty years ago. The infant-mortality rate at Paddington is now 29, and marasmus is rarely seen, although occasionally pyloric obstruction is still overlooked to remind us of it. "Infantile dyspepsia," however, still exists, and the danger of overfeeding continues to be emphasised by many. It is my experience, as an examiner at university finals and in the recent past at the D.C.H. examination, to be told by candidates that overfeeding is much more common than underfeeding. Half-cream dried milk—which is nothing more or less than dried skimmed milk—is recommended for healthy infants under the age of 3 months, and partially digested milk foods are still considered helpful. At my own clinics underweight babies who are vomiting, constipated, passing abnormal stools, or not progressing are referred to me as cases of fat-intolerance, pyloric stenosis, or gastro-enteritis; and contact with young postgraduates produces the strong impression that they look on infant feeding as a hazardous business, with the risk of overfeeding and the production of "infantile dyspepsia" and fat-intolerance as the dangers most to be feared.

PRINCIPLES OF INFANT FEEDING

After more than forty years' experience of children's practice and university teaching I should like to offer to others the following principles of infant feeding.

(1) *Generous feeding is essential*

I used to teach that the human infant should double his weight in six months. I soon realised that many healthy breast-fed babies nearly treble their weight in this time. The baby who weighed 7 lb. at birth is a poor specimen if only 14 lb. at six months. Thirty years ago I taught my students that the baby required $2^{1}/_{2}$ oz. of breast-milk or its equivalent in artificial food for each pound of body-weight. Twenty years ago I taught that the infant required $2^{1}/_{2}$ oz. of breast-milk or its equivalent for every pound of *expected* weight—i.e., the weight that the particular infant should have reached if progress had been normal. Still later I felt that this quantity was minimal, and today I am inclined to throw aside all these standard quantities and to allow the infant to have what he or she will take. The practice of "following the baby" is sound, because we can never be sure what a particular infant needs. Those infants who are well down in weight for their age certainly will take an amount of daily food far in excess of minimum requirements, and they continue to do so until they have "taken in the slack." To me it is fundamental that this rapid growth of tissue during the early months of life must be met by generous feeding. If this point is conceded, I submit that Nature would never have provided an infant with a digestive system so delicately balanced that overfeeding or risk of death from harm or illness produced by the food itself could be a possibility. The evidence demonstrates beyond reasonable doubt that starvation and underfeeding in any degree are the dangers most to be avoided and against which the infant has no defence.

(2) *Most babies will progress satisfactorily on the most diverse types of food, so long as the food given is adequate in quantity and well concentrated and can be taken easily by the baby*

All of us agree that breast-milk is the ideal food for the infant. If, after patient trial, breast-milk is found insufficient, the feeds must be supplemented by additional milk food given from a bottle. It is quite wrong, and indeed cruel, to deny an infant additional food because of the mistaken idea that there is something immoral or harmful in making use of some other milk. The proof of the pudding is in the eating, and, if progress is not being made when the child is fed entirely by the mother, something should be done about it at once. There is nothing harmful in "breast and bottle," but everything may go wrong if the feeding technique is at fault. Those doctors and nurses who suggest that breast-milk has "gone off" or is poor in quality are hardly ever right, and the possibility of breast-milk being the cause of "dyspepsia," "colic," or loose stools may be discounted.

Overfeeding at the breast is considered by many to be of common occurrence. This has not been my experience, and indeed I believe it to be exceptionally rare; but underfeeding is only too common. The amount taken at a feed may vary greatly, and a month-old infant may take anything from 2 to 6 oz. Babies are not like penny-in-the-slot machines, and I feel sure that we have done harm in insisting on exact quantities, exact times, and feeding by the clock. Once upon a time there were no clocks, and the untutored mother of the past—like that of the present—would never dream of waking her baby out of sleep to administer another feed. From the mother's point of view regularity is something to be striven for. My own practice has been to begin feeding babies three-hourly for six feeds a day. Where sleep is sound and progress satisfactory the feeds may be four-hourly or thereabouts. The infant must not be encouraged to feed between 10 P.M. and 6 A.M., but if he is wakeful and hungry it is foolish not to give food. We should aim at sufficient food by day to prevent hunger and wakefulness at night. I appeal for far more common sense and less adherence to regulations. Let us rely more on the mother and on her attitude and feelings towards her baby, for by so doing we shall engender an enhanced degree of confidence in herself.

When the bottle is used as complementary to the breast, or when breast-milk is not available, the "bran-tub" method of trying to find a suitable food is wrong. The ideal alternative continues to be boiled fresh milk with added sugar. My practice has been to order a 4 : 1 mixture, with the addition of a large flat teaspoonful of sugar—'Dextri-Maltose' is particularly suitable—to every 4 oz. Such a mixture can be given without alteration up to the age of weaning. The defect with cow's milk is the shortage of sugar. I have never been convinced that healthy babies suffer from fat intolerance when a "milk, water, sugar" mixture is used, nor does sugar in the quantity recommended cause acid stools.

There are, however, situations and occasions when a dried milk is the better choice. A whole-cream dried milk should be used to which sugar has been added by the makers—'Modilac' (Cow & Gate) and 'Ostermilk no. 1' (Glaxo) are suitable—or sugar can be used with National Dried Milk.

The feeding of healthy babies with a half-cream dried milk cannot be too strongly deprecated. This is feeding with skimmed milk. I feel sure that those who recommend it would be shocked to hear of anyone feeding healthy infants with fresh skimmed milk. Its use seems to imply that healthy infants during the early months of life cannot digest the amount of fat in a simple "milk, sugar, water" mixture, and that "dyspepsia" will result. We should remember that if, before the milk is dried, part of the fat is removed, the resulting powder will be relatively heavier, and the space taken up by the protein in the packet will be much greater to fill the space produced by the removal of fat; if sugar has been added by the manufacturers, the relative amount of fat will be still further reduced. Those, therefore, who favour the routine feeding of healthy infants during the early months with a half-cream preparation are providing the infant with a much reduced fat ration and at the same time are giving the infant an amount of protein and nitrogenous material in excess of that in fresh whole milk, although most authorities agree that the modification of cow's milk to reduce the excess of protein is desirable.

(3) *The symptoms of "infantile dyspepsia" are generally caused by mistakes in feeding technique*

The main causes of vomiting, posseting, infrequent or abnormal stools, "colic," "wind," and excessive crying during the breast- or bottle-feeding period may be summarised as follows:

Underfeeding due to the fear of overfeeding.

Strict adherence to the quantities indicated by academic dictates.

Feeding according to *present* weight rather than *expected* weight.

Following the directions set out on the packet of dried milk. These are usually calculated for an infant whose birth weight was $6^{1}/_{2}$ lb.

Feeding all infants four-hourly from the start.

Using a bottle open at one end only.

Using a teat which will not allow an easy flow of milk or which collapses in the infant's mouth like blotting-paper, either because of age or continual boiling.

Allowing the infant to feed for twenty minutes or longer.

Administering quantities of water and glucose solution between the feeds.

Making the feed too hot (I have twice seen a baby scalded about the face and neck by the contents of the bottle).

Misinterpreting the symptoms as those of subacute gastro-enteritis, and treating and feeding accordingly.

VOMITING, POSSETING, AND REGURGITATION

At the outset I spoke of the importance, when an infant begins to return his food, of making sure that there is no congenital obstruction and that he has no acute sudden illness such as gastro-enteritis or whooping-cough.

Most infants who bring their food back do so because they have learnt during the early weeks of life to suck air when feeding from the breast. When a mother breast-feeds the baby and has adequate milk which comes easily, the baby is satisfied in about seven minutes. Allowing the baby to continue sucking from the empty breast, or from a bottle from which he cannot easily get the milk, is a common cause of excessive air-swallowing. If, therefore, the infant is still willing to suck from breast or bottle at the end of twenty minutes, either there is insufficient milk to satisfy him or he cannot get it. This habit of excessive air-swallowing, which so often is the cause of vomiting and posseting, may be easily acquired, even during the early days and weeks of life, and once learnt is not readily given up.

Vomiting may be explosive, but often there is also a more or less continuous return of a few mouthfuls of very acid curdy fluid. To this the word "posseting" has been given, and, rarely, such an infant may have a congenital muscular defect of the lower end of the œsophagus which allows stomach contents to "well up" into the œsophagus during contractions of the stomach. Most posseting infants, however, learn the habit of bringing their food back (rumination) and enjoy the experience of so doing. Normal babies are hungry babies whose only object in life is to get food, and if they are not fully satisfied they will resort to this regurgitation or rumination—even the very young ones will do this—so as to experience the pleasure of going through again that which they have managed to take.

I do not myself believe that the return of food, which has so often in the past been explained on the basis of overfeeding and fat intolerance, has anything to do with either of these supposed causes. Some babies do, no doubt, return a few mouthfuls of milk after a feed, and may continue to behave in this way until they reach the age of weaning, but to label such babies as dyspeptic is, I feel sure, wrong. Clean wholesome milk food does not and cannot produce dyspepsia, colic, wind, or excessive acidity. It is a continuing insufficiency in volume or quality which so often causes harm. The repeated return of acid material by the unsatisfied baby is due to expectancy, hunger, and nervous upset causing a free secretion of gastric juice which is not used up by a full-strength feed. Much the same thing happens when a baby soils a napkin at every feed. Its eagerness to get food leads to active peristalsis and a bowel movement at the time of a feed.

SCREAMING, EXCESSIVE CRYING, "COLIC," AND SLEEPLESSNESS

Air-swallowing probably causes some discomfort. It may certainly produce abdominal distension, and very possibly the swallowed air will pass into the bowel and produce disturbances in peristaltic action. If this happens, the child may cry. When we are told by mothers that an infant screams, draws up its legs, and has "colic," we must be careful not to accept this interpretation of the screaming too readily. Who can be sure that a baby is in pain? By far the most likely explanation is that the screaming and so-called colic are due to hunger, frustration, and nervous upset. My advice to those who doubt this is to try the experiment of giving such an infant a generous feed, ensuring that he can get it easily and is fully satisfied. Quick feeding —ten to twelve minutes as a maximum—does much to prevent excessive air-swallowing.

ABNORMAL AND EXCESSIVE NUMBER OF STOOLS

The stools of normal infants progressing satisfactorily may vary in number from 3 a week to 6 or 7 in twenty-four hours. It is not uncommon for a breast-fed baby who is putting on weight normally to produce only 2 or 3 stools a week, and such stools are normal in consistence and colour and not dry, hard, and pellety like the stools of some bottle-fed babies. With bottle-fed babies infrequent stools may be due to lack of food, but part of the infrequency results from the consistence of the stool—the so-called soap fat stool—which is not unusual when cow's milk, dried or fresh, is given.

The hungry, eager, sleepless, and nervously upset baby may have a stool with every feed, and such stools may be green, liquid, curdy, and of abnormal colour and odour. Intestinal juices are actively secreted, peristalsis is vigorous, and the condition is not unlike the so-called lienteric diarrhœa of older infants and children. At one time I used to take a great interest in the stools and went so far as to make coloured drawings of them and have their exact numbers recorded by the nurses: if they were too frequent or abnormal, the feeds would be cut down and the proportion of the different ingredients altered—fat or sugar would be lowered or the food predigested, and so on—but I have for a long time given this up. Now I am more interested to watch the infant to see that he is satisfied. Over and over again one has seen the stools of a restless hungry infant become normal in number and consistence merely by increasing the food, which must be well concentrated, properly measured and taken in adequate amounts, from a boat-shaped bottle through an easy teat. It has often amused me to watch doctors awaiting the return of an infant's stools to normal while the baby is being given quantities of glucose substance, or a weakened feed which could not possibly produce a normal stool. It should also be remembered that redness and rawness around the anus is by no means a certain sign of bowel infection: indeed, babies with gastro-enteritis do not often have soreness in this area. On the other hand, intestinal juices which, owing to hunger, nervous upset, and overactive peristalsis, have been passed through the bowel too quickly and have not been used up in the digestion of food may cause anal irritation and soreness, and this may happen even in the neonatal period.

ENVOI

The feeding of a baby is not always straightforward, even when technique is satisfactory and adequate food is supplied which the child can easily get. The risk of infection is always in the offing, especially in institutional practice. When once an infant has developed an infection of the nose, nasopharynx, ear, bronchial tubes, or urinary or intestinal tract, the ability to take food and to absorb it may be temporarily and sometimes severely reduced. Breast-feeding may break down completely when an infant in the early days and weeks of life develops acute dry or moist rhinitis. A *stomatitis* due to thrush or streptococcus may mean the refusal of feeds and loss of weight, followed by œsophagitis which may cause considerable vomiting and lead on to marasmus. A true gastro-enteritis infection may result in serious nutritional breakdown. Listlessness and refusal to feed may be due to the infant's becoming chilled, as proved by the rectal temperature failing to register above 97°F. Repeated infections may lead to the marasmic state, and the more severe the grade of marasmus the less is the ability to tolerate food of any kind. (It would indeed by quite imposible for an infant with advanced marasmus during the days preceding its death to take and absorb the amount of food suited to its expected weight.) All these conditions therefore require their proper prevention and management; but they do not in any way invalidate the truth of the principles which I have submitted—namely, that the food itself is not the cause of "infantile dyspepsia," and that babies must be generously fed.

Dr. Robert Kelly Library
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THE MANAGEMENT OF AN ILEOSTOMY INCLUDING ITS COMPLICATIONS

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An ileostomy must work perfectly if the surgical treatment of ulcerative colitis is not to fall into disrepute; the closest attention must therefore be paid to the minutiæ of technique and to subsequent care.

The ileum should be divided and the ends separated so that the functioning stoma presents as a terminal vent about $1-1^{1}/_{2}$ in. long (Hardy et al. 1949). A loop ileostomy is still regarded by some surgeons as justifiable in a serious case (Lahey 1951); but it should be avoided if possible, because an ileostomy bag cannot be applied effectively to it. Where a primary colectomy without pre-existing ileostomy is done, the terminal ileum forms the stoma, and the same principles apply.

ILEOSTOMY BAGS

Generally an ileostomy acts after meals and during the night, though some of the contents of the small bowel may be voided at any time. It must not be thought that one type of bag suits all patients—indeed a few prefer the old rigid cup appliance—but usually the Koenig-Rutzen type of bag is most favoured, and most makes of bag act on the same principle of adherence to the skin, from the simple disposable type to the more complicated kind in two pieces with an adherent flange and removable bag.

The cement or glue is not always satisfactory, but this is occasionally the fault of the patient, who is unaware that it should not be applied too liberally to the flange of the bag, and that the flange should not be pressed on to the skin until the cement begins to become tacky—just like mending a puncture. If the glue fails, further support and a more perfect seal can be obtained by strapping the flange to the abdominal wall with a waterproof adhesive—e.g., 'Sleek.'

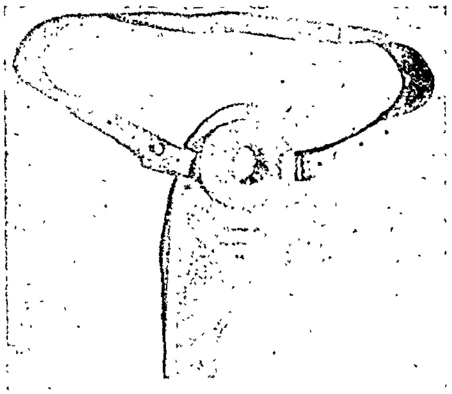


Fig. 1—Koenig-Rutzen bag with belt.

A collar can be placed in the neck between bag and flange and attached to a light belt to give patients an added sense of security; or an elastic corset can be worn with a hole cut to accommodate the bag. A belt is attached to the flange of some bags (fig. 1), but this tends to interfere with an adhesive seal.

A bag seldom sticks firmly from the outset, and there is often a tendency to leak on the outer side during the first month or two. This naturally disappoints the patient, who should be reassured, for, if the stoma has been placed correctly, the leak will cease as the patient puts on weight and the gutter between stoma and anterior superior iliac spine fills up. There is a further tendency to leak at night, for recumbency causes the ileal contents to form a pool over the stoma instead of draining into the bag; the leak occurs on the lateral side and is controlled by reinforcement with adhesive.

Most patients remove the bag once or twice daily, but it can be worn without change for longer periods—even up to a week. Odour is hardly noticeable, since the contents of the ileum are inoffensive and do not react with rubber in the same way as those from the large bowel. Most rubber bags require renewal after 4–6 months, though some patients seem able to maintain them in adequate repair for a longer time.

EXCORIATION

Excoriation of the skin often develops round the ileostomy and may last for six weeks after the operation. Once the skin heals, the trouble seldom recurs; but one woman reported repeated excoriation at the time of her periods, and another developed skin sensitivity to the cement three years after operation. A faulty stoma, or a fistula which constantly discharges at skin level, will induce persistent ulceration; similarly a persistent retrograde discharge of pus will damage the skin round the distal stoma.

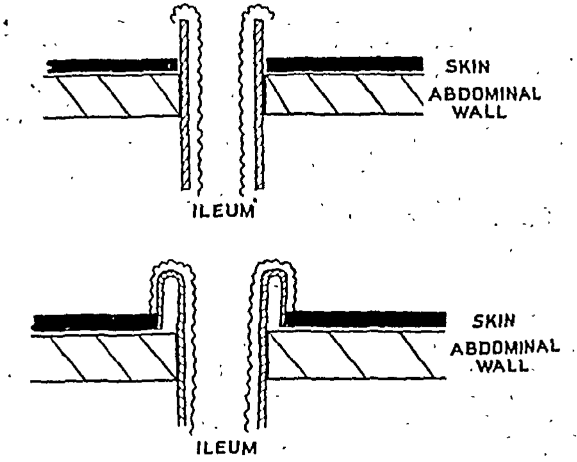


Fig. 2—Usual ileostomy (above) and ileostomy with everted end (below).

Several factors seem to contribute to this, chief of which are the continuous moisture and the trauma resulting from repeated application of the bag. Theoretically, responsibility might rest with the proteolytic enzymes sometimes present in the ileal contents, for they act upon denatured protein and could therefore digest the outer layer of the skin. However, no correlation has been found between the presence of enzyme and excoriation; wetting agents, such as cetyl sulphate, which destroy enzyme activity have not given complete protection to the skin, and the application of dressings containing ileal contents have not caused excoriation in areas remote from the ileostomy, even when ulceration has been present round the stoma.

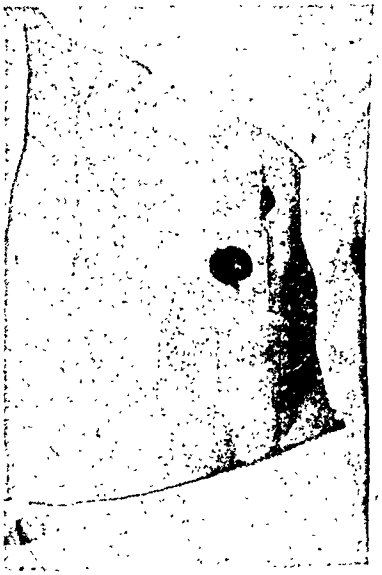


Fig. 3—Everted ileostomy, with mucosa sutured to skin, immediately after operation.

It is helpful to obtain drainage into a bag from the

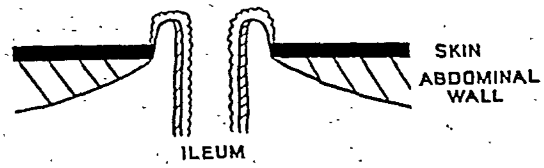


Fig. 4—Prolapse starting as herniation owing to damage to abdominal wall (cf. fig. 2).

outset and, to avoid the shearing effect of the adherent flange on the outer layers of constantly moist skin, it is best to build up a pad of gauze round the stoma for the flange to rest on. Both flange and dressing are next sealed off with adhesive, which adheres to the skin where it is not affected by ileostomy drainage. Protection in this manner may continue for two or three weeks after operation, by which time it should be possible to start using the cement.

Where excoriation persists because an inefficient stoma discharges its contents at skin level, only further operation and refashioning of the ileostomy will bring about any improvement; to rely on dressings and ointments in such cases is only to encourage vain hope.

INTESTINAL OBSTRUCTION

Intestinal obstruction is the commonest serious complication of ileostomy, but not much has been published about it. Warren and McKittrick (1951), however, have given a good account of it, using the title "ileostomy dysfunction" for the particular syndrome arising from partial obstruction which more often occurs; it was a major complication in 61·9% of their 210 patients. In my series of 37 ileostomies there have been 10 cases of obstruction, 1 causing the death of the patient, 2 requiring laparotomy for relief of adhesions, and 7 recovering without operation. Obstruction has not followed ileostomy done as part of the operation of primary colectomy in 9 further cases.

The site of obstruction may be at the stoma, at the abdominal wall, or within the abdomen owing to internal herniation or to adhesions. (Stenosis of the stoma is considered below.) If any part of the abdominal wall, especially the anterior rectus sheath or external oblique aponeurosis, is sewn with tension round the emerging ileum, this may precipitate obstruction in the relatively adynamic phase which follows the operation; it is avoided by relieving incisions in these structures. Likewise obstructions from snaring in the para-ileal gutter or at the site of mesenteric fixation (Hardy et al. 1949) is due to technical failure and can be avoided. It may even be that the fine adhesions which cause angulation and fixation of normally mobile small bowel (Brooke 1951) can be prevented; in the last 9 cases streptodornase and streptokinase have been injected into the peritoneal cavity in the hope of preventing the formation of these adhesions, and no obstruction has arisen in these 9 cases compared with an incidence of 1 in 3 before this.

The treatment of obstruction has been discussed elsewhere (Warren and McKittrick 1951, Brooke 1951) and needs no further mention here.

STENOSIS

Stenosis at the stoma arises, as Warren and McKittrick (1951) state, from scar tissue formed by the granulations that cover the raw serosal surface of the protruding ileum during the two postoperative weeks before the gradual evagination of the mucosa has brought that surface into continuity with the skin edge. It has complicated 4 of the 37 cases previously mentioned. Skin grafting (Dragstedt et al. 1941) should eliminate this but has not always proved satisfactory; for the graft, whether it be full-thickness or split-skin, is not infrequently followed by ulceration, stenosis, and even a fistula, though it is only fair to say that these difficulties have not been encountered at the Mayo Clinic (C. W. Mayo, personal communication).

Wells (1952) describes a "spout" ileostomy and states that the results are good, but his report is couched only in very general terms. A more simple device is to evaginate the ileal end at the time of operation and suture the mucosa to the skin (figs. 2 and 3); no complications have accrued from this. For the first few days the "bud" appears flattened on the skin, but it does not retract and should not do so if the mesentery has been tethered to the anterior abdominal wall; it soon stands out in conical form. Prolapse, which might be expected to follow this manœuvre, has not been encountered.

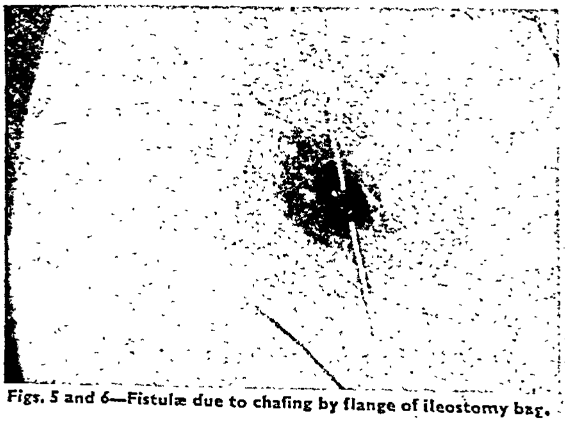
When stenosis develops it can sometimes be relieved by simple dilatation but may necessitate operation for its relief. It occasionally presents as retraction of the "bud"; in these cases contraction of the bowel wall causes the stoma to be withdrawn below the constriction, from which it cannot escape.

Fig. 5.

PROLAPSE

Prolapse, in the experience of most workers in this field, is a common complication—13% according to Warren and McKittrick (1951). In my series of 37 ileostomies 2 have prolapsed, and none of the 9 primary colectomies have given trouble in this way.

To prevent this complication the first principle is to fix the mesentery, as has been described elsewhere (Hardy et al. 1949, Brooke 1951). Mesenteric fixation will not, however, secure the bowel if the abdominal wall round the stoma has been damaged by infection or by further operation. In these circumstances the abdominal wall adjacent to the ileum becomes thin and fibrotic, and the gap through which the ileum passes widens so that



Figs. 5 and 6—Fistulæ due to chafing by flange of ileostomy bag.

herniation inevitably ensues; herniation thus initiates this type of prolapse (fig. 4). It is significant that 1 of the 2 cases of prolapse occurred after colectomy when the mesentery of the emerging ileal limb became detached and was not sutured down; this was cured by refixing the mesentery. In the other case prolapse followed a revision of the ileostomy for fistula; this was cured by removing the ileostomy stoma to a site where the tissues of the abdominal wall were undamaged.

The herniation type of prolapse can sometimes be controlled by pressure from outside the bag through a pad held opposite the stoma, but this will not prevent most cases of prolapse, for these develop as a form of intussusception. The operation, so commonly done for prolapse, of simply lopping off the extruded bowel is to be condemned outright. It is quite indefensible for two reasons: (1) it does not cure the prolapse, which almost invariably recurs; and (2) it removes an absorptive area of the bowel, every inch of which the patient requires.

For the operative cure of prolapse the abdomen should be opened through an incision remote from the ileostomy, which is then inspected from within as well as outside. If it is found by palpation that the abdominal wall alongside the ileum is attenuated, or that a finger passed from inside the abdomen presents at the stoma submucosally (fig. 4), the ileostomy should be detached and drawn out through a stab incision elsewhere, and finally the mesentery should be attached with care across the para-ileal gutter. If the ileum is discovered to be adherent throughout the depth of the abdominal wall in the normal way, mesenteric fixation with non-absorbable sutures should suffice.

FISTULÆ

Fistulæ form for two reasons. The ileal wall may be damaged or weakened at the time of operation; a fixation suture through serosa and muscle alone without penetration of the mucosa is particularly liable to cause a subsequent breakdown of the whole thickness of the bowel wall. A suture or ligature lying close to the ileum but not penetrating it in any way can lead to the same result. In these circumstances the fistula will appear in the first ten days or so after the operation. A fistula at skin level develops at any time after the operation through chafing of the stoma against the flange of the bag (figs. 5 and 6). The site of this fistula is inferior, and the fistula is probably caused where a stoma is placed too close to the groin, with the result that the flange is pushed up against the stoma when the patient sits down. It is also more liable to occur when the flange is reinforced with metal.

Fistulæ are avoided therefore by the elimination of fixation sutures, by suturing without tension the structures round the ileum, and by the proper siting of the stoma; it is also advisable not to use a bag with a flange reinforced with metal. The formation of a new ileostomy by further operation is the only cure for either type of fistula, and this must be done because persistence of a fistula, even though it may not pass deep to the skin, will cause excoriation and render the bag inefficient.

I wish to thank Dr. H. G. Sammons, of the department of pharmacology, University of Birmingham, for assessing the proteolytic activity of ileal discharges.

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ANTIBIOTICS AND AMŒBIC DYSENTERY

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IT has been known for many years that the ingestion of *Entamœba histolytica* does not necessarily mean that the patient will have either dysentery or any other manifestation associated with this parasite. The classical experiments of Walker and Sellards (1913) showed that only a proportion of volunteers deliberately infected with *E. histolytica* developed dysentery, although the infestation was well established. Westphal (1937), who infected himself with washed cysts from a case of dysentery, did not develop symptoms until he followed his diet of amœbæ with one of the associated fæcal flora from the same case. Differences in associated bacterial flora have been used by many workers, notably Deschiens (1937), to explain the difference in incidence of acute amœbic dysentery in warm and in temperate zones. Mathis (1918) stated that a bacterial flora adapted to a tropical humid climate might in a person coming from the temperate zones create conditions favourable for the development of the "aggressive" amœba. Conversely it has been the experience of doctors working in the tropics that spontaneous remissions in chronic amœbiasis can occur on transfer to a temperate zone.

Knotts and Thompson (1942) used an antibacterial approach to the treatment of amœbiasis in 1942, when they treated six cases of proved amœbiasis with success.

Payne (1945) found both sulphapyridine and sulphaguanidine clinically effective.

Hargreaves (1944) reported that penicillin was effective in saving the life of a moribund patient with dysentery, and he later (Hargreaves 1945) reported the successful use of penicillin and succinyl sulphathiazole in conjunction with emetine, bismuth iodide, and chiniofon.

Blanc and Siguier (1946), working in Indo-China, reported very favourably on the use of emetine, penicillin, and sulphaguanidine.

Halawani et al. (1946), in Egypt; Achitouv-Verdi (1945), in Turkey; Ellenberg (1946), in the United States; and Karl and Sloan (1946), in the India-Burma theatre of war, all reported on the value of sulphonamides as adjuvant treatments.

Armstrong, Wilmot, and Elsdon-Dew (1949) were impressed with the results of the treatment with penicillin, succinyl sulphathiazole, emetine, and 'Diodoquin,' and Armstrong, Marot, and Elsdon-Dew (1950a) reported on the value of penicillin alone and of succinyl sulphathiazole alone.

The next advance was published by McVay et al. (1949, 1950), who reported the effectiveness of aureomycin by itself.

Almost simultaneously Hughes (1950), Gutch (1950, 1951) and ourselves (Armstrong et al. 1950b) published further results indicating the effectiveness of aureomycin in the treatment of amœbiasis. Though these workers all reported relapses, there were indications that aureomycin had a directly amœbicidal action in addition to the bacterial sterilising effect on the bowel reported by Dearing and Heilman (1950).

Jones (1950) pointed out the difficulties in distinguishing such anti-amœbic from antibacterial effects in vitro. These difficulties were largely overcome by Hewitt et al. (1950), who showed that exposure of amœbæ to aureomycin for an hour was sufficient to prevent growth after adequate washing and reseeding under ideal conditions.

The next antibiotic to enter the field was bacitracin.

Most et al. (1950b) reported that there was complete recovery, with disappearance of amœbæ, in 8 severe cases, and 66% of mildly symptomatic or asymptomatic patients who received the treatment were cleared. Most et al. (1950a compare aureomycin and bacitracin and mention that chloromycetin was usually found ineffective.

Next, Most and van Assendelft (1950) reported on the effects of terramycin, which they found completely effective in 21 out of 22 cases. In a further paper (1951) they report results in 54 cases and point out that the optimal dosage is 2 g. a day for ten days.

The adequacy of this form of treatment was confirmed by Nor-El-Din (1951), in Egypt, who reported complete cure with two relapses, one after a month and another after six weeks. After treating 9 monkeys under controlled conditions Hrenoff (1951) found relapses in five, nine, and eleven weeks.

Conn (1951), basing his work on that done by Thompson et al. (1950), tried both aureomycin and chloramphenicol. With the former they had 3 failures out of 17, and with the latter 3 failures out of 6.

Felsenfeld et al. (1950) reported that neomycin showed a strong activity in vitro and in vivo against *E. histolytica.*

It will be seen that many different antibiotics and other antibacterial drugs have been tried in amœbiasis, but it is very difficult to compare and contrast the results. The standards of diagnosis, of severity, and of cure vary from one worker to another. Since amœbiasis may vary in its manifestations from complete quiescence to fulminant dysentery, it is impossible to compare the various types of therapy.

METHODS

The high incidence of amœbic dysentery in the Durban African has enabled us to use a statistical approach to assess the results of therapy. We were able not only to use 50 cases as a standard basis for assessment but also to select cases so that the clinical and laboratory manifestations were, so far as possible, uniform. When there was a high failure-rate among the early cases treated with a particular drug and it could be shown statistically that the drug was not likely to be of much value, that series was discarded. Occasionally, shortage of a drug limited the number of cases which could be treated with a particular drug.

All the patients accepted for the trials were complaining of diarrhœa with blood and mucus, showed ulceration on sigmoidoscopy, and had actively motile *E. histolytica* in stools or ulcer scrapings. Patients passing cysts were not accepted. In the Durban African, for reasons which we do not understand, amœbic dysentery tends to be unusually severe. We excluded patients who showed chloride deficiency, abdominal distension, sloughs on sigmoidoscopy, or other signs which we have found to presage perforation or ileus, because we thought it unjustifiable to experiment on such severely ill patients. Any cases showing liver manifestations were also excluded. The cases accepted therefore represent a relatively uniform population.

Sigmoidoscopy was always done before treatment. In the earlier series it was repeated at ten and twenty days, and in the later series at intermediate intervals as well and at twenty-seven days after the start of treatment. With certain drugs sigmoidoscopy was done daily, so that the day of healing and the day of disappearance of amœbæ could be determined. Ulcer scrapings were examined directly. Stools were examined by saline smear, zinc-sulphate flotation, and, where indicated, by staining.

Results were classified into four categories:

(1) *Success:* patient symptom-free; all ulcers healed, and no amœbæ found in stools.

(2) *Probable failure:* patient usually symptom-free; one or more ulcers still open, but amœbæ not found in stools or scrapings.

(3) *Cyst-passer:* patient symptom-free; ulcers healed, cysts present in stools.

(4) *Absolute failure:* open ulcers and/or amœbæ still present.

At the outset of this work we did not know the relative efficacy of even the recognised amœbicides. We therefore tested the known amœbicides separately; but, when later experience indicated that certain additional therapies were likely to be successful, we could no longer risk the lives of patients who were obviously deteriorating. These patients were removed from the series and given additional drugs. Such cases that had had five days or more of a particular test therapy were regarded as failures for that therapy; but, where a case had to be removed from a series before five days of the test therapy, the case was not included, because it was felt that the drug had not had a fair opportunity.

Under the heading "Combined Failure-Rate" we have included all those who still harboured parasites. This figure is the sum of the figures for absolute failures, cyst passers, and those removed from treatment.

Our records are nearly complete as regards immediate result, but our follow-up studies have perforce been very incomplete. The African is careless of his health and sees little reason to return for follow-up if he is well. Since few of our patients have permanent addresses, it is impossible to re-establish the contact broken on discharge, and we have to rely only on the individual goodwill of patients for follow-up studies. Even with a bribe coöperation has been poor. Though we have little evidence on the presence or absence of amœbæ as time passes after the end of treatment, we have some evidence on the incidence of symptomatic relapse. Our patients are very satisfied with the attention paid to them, and most of them return to us if symptoms recur. We are therefore in a position to give the figures of relapse or reinfection in those who return to us. Probably this figure is a reasonable approximation of symptomatic relapse and comparable from one series to another. This is, of course, a minimal clinical and parasitic relapse-rate, which leaves out the few who go elsewhere and all cases of parasitic relapse without symptoms.

RESULTS

Procaine Penicillin

Details of this series of 54 cases were given in a previous paper (Armstrong et al. 1950a). The dosage was 300,000 units in oil daily for twenty days (total 6,000,000 units). By the twentieth day there was considerable improvement in all the cases, and in 39% all visible ulcers had healed and amœbæ had disappeared (table I). Even without further treatment there was still improvement between the twentieth and twenty-seventh days, and at this stage 46% of the cases had been cleared of their ulcers and amœbæ.

TABLE I—RESULTS WITH PROCAINE PENICILLIN 300,000 UNITS IN OIL DAILY FOR TWENTY DAYS (TOTAL 6,000,000 UNITS)

Assessment	No. of cases (total 54)		
	At 10 days	At 20 days	At 27 days
Successes	12 (*22·2%*)	21 (*38·9%*)	25 (*46·3%*)
Probable failures	16 (*29·6%*)	12 (*22·2%*)	9 (*16·7%*)
Cyst-passers	Nil	Nil	Nil
Absolute failures	26 (*48·2%*)	19 (*35·2%*)	8 (*14·8%*)
Removed from treatment	Nil	2 (*3·7%*)	12 (*22·2%*)
Combined failure-rate	48·2%	38·9%	37·0%

Of 15 cases that had not responded to penicillin 11 improved greatly on succinyl sulphathiazole, and 7 of these were classified as successes. However, 1 of these so-called successes returned fourteen days later and quickly died of a fulminating amœbic colitis, providing tragic proof that we had neither eradicated the parasite nor permanently curbed its powers of invasion.

Succinyl Sulphathiazole

The dosage in these 57 cases was 15 g. initially, followed by 3 g. four-hourly five times a day. This dosage is double that given by Hargreaves (1945) in his original course, and was continued for twenty days instead of 7.

TABLE II—RESULTS WITH SUCCINYL SULPHATHIAZOLE 15 G. INITIALLY, FOLLOWED BY 3 G. FOUR-HOURLY FIVE TIMES A DAY FOR TWENTY DAYS (TOTAL 315 G.)

Assessment	No. of cases (total 57)		
	At 10 days	At 20 days	At 27 days
Successes	9 (*15·8%*)	22 (*38·6%*)	31 (*54·4%*)
Probable failures ..	26 (*45·6%*)	15 (*26·3%*)	9 (*15·8%*)
Cyst-passers	Nil	Nil	Nil
Absolute failures ..	21 (*36·8%*)	18 (*31·6%*)	4 (*7·0%*)
Removed from treatment	1 (*1·8%*)	2 (*3·5%*)	13 (*22·8%*)
Combined failure-rate..	38·6%	35·1%	29·8%

Throughout this series, as in that treated with penicillin, there was a steady fall in the number of failures and as steady a rise in the number of successes even after treatment had ceased (table II).

It is particularly worthy of note that after only ten days' treatment with succinyl sulphathiazole 62·5% of these patients had been rendered free not only of their symptoms but also of their amœbæ. This is a matter of first importance and indicates the danger of treating cases of undiagnosed dysentery with sulphonamides. Such a practice would lead to the suppression of the correct diagnosis in many cases of amœbic dysentery.

Procaine Penicillin and Succinyl Sulphathiazole

The results (table III) show that these two substances have a synergistic effect. Of the 50 patients only 3 showed parasites on the twenty-seventh day, and 1 of these was a symptomless cyst-passer. When it is remembered that neither of the drugs used is considered to have any action other than antibacterial, the results are remarkable.

TABLE III—RESULTS OF COMBINED TREATMENT WITH PROCAINE PENICILLIN AND SUCCINYL SULPHATHIAZOLE

Assessment	*No. of cases (total 50)*		
	At 10 days	At 20 days	At 27 days
Successes	34 (*68%*)	43 (*86%*)	46 (*92%*)
Probable failures ..	15 (*30%*)	6 (*12%*)	1 (*2%*)
Cyst-passers	Nil	Nil	1 (*2%*)
Absolute failures ..	1 (*2%*)	Nil	1 (*2%*)
Removed[1] from treatment	Nil	1 (2%)	1 (2%)
Combined failure-rate..	2%	2%	6%

Phthalylsulphacetamide

A series was begun in which treatment was with phthalylsulphacetamide 3 g. four-hourly five times a day for twenty days (total 300 g.). When only 12 cases had been completed, it was apparent (table IV) that, in this dosage, this sulphonamide was inferior to succinyl sulphathiazole; so there was no point in investigating it further.

Streptomycin

The dosage in 17 cases was 2 g. daily by mouth for ten days (total 20 g.). It will be seen from table V that it was necessary to remove 7 of the cases from the therapy before the test period had elapsed. Streptomycin manifested an unusual feature: at one time or another during the course of the therapy no fewer than 8 of the 17 cases passed cysts, a phenomenon seen before in isolated cases only.

TABLE IV—RESULTS WITH PHTHALYLSULPHACETAMIDE 3 G. FOUR-HOURLY FIVE TIMES A DAY FOR TWENTY DAYS (TOTAL 300 G.)

Assessment	No. of cases (total 12)	
	At 10 days	At 20 days
Successes	Nil	2 (*16·6%*)
Probable failures	4 (*33·3%*)	2 (*16·6%*)
Cyst-passers	Nil	Nil
Absolute failures	8 (*66·6%*)	8 (*66·6%*)
Failure-rate	66·6%	66·6%

Aureomycin by Mouth

This series has been discussed at length elsewhere (Armstrong et al. 1950b) and the results are shown in table VI. The rather small dose of 1 g. was given daily for fifteen days to 52 patients. Daily sigmoidoscopy showed a remarkably rapid rate of healing. 12 cases (24·9%) were healed by the fourth day, and 29 (55·7%) by the seventh day. Disappearance of amœbæ was equally rapid. By the fourth day 71%, and by the ninth day 98%, of patients had been cleared of amœbæ. It was found in most cases that on the third and fourth days the amœbæ increased greatly in size, sometimes reaching a diameter of 90 µ. A day later they had usually vanished.

TABLE V—RESULTS WITH STREPTOMYCIN 2 G. DAILY FOR TEN DAYS

Assessment	No. of cases (total 17)		
	At 10 days	At 20 days	At 27 days
Successes	5 (*29·4%*)	4 (*23·5%*)	4 (*23·5%*)
Probable failures ..	4 (*23·5%*)	2 (*11·8%*)	1 (*5·9%*)
Cyst-passers	2 (*11·8%*)	3 (*17·6%*)	2 (*11·8%*)
Absolute failures ..	6 (*35·3%*)	2 (*11·8%*)	3 (*17·6%*)
Removed from treatment	Nil	6 (*35·3%*)	7 (*41·2%*)
Combined failure-rate..	47·1%	64·7%	70·6%

It was necessary to remove only 1 case from this series owing to deterioration. Within a month of completion of treatment 6 of our patients, classed as successes, had relapsed with proved amœbic dysentery and 1, though symptom-free, had cysts in his stools. This cyst-passer was symptom-free and normal on sigmoidoscopy, with a negative casual stool, at seven months. 20 successes were seen at one month, 8 at two months, 2 at three months, and 1 at four months. 1 patient was readmitted at eleven months with clinical dysentery. 1 was symptom-free at eleven months, and another at sixteen and a half months.

Intravenous Aureomycin

We gave aureomycin intravenously to 2 cases:

CASE 1 received 300 mg. twelve-hourly for eleven doses. At the end of this time the aureomycin was stopped because all the ulcers had healed. Trophozoites disappeared on the fourth day, and all the ulcers were healed on the fifth day. Cysts were present on the seventeenth, eighteenth, and nineteenth days, though all the ulcers remained healed on the tenth, fifteenth, twentieth, and twenty-seventh days. Five weeks later, though the patient was symptom-free, open ulcers and trophozoites were present.

TABLE VI—RESULTS WITH ORAL AUREOMYCIN 1 G. DAILY FOR *FIFTEEN DAYS*

Assessment	No. of cases (total 52)		
	At 10 days	*At 20 days*	*At 27 days*
Successes	35 (*67·3%*)	49 (*94·2%*)	48 (*92·3%*)
Probable failures ..	16 (*30·8%*)	2 (*3·8%*)	2 (*3·8%*)
Cyst-passers	Nil	Nil	Nil
Absolute failures ..	1 (*1·9%*)	1 (*1·9%*)	1 (*1·9%*)
Removed from treatment	Nil	Nil	1 (*1·9%*)
Combined failure-rate..	1·9%	1·9%	3·8%

CASE 2 received 300 mg. twelve-hourly for eight doses. All the ulcers were healed by the fourth day, and trophozoites disappeared on the third day. No ulcers were seen up to the twenty-seventh day, but cysts were *found on the* twentieth

TABLE VII—RESULTS WITH TERRAMYCIN 1 G. DAILY FOR FIFTEEN DAYS

Assessment	No. of cases (total 49)		
	At 10 days	At 20 days	At 27 days
Successes	43 (*87·7%*)	44 (*89·8%*)	45 (*91·8%*)
Probable failures	4 (*8·2%*)	2 (*4·1%*)	Nil
Cyst-passers	Nil	Nil	Nil
Absolute failures	2 (*4·1%*)	1 (*2·0%*)	Nil
Removed from treatment	Nil	2 (*4·1%*)	4 (*8·2%*)
Combined failure-rate	4·1%	6·1%	8·2%

and twenty-seventh days. Four weeks later the patient had diarrhœa, and trophozoites and ulcers were found.

Terramycin

Terramycin 1 g. daily in divided doses was given to 49 patients (table VII). There were originally 51, but 2 developed hepatitis which progressed in spite of terramycin treatment and necessitated the use of emetine on the sixteenth day in one case and chloroquin on the sixth day in the second. Both cases were "successes" from the intestinal standpoint before the extra drugs were used. It was decided, however, to discard them from the series as not conforming to our usual standard. Follow-up was, as always, very incomplete. At one month 20 cases returned, 18 being successes and 2 failures in full relapse. At two months there were 4 successes and 1 failure. At three and four months there were 3 and 1 successes respectively. At six months 1 absolute failure returned. At eight months 1 success returned. From the follow-up figures available to us it is not possible to compare the late effects of aureomycin and terramycin with any accuracy. Daily sigmoidoscopy showed a rate of healing and a rate of disappearance of ulcers which appeared to differ in no way from the results with aureomycin. 8 cases (16·3%) were healed by the fourth day and 32 (65·0%) by the seventh day. By the fourth day 77·6%, and by the seventh day 89·7%, had been cleared of amœbæ. Giant forms of amœba were not seen during treatment with terramycin.

TABLE VIII—RESULTS WITH CHLORAMPHENICOL 4 G. DAILY FOR THREE DAYS FOLLOWED BY 2 G. DAILY FOR NINE DAYS (TOTAL 30 G.)

Assessment	No. of cases (total 16)		
	At 10 days	At 20 days	At 27 days
Successes	13 (*81·3%*)	12 (*75·0%*)	10 (*62·5%*)
Probable failures	2 (*12·5%*)	Nil	Nil
Cyst-passers	1 (*6·2%*)	3 (*18·8%*)	3 (*18·8%*)
Absolute failures	Nil	1 (*6·2%*)	2 (*12·5%*)
Removed from treatment	Nil	Nil	1 (*6·2%*)
Combined failure-rate	6·2%	25·0%	37·5%

Chloramphenicol

The results of treating 16 patients with chloramphenicol 4 g. daily for three days, followed by 2 g. daily for nine days, are shown in table VIII. Initially, these patients progressed well. All were free from amœbæ by the fifth day, and 14 were healed on the tenth and fifteenth days. However, both parasitic and symptomatic relapses were frequent and early. There were 3 absolute failures: 1 on the twentieth, 1 on the twenty-fifth, and 1 on the twenty-sixth day after treatment had started.

TABLE IX—RESULTS WITH NEOMYCIN 40,000 UNITS INITIALLY FOLLOWED BY 10,000 UNITS FOUR-HOURLY FOR TEN DAYS (TOTAL 540,000 UNITS)

Assessment	No. of cases (total 12)		
	At 10 days	At 20 days	At 27 days
Successes	5 (*41·7%*)	5 (*41·7%*)	4 (*33·3%*)
Probable failures	2 (*16·7%*)	Nil	Nil
Cyst-passers	Nil	Nil	Nil
Absolute failures	4 (*33·3%*)	Nil	1 (*8·3%*)
Removed from treatment	1 (*8·3%*)	7 (*58·3%*)	7 (*58·3%*)
Combined failure-rate	41·6%	58·3%	66·6%

Of 15 successes at twenty days and 13 successes at twenty-eight days, 3 were passing cysts. At the end of eight months a further 4 successful cases had a full relapse with ulcers and trophozoites in the stools. At the outset healing of ulcers and disappearance of amœbæ were as rapid and dramatic as with aureomycin and terramycin, but we noticed that some inflammation often remained in the bowel. As with streptomycin, there were tendencies to form cysts and towards symptomatic relapse.

TABLE X—RESULTS WITH BACITRACIN 40,000 UNITS INITIALLY FOLLOWED BY 10,000 UNITS FOUR-HOURLY FOR TEN DAYS (TOTAL 540,000 UNITS)

Assessment	No. of cases (total 12)		
	At 10 days	At 20 days	At 27 days
Successes	10 (*83·3%*)	9 (*75·0%*)	8 (*66·6%*)
Probable failures	Nil	Nil	1 (*8·3%*)
Cyst-passers	Nil	Nil	Nil
Absolute failures	1 (*8·3%*)	Nil	Nil
Removed from treatment	1 (*8·3%*)	3 (*25·0%*)	3 (*25·0%*)
Combined failure-rate	16·6%	25·0%	25·0%

Neomycin

Of the 12 patients to whom we gave neomycin 40,000 units initially, followed by 10,000 units four-hourly for ten days, no less than 7 had to be removed from treatment owing to deterioration of their condition, and it will also be seen (table IX) that 1 case classed as a "success" at twenty days had reverted to an absolute failure at twenty-seven days.

Bacitracin

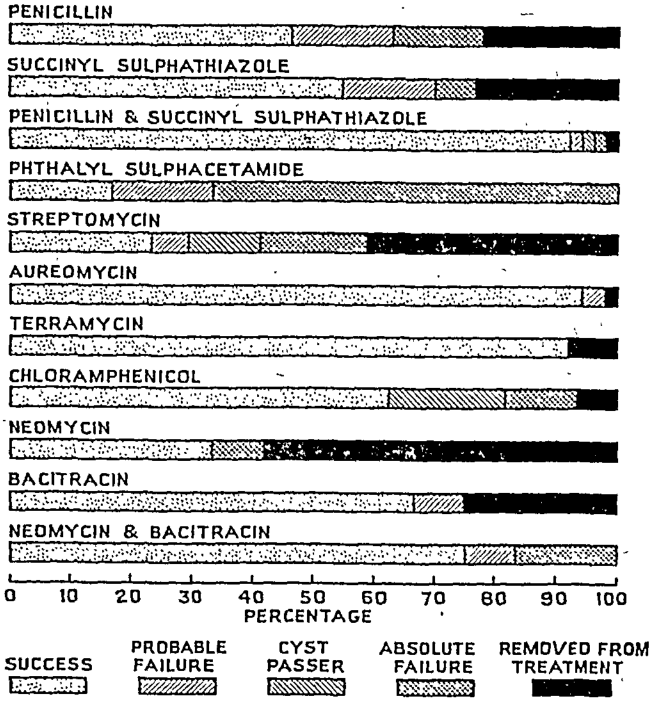
Bacitracin 40,000 units initially, followed by 10,000 units four-hourly for ten days, was given to 12 patients. It will be seen (table X) that some of the patients initially classed as successes were given other treatment before their period of observation was complete, because of deterioration in their clinical condition and/or reappearance of ulcers or parasites.

TABLE XI—RESULTS WITH BACITRACIN AND NEOMYCIN 20,000 UNITS OF EACH INITIALLY, FOLLOWED BY 5000 UNITS OF EACH FOUR-HOURLY FOR TEN DAYS (TOTAL 270,000 UNITS OF EACH)

Assessment	No. of cases (total 12)		
	At 10 days	At 20 days	At 27 days
Successes	10 (*83·3%*)	11 (*91·7%*)	9 (*75·0%*)
Probable failures	2 (*16·7%*)	Nil	1 (*8·3%*)
Cyst-passers	Nil	1 (*8·3%*)	Nil
Absolute failures	Nil	Nil	2 (*16·7%*)
Combined failure-rate	Nil	8·3%	16·7%

Bacitracin and Neomycin

The results of treating 12 patients with bacitracin and neomycin 20,000 units of each initially, followed by 5000 units of each four-hourly for ten days, are shown in table XI. No case deteriorated sufficiently to warrant removal from the series. Indeed in all 12 cases healing of ulcers was complete by the twentieth day, and all were classed as successes. One of these patients, however, was passing cysts, but still had no ulcers on the twenty-seventh day. 1 successful case discharged himself on the twentieth day and is considered to have been a success



Results of treatment of amœbic dysentery with antibiotics.

at twenty-seven days. 2 absolute and 1 probable failures were found at twenty-seven days; all 3 had reverted from successes at twenty days.

DISCUSSION

From the foregoing results, which are illustrated in the accompanying figure, it will be seen that certain of the antibiotic drugs can produce an immediate apparent cure in a very high proportion of cases of the acute ulcerative amœbiasis which we encounter here in Durban. Apparently we can profoundly modify the course of the disease by an attack on the bacterial flora associated with the parasite. The disappearance of the parasite in these circumstances suggests that the bacterial flora in some way supports the amœba. Not all antibiotics operate in the same way. For example, the use of penicillin left some 30% of cases with amœbæ, and the same may be said of succinyl sulphathiazole. However, in combination these two drugs left only 3 out of the 50 cases harbouring parasites—a degree of success attained also by aureomycin and terramycin. In comparison with succinyl sulphathiazole the other sulphonamide tried, phthalylsulphacetamide, had relatively little effect. Streptomycin only cleared some 30% of cases of their amœbæ, as did neomycin. Bacitracin and chloramphenicol each cleared some 80%, and there was, if anything, a slight improvement on this figure by the combination of neomycin and bacitracin.

In deciding which is the most effective agent it is wise to watch the progress of the figures as well as the actual figures themselves. If the combined failure-rate is watched for each drug at ten, twenty, and twenty-seven days, it will be seen that there is a decline in the case of both penicillin and succinyl sulphathiazole; an insignificant change or no change in the highly effective drugs aureomycin, terramycin, and combined penicillin and succinyl sulphathiazole; and a steady and significant increase in the numbers of failures with the relatively unsuccessful drugs streptomycin, chloramphenicol, neomycin, bacitracin, and combined bacitracin and neomycin. From this we conclude that the most effective agents in this respect are aureomycin, terramycin, and penicillin and succinyl sulphathiazole used in combination.

It is apparent from these facts that the wider the range of bacteria attacked the higher is the proportion of successes in any given series. It seems from this that a wide variety of organisms can support the amœbæ in the bowel.

In the present cases the establishment of a cyst-passing phase was a rarity; yet under the action of streptomycin and chloramphenicol many of these cases were converted from the acute trophozoite-passing phase to that of the symptomless cyst-passer. Attempts to duplicate this in vitro were unsuccessful.

Although aureomycin given by mouth did not produce cyst-passers, both the patients treated with this drug intravenously passed through a cyst-passing phase before relapsing. Possibly this was due to the short duration of treatment.

So far we have been discussing the effect of the antibiotics as if this effect was only through the associated bacterial flora, but there is more than a little evidence that certain of the antibiotics may have a directly *amœbicidal* effect.

The assessment of such an effect is most difficult in vitro because *E. histolytica* will not grow alone. To assess how much of an antibiotic's effect has been on the amœba itself and how much on the associated bacteria is practically impossible. However, by exposing amœbæ to various agents, washing them, and replacing them in their original flora, it is possible to form some idea about whether a particular antibiotic has a direct effect. In our hands, as in those of other workers (Hewitt et al. 1950), aureomycin and terramycin are amœbicidal in concentrations likely to be reached in the bowel.

We have shown (Wilmot et al. 1952) that aureomycin has little or no effect on amœbic liver abscess, where there is no confusion between antibacterial and antiamœbic effect. This suggests that the action of aureomycin in bowel cases is mainly on the symbiotic bacteria.

A further feature of the antibiotic treatment of amœbiasis is the rapidity with which the lesions heal and the amœbæ disappear. Under aureomycin therapy, on the tenth day 67% of cases had been cleared of their ulcers, and 98% of their amœbæ. Under terramycin 84% had been cleared of their ulcers, and 94% of their amœbæ. It will be seen that there is little difference between aureomycin and terramycin in this respect.

One of the criticisms of antibiotic therapy made by most workers is that there is a high relapse-rate. As mentioned before, we are unable, from the nature of the cases on which we are working, to give any accurate estimates of the relapse-rates under different varieties

TABLE XII—FOLLOW-UP RESULTS

—		Penicillin and succinyl sulphathiazole	Aureomycin	Terramycin	Strepto-mycin	Bacitracin	Bacitracin and neomycin
No. treated		54	52	49	17	12	12
No. discharged as cured		46	48	42	6	8	8
One month	Presenting	22	26	20	2	2	5
	Success ..	21	20	18	2	1	3
	Failure ..	1	6	2	..	1	2
Two months	Presenting	5	8	5	..	1	2
	Success ..	2	8	4	..	1	2
	Failure ..	3	..	1	..	..	..
Three months	Presenting	3	2	3	..	..	1
	Success ..	1	2	3	..	..	1
	Failure ..	2	..	..	..	..	..
Four months	Presenting	1	1	1	1	..	..
	Success ..	1	1	1	..	..	..
	Failure ..	..	..	1	1	..	..
Six months	Presenting	..	..	1	..	..	..
	Success ..	..	..	..	..	..	..
	Failure ..	..	..	1	..	..	..

of therapy—not only do the patients not return until they are ill, but also one has to bear in mind that the Bantu in Durban is not only extremely susceptible but is also, from the nature of his home surroundings, very heavily exposed to a new infection. Nevertheless there can be little doubt that relapses take place after antibiotic treatment. Table XII gives some indication of the relapses as seen. All that can be said from this table is that relapses occur after antibiotic treatment as indeed they do after any other form of therapy. We have no evidence that they are more frequent.

It therefore seems that, though the antibiotics can clear the clinical condition in severe dysentery and remove amœbæ from most of them, it is advisable to use some direct amœbicide in addition.

SUMMARY

Certain antibiotic drugs are very effective when used alone in the treatment of acute amœbic dysentery. Not only do ulcers and symptoms clear up, but also in many cases the amœbæ disappear. In this respect aureomycin, terramycin, and a combination of penicillin and succinyl sulphathiazole are the most effective. Treatment with them produces a much higher immediate cure-rate than can be obtained with any single directly amœbicidal drug (see Wilmot et al. 1951).

Probably the main action of the antibiotics is on organisms other than the amœba. Whether these organisms assist the amœba by attacking the host or by the supply of essential factors remains in doubt. There is in-vitro evidence that aureomycin and terramycin have some direct anti-amœbic effect.

To ensure success it seems that the antibiotics used should have the widest possible antibacterial "spectrum," for it is known that more than one species of bacterium can support the amœba, and all possible symbionts should be removed.

Under the action of certain antibiotics, notably chloramphenicol and streptomycin, acute dysenteric cases may be converted to symptomless cyst passing. It seems that an inadequate antibiotic or inadequate dosage will curb invasiveness and promote cyst passing.

With aureomycin and terramycin early relapses after four to eight weeks are fairly usual. With the other antibiotics relapses are common. We therefore feel that established amœbicides should at present be used in conjunction with antibiotics.

Work of this nature could not be carried out without the coöperation of the manufacturers and it is with the greatest of pleasure that we record our thanks to the Schering Corporation, Bloomfield, N.J., for the supply of phthalylsulphacetamide and streptomycin; Lederle Laboratories, New York, for the supply of the very large quantities of aureomycin we have used; Chas. Pfizer & Co. Inc., Brooklyn, N.Y., for the very generous supply of terramycin; Parke, Davis & Co., Detroit, Mich., for large supplies of chloramphenicol; and Commercial Solvents, Terre Haute, Indiana, for the supply of neomycin and bacitracin. Not only have these companies been most generous in making the material available, but they have also been of the greatest assistance with the supply of literature and advice.

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A METHOD OF ASSESSING THE MECHANICAL PROPERTIES OF LUNGS AND AIR-PASSAGES

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THIS paper describes a method of estimating the force needed to ventilate the lungs. When this force is increased, the method helps to define its cause; it also provides an objective test for bronchodilator drugs.

METHOD

Principle

The respiratory muscles have to overcome two types of force: elastic force due to the stretching of the lungs and therefore depending on the depth of inspiration; and viscous force due mainly to the resistance offered by the air-passages to the flow of air and therefore depending on the rate of air movement.

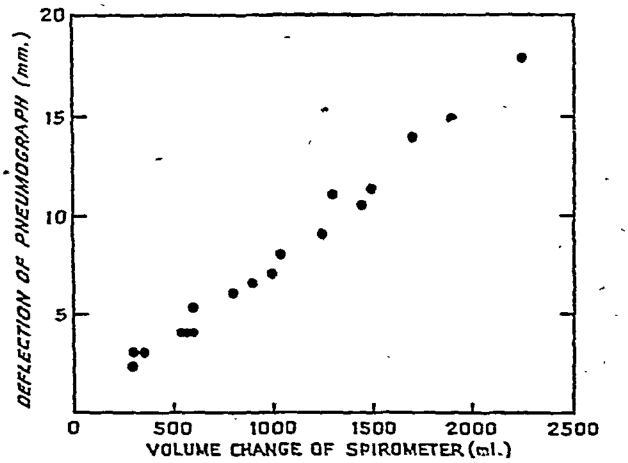

Fig. 1—The approximate linear relationship between expansion of trunk and tidal air measured with a spirometer.

Fibrosis renders the lungs less distensible and increases the first type of force: bronchiolar narrowing, or other impediment to airflow, increases the second. Simultaneous records of the total force applied to the lungs and of the resulting movement allow an assessment of the contributions of the elastic and viscous components. The total force is proportional to the pressure round the lungs—i.e., the intrathoracic pressure. To estimate this we have measured the pressure in the œsophagus. Lung

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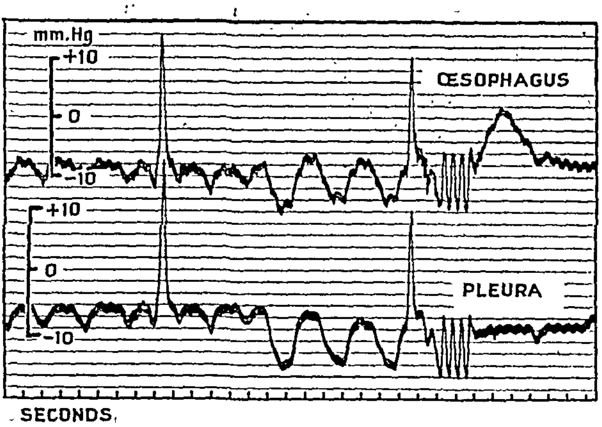

Fig. 2—Dynamic agreement of œsophageal and pleural pressures in a case of spontaneous pneumothorax. The spikes are due to small coughs. At the right of the tracing the œsophageal pressure rises in a characteristic way due to a swallow. Time is marked in seconds.

expansion has been estimated from records of increase in the girth of the chest and abdomen.

Procedure

A 'Polythene' tube of about 1 mm. external and 0·5 mm. internal diameter is prepared by cutting two or three lateral holes near one end. This end is passed through the nose into the œsophagus. The free end is attached to a capacitance manometer, and the system is filled with water. The fine plastic tube disturbs the patient less than does a tube of the Ryle type.

To record trunk expansion a length of "elephant" tubing is lightly strapped round the chest and another round the abdomen. The two lengths are joined by a Y connection to a second manometer, which records the decrease in pressure produced by stretching the tubing. The output of this manometer may be passed through a circuit that gives the rate of change of expansion as an additional record.

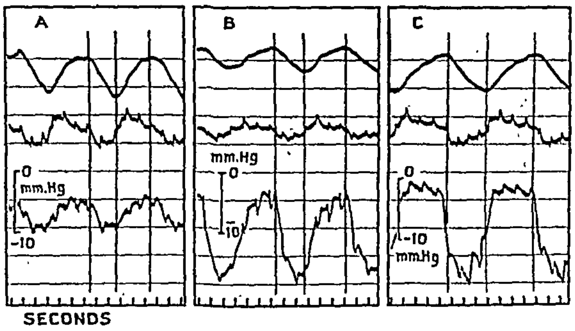

Fig. 3—Pneumograph, pneumotachygraph, and œsophageal pressure from a normal person: A, unimpeded breathing; B, breathing from a closed tank, simulating increased elastic forces; C, breathing through a narrow tube, simulating increased viscous forces. Note different form and timing of enhanced intrathoracic pressure swing in the last two sections.

Validation

Fig. 1 shows that the deflection produced by the pneumograph agrees well with the amount of air inspired.

When a person blows (or sucks) against a mercury column, the applied pressure is found to be transmitted to the œsophagus and fully maintained there. Fig. 2 shows that changes in intrapleural pressure are duplicated in the œsophageal.

ILLUSTRATIVE RESULTS

Fig. 3 is from the record of a normal person and shows the differing effects of factitious increases in elastic and viscous forces.

Fig. 4 illustrates the corresponding patterns in pathological states.

Fig. 5 illustrates an unequivocal bronchodilator response to a drug.

DISCUSSION

The method here described relates the pressure applied to the lungs to their consequent movement, and thus defines their mechanical impedance. An increase in this is one factor in the production of dyspnœa. When it is increased, it is of interest whether the viscous or the elastic component is chiefly responsible. An inspection of the records will usually answer this question; or, if necessary, the magnitude of the components may be estimated by a method due to von Neergaard and Wirz (1927). The analysis depends on the fact that at the end of an inspiration, when there is no air movement, the recorded pressure is due to elastic forces only. By comparing a series of respirations of differing depth it is possible to construct an elastic (depth-pressure) characteristic for the subject. One may then subtract from the observed pressure at any point of a respiratory cycle that part due to lung stretch. What remains must be due to viscous forces and is related to the rate of airflow at that moment. The viscous characteristic may thus be constructed.

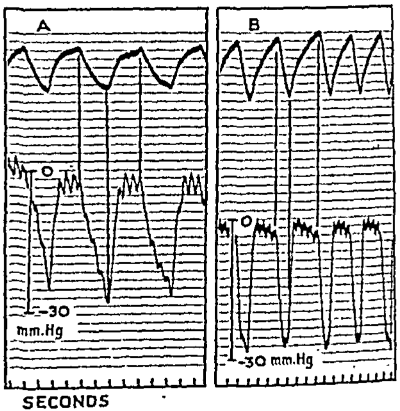

Fig. 4—Pneumograph and intra-œsophageal pressure: A, from a case of pulmonary fibrosis, illustrating increased elastic forces (cf. fig. 3B); B, from a case of severe asthma, illustrating increased viscous forces (cf. fig. 3C).

Previous workers have measured the intrapleural pressure in patients with pneumothorax, but this technique is not generally applicable. We are satisfied that the intra-œsophageal pressure, which can be measured in any patient with very little disturbance, is an adequate substitute.

We have measured trunk expansion, rather than air movement, for greater comfort to the patient and for greater ease of recording. We consider this, and the "pneumotachygraph" obtained by electrical differentiation, adequate for visual analysis, but for the quanti-

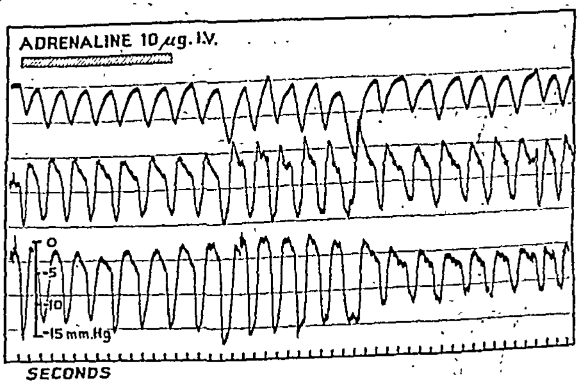

Fig. 5—Pneumograph, pneumotachygraph, and intra-œsophageal pressure in moderate asthma, showing effect of adrenaline. After brief stimulation of respiration adrenaline dilates bronchioles and decreases intrathoracic pressure swing.

tative treatment outlined above a direct record of airflow would be preferred.

When applying the method to the assessment of bronchodilator drugs one selects from the record, before and after treatment, respiratory cycles which agree in their volume patterns. One thus eliminates any action of the drug on respiratory drive; any change in the pressure pattern may then be attributed to an effect on the bronchioles.

SUMMARY

The pressure in the œsophagus is readily measured, and is a satisfactory index of the general intrathoracic pressure.

By simultaneous measurement of œsophageal pressure and trunk expansion it is possible to estimate and analyse the force needed to expand the lungs.

Some applications are described and illustrated.

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EOSINOPENIC RESPONSE TO A.C.T.H. ADMINISTERED INTRAVENOUSLY AT VARIOUS RATES

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During the past two years several workers (Gordon et al. 1951, Renold et al. 1951, McIntosh and Holmes 1951, Mandel et al. 1951) have advocated the intravenous route as the most effective and economical way of giving adrenocorticotropic hormone (A.C.T.H.). Though isolated incidents of reactions have been reported (Mandel et al. 1951, Wilson 1951), the opinion from major centres where this technique has been widely used is that such incidents are exceedingly rare. McIntosh and Holmes (1951) gave various doses of intravenous A.C.T.H. over 24-hour periods to two patients, and suggested that there is a minimum dose which will produce a maximum or nearly maximum stimulation of the adrenal cortex.

The present study extends these observations and relates the dose of continuously administered intravenous A.C.T.H. to the rate of the eosinopenic response.

METHODS

A.C.T.H. (Armour L-A 1-A)* was given to five patients by intravenous drip, the diluent used in all cases being 5% dextrose water. Each patient was given a series of such infusions, the quantity of A.C.T.H. differing in each. The amount of diluent used was 800 or 1000 ml., and in all cases the material was given over 8 hours. The total amount of A.C.T.H. given varied from 0·4 to 20 mg., and this dose was expressed in mg. per hour, thus varying from 0·05 to 2·5 mg. per hour.

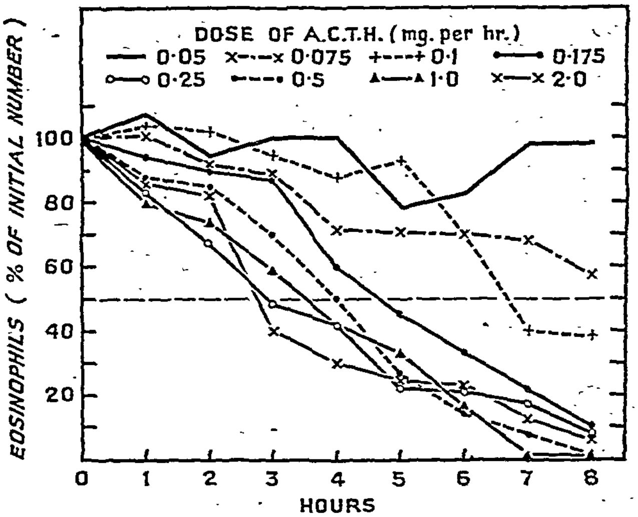

Fig. 1—Eosinopenic response in case 1.

During each infusion eosinophil-counts were made at short intervals, hourly in most cases. The counts were done by Thorn's modification of Dunger's method.

The observations were made at intervals of 3–5 days to exclude the possible occurrence of progressive adreno-cortical hyperplasia.

RESULTS

Fig. 1 shows the results obtained in case 1. It will be seen that the graphs fall into three main groups. Group I representing 0·05 mg. per hour, shows no progressive fall in the number of eosinophils. Group III is that in which a fall of 50% or more in eosinophils has occurred within 4 hours: it includes all doses of 0·25 mg. per hour or greater. Group II, with a range of dosage from 0·075 to 0·175 mg. per hour, lies in an intermediate position between the other two, with an apparently progressive increase in rate and degree of fall of the eosinophils.

Case 2 (fig. 2) shows a very similar picture. It will be seen that, though the intermediate group lies in the same dose range, the rate and amount of fall are greater than in case 1. A further point clearly illustrated by case 2 is that, once a fully effective dose is given, further

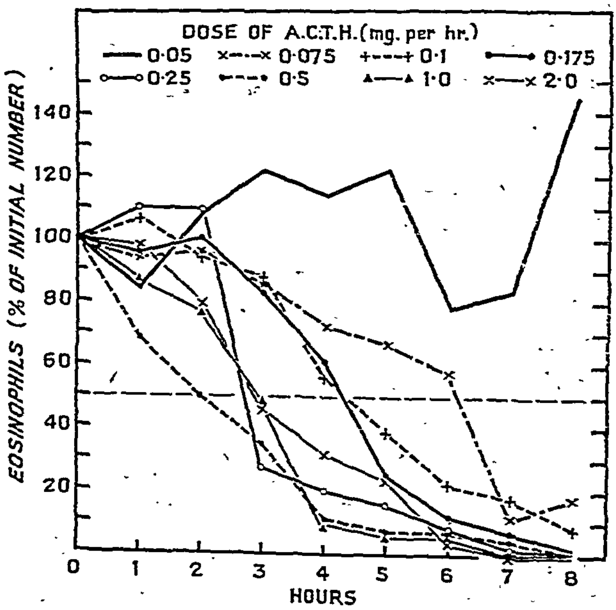

Fig. 2—Eosinopenic response in case 2.

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* Lot nos. K 30002 and J 26311

increases do not affect the rate and amount of fall; for example, in this case 0·25 mg. per hour appears to produce a more rapid fall than 2 mg. per hour. These minor differences are not considered significant but may be explained by inaccuracies inherent in counting eosinophils.

Similar results were obtained in three other cases. When 5% dextrose water alone was given, there was no eosinopenic response. In case 4 two infusions were given with the same amount of A.C.T.H. (0·25 mg. per hour), and the results showed that the graphs were reproducible at different times in the same patient. The minimum *dose that is fully effective varied in the different patients*, case 5 showing a full response to 0·12 mg. per hour, whereas cases 1 and 2 required 0·25 mg. per hour.

From these observations it is clear that the minimum effective dose of intravenous A.C.T.H. which produced a maximum fall in number of circulating eosinophils in the minimum time lay between 0·1 and 0·25 mg. per hour in the five patients studied. Though the minimum effective doses found in these five cases were all of the same order, there were minor variations, and it is likely that each individual has his own critical level at which a full eosinopenic response occurs. It is noteworthy that the difference between a non-effective dose and a fully effective one is very small. This fact was emphasised in an accidental finding during two infusions given to two patients. In these two infusions the intended dose was 0·1 mg. per hour. However, after about 4 hours it was noted that less than half the infusion had been given, and in an attempt to adjust this the rate of flow was increased. Though no effect on the eosinophils had been observed during the first period before alteration of the rate of flow, in the second period a partial response took *place in each case.*

DISCUSSION

Gordon et al. (1951), using relatively large amounts of A.C.T.H. intravenously, demonstrated an enormous increase in adrenal cortical activity. Renold et al. (1951) showed that considerably smaller doses were equally effective, a full eosinopenic response being obtained with 20 mg. given intravenously in 48 hours, or at a dose of rather less than 0·5 mg. per hour. McIntosh and Holmes *(1951) obtained* a full eosinopenic response with 5 mg. given in 24 hours on an hourly dose of just over 0·2 mg. Mandel et *al.* (1951) found a similar dose to be effective. Our studies go further and establish clearly the minimum rate of intravenous A.C.T.H. dosage required to produce a full eosinopenic response. This rate varies from *0·1 to* 0·25 mg. per hour in the cases observed. As a corollary to this it seems logical to suggest that the amount of A.C.T.H. produced by the pituitary in response to stress, over and above the normal rate of secretion, must be at least 0·10–0·25 mg. per hour.

Swanson (1951) and Renold et al. (1951) have reported anomalous results with the intramuscular Thorn test. In a small but significant number of persons A.C.T.H. appears to be inhibited or destroyed locally at the site of the injection, and false results are obtained. Data *suggesting such an effect are being reported by one of us* (H. W. M.) confirming earlier experience (Mandel et al. 1951). It therefore seems reasonable to suggest that this test is most satisfactorily made by giving the hormone in an 8-hour intravenous drip as proposed by Renold *et* al. (1951). We feel, also, that there is an advantage in making at least two eosinophil-counts between the sixth and eighth hours to eliminate errors due to technique, and to safeguard against false results produced by the diurnal variations in eosinophil levels suggested by Rud (1947) and recently confirmed by Swanson et al. (1952). Our present results indicate that as little as 2 mg. of A.C.T.H. would be sufficient for such a test in most cases, although we advise 5 mg. for a routine test.

Case no.	Age (yr.)	Weight (lb.)	Disorder	Previous history of allergy	Minimal effective eosinopenic dose of A.C.T.H. (mg. per hr.)
1	51	170	Rheumatoid arthritis	No	0·25
2	35	80	Rheumatoid arthritis	No	0·25
3	34	142	Alopecia universalis	Yes	0·25
4	48	164	Alopecia universalis	Yes	0·10
5	42	205	Rheumatoid arthritis	No	0·12

Our small group of patients demonstrate minor variations in the minimum effective eosinopenic dose o A.C.T.H. In the accompanying table have been listed few salient points about the five patients, includin weight, age, disorder present, history of allergy, an minimum effective dose of A.C.T.H. No relations betwee these factors and the minimum effective dose of A.C.T.I are apparent.

Our observations reopen a further question. Is th eosinopenic *response merely a sensitive indicator* increased adrenal cortical secretion, or does it represen a full stimulation of the adrenal cortex over any fixe period of time? To answer this question a correlatio between data of this type and measurements of oth adrenocortical activities might give useful informatio Such studies are now in progress and will be reported.

SUMMARY AND CONCLUSION

Various amounts of A.C.T.H. were given intravenousl over an 8-hour period to five patients, and it was foun *that 0·10–0·25 mg. per hour was required to produce* maximum eosinopenic response.

The administration of quantities ten times this amou was no more effective and produced the same type response.

There is a minimum rate of intravenous administratio *of* A.C.T.H. which produces a maximum eosinope response. The implications of this finding with regard therapy and testing adrenocortical function are discusse

These observations were made in the course of projec supported by the National Research Council of Canada. T Fellowship in Clinical Investigation is supported by t Medical Board of the Vancouver General Hospital.

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"... Creative imagination in abundance is needed f formulating a problem and planning experiments for i solution, but once an experiment is under way, the investigat should switch from an imaginary *realm to* one of reality an with meticulous care collect and record data which the should be *handled in an* enthusiastically cold-blooded manne Thus, a good scientific investigator knows when to give h imagination a *loose* rein, and when to bridle it thoroughl ... After an hypothesis has been tested by experiment, *the* findings become a part of accumulated knowledge. But this is not the end of scientific inquiry. The new knowledge must be integrated with the old to replace erroneous concepts, broaden those still accepted, or aid in the formation of new ones, from which new hypotheses and experiments originate. In this way, scientific inquiry is a never ending process, each step forward beginning and ending with hypotheses."—THOMAS M. RIVERS, M.D., *in Frontiers in Medicine*. New York, 1951.

NUTRITIONAL NEUROPATHY IN PRISONERS-OF-WAR REPATRIATED FROM HONG-KONG

A FOLLOW-UP

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This is a follow-up of patients with nutritional neuropathy seen by one of us (C. A. C.) at the Royal Naval Hospital, Sydney, Australia, in 1945. At that time 200 recently released prisoners-of-war came into our hands, and 74 of them showed grossly abnormal neurological signs referable to their malnutrition. The principal features were optic atrophy with scotomata, ataxia, and sometimes deafness (Clarke and Sneddon 1946). The syndrome was described by other workers, and the whole subject comprehensively reviewed by Spillane (1947) and by Smith and Woodruff (1951).

The follow-up was designed to find out whether the condition of these seriously disabled patients had remained stationary, become worse, or improved; 53 case-histories were traced, and detailed letters of inquiry were sent. There were 34 replies, but in 5 of them the evidence was insufficient to make an accurate assessment and they are therefore excluded from the series. Later, 8 of the remaining 29 patients were personally examined by us at the David Lewis Northern Hospital, Liverpool. The following extracts from the letters vividly illustrate the residual disabilities:

> "Should say no alteration in eyes either way since leaving Sydney. . . . I am not able to recognise faces even at four or five paces in ordinary light. . . . The weakness of the legs has not disappeared, but there has been a considerable improvement. Numbness and tingling of the legs are still very much in evidence. . . ."

> "My sight is the same as in 1945. I cannot read a newspaper with or without glasses. . . . My legs have improved to some extent . . . balance still a little unsure when walking slowly. . . ."

> "I do not seem to have control over my toes. . . . My balance has improved a little—although when washing my face with eyes closed it is not so good, but I have full confidence standing in the bath with my eyes open. My eyes seem a little better some days. I can read the headlines of a paper, but I must confess I would be lost without my high-power reading-glass, which has three lenses. It helps me a lot. I hold it about 1 in. from my eyes and 2 in. from the paper. I am a 'borderline' case of St. Dunstan's."

> "My sight is certainly no worse and, I think, slightly better than in 1945. With the aid of a special pair of binocular spectacles with magnifying lens I can read twelve pages of a decently printed book in an hour."

> "The deafness has improved compared to what it was. It is still pretty bad. . . . I have been given a hearing-aid, but it is not much use, and if people are talking to each other I can hear voices but not pick out the words."

> "The eyes have not improved, and now I'm registered as blind. The hands are much better and seem normal except that the finger-tips sometimes lose feeling and the ability to read Braille. . . . You will realise by the above that my correspondence was written by another."

> "My eyes are still in the same condition as in Australia. They haven't got any worse or any better. I am unable to read or play in sports or enjoy pictures, but I can see to get about. I have a steady job on the council road-sweeping. I get a pension of a hundred per cent. for my eyes."

> "As for the pinprick, I think it is about the same. In some places it is sharp and in others it is blunt. . . . I still do not know where my feet are unless I see them, but if the bottoms of my feet are touched I jump a mile."

ANALYSIS OF FOLLOW-UP

Visual Disturbances

Of the 29 patients 26 had some disturbance of visual acuity in 1945. In 15 of these we assessed it as severe and in 11 as mild. In 1951 14 of the severe cases remained unchanged and 1 was slightly worse. In the mild group 6 were unchanged, 2 had fully recovered, 1 had improved, and 2 had deteriorated. The assessment was made on the patients' statements in about half the cases, and in the remainder from the Ministry of Pensions records or our own examination.

Where objective records were available, examination showed that in 13 patients who had had scotomata in 1945, whether severe (9) or mild (4), there was no change in 1951. Similarly there was no change in the 9 cases with optic atrophy of which we had records. Of the cases showing macular degeneration, only 2 objective examination reports in 1951 were available, and both of these showed no change since 1945.

Deafness

There were 10 cases in this group; 6 severe and 4 mild. In 5 of the severe group there was no change in 1951, and 1 patient said that he had deteriorated; 2 of the mild cases had recovered (1 by 1945), and 2 had improved.

Posterior-column Lesion

18 patients had been affected in 1945; 7 severely and 11 mildly. In 1951 4 of the severe group were unchanged, 1 was worse, and 2 had improved. In the mild group 4 had completely recovered, 4 had improved, and 3 were unchanged.

Peripheral-nerve Lesion

In 1945 18 cases showed evidence of peripheral neuropathy (analgesia, anæsthesia, and diminished tendon-reflexes): 12 were assessed as mild and 6 severe. 7 of the mild cases had improved, and 5 had completely recovered by 1951. 4 of the severe cases were unchanged, 1 had improved, and 1 had recovered. In 4 patients knee and ankle reflexes, which had been absent in 1945, had returned by 1951.

Hyperæsthesia of Soles

In 4 patients this had been severe in 1945. Six years later the condition was unchanged in 2, and 2 had recovered.

"Electric Feet"

This symptom was still present in 1951 in 4 of the 5 cases where it had been a pronounced feature earlier; 1 patient had recovered.

Foot-drop

There were 4 cases of bilateral foot-drop in 1945, and after six years 2 were unchanged and 2 had somewhat improved.

Lateral-column Lesion

1 patient had been seen in 1945 in whom the signs resembled amyotrophic lateral sclerosis. In 1951 his condition had changed very little, and the case is reported in detail below (case 5).

Miscellaneous

1 typical case of dystrophia myotonica was found in the follow-up. The patient had deteriorated slightly in the six years (see case 6 below). In 1945 his condition

had been diagnosed as beriberi, but the correct diagnosis had been made earlier when he was in the prison camp.

ILLUSTRATIVE CASE-RECORDS

Case 1.—Now aged 30, he was taken prisoner on Christmas Day, 1941.

April, 1942.—Dysentery followed by chronic diarrhœa off and on for four months.

May, 1942.—Sore tongue, angular stomatitis, and numbness of feet and hands.

August, 1942.—Blurred vision with gradual development of blind spot.

October, 1942.—Supplies of eggs and milk and nicotinic acid became available, and weakness and numbness of the extremities improved. Eyes improved slightly to January, 1943; static since.

1945.—Visual acuity rt. and lt. 2/60 only. Large absolute central scotomata and optic atrophy; no macular changes. Ankle reflexes absent; knee reflexes diminished. Vibration sense absent at ankles; positive rombergism. Sense to pinprick defective on outer side of legs.

1951.—Visual acuity for hand movements only. Scotomata and optic atrophy all unchanged. Unable to read a newspaper. Tendon reflexes now normal. Diminished vibration sense and sense of position in both legs. Deep sensation absent. Slight rombergism, but has improved. Touch and sense to pinprick, heat, and cold all normal.

Summary.—Main disability now defective eyesight. He can work as a full-time physiotherapist.

Case 2.—Now aged 58, he was taken prisoner on Christmas Day, 1941.

May, 1942.—Œdema of the ankles.

September, 1942.—Deterioration of vision with blind spots.

May, 1943.—Scrotal dermatitis.

March, 1944.—Numbness of legs and ataxia.

August, 1944.—Foot-drop.

1945.—Visual acuity rt. (corr.) 6/9, lt. (corr.) 6/7·5. Very small relative scotoma present in right eye. Temporal pallor of discs. Leg reflexes absent. Vibration sense in legs absent. Rombergism and glove-and-stocking anæsthesia present.

1951.—Eyes unchanged. Absent leg reflexes. Gross posterior-column loss with rombergism. Glove-and-stocking anæsthesia as in 1945. Hyperæsthesia of soles.

Summary.—Well-marked persistence of posterior-column and peripheral-nerve changes. Eyes subjectively improved between 1941 and 1945.

Case 3.—Now aged 39, he was taken prisoner on Christmas Day, 1941.

May, 1942.—Slight deafness developed.

November, 1942.—Amblyopia.

December, 1942.—Ataxia.

February, 1943.—Numbness of the feet.

1945.—Visual acuity, rt. 6/60, lt. 6/60 (uncorrectable). Bilateral absolute central scotomata. Discs pale. Hearing now normal. Absent leg reflexes. Posterior-column loss in legs. Anæsthesia of legs. Hyperæsthesia of feet.

1951.—Visual acuity unchanged. Scotomata and discs unchanged. Leg reflexes present but diminished. Very slight posterior-column loss in legs. Very slight loss of pain sensibility in legs.

Summary.—Vision unchanged. Great improvement in legs.

Case 4.—Now aged 49, he was taken prisoner on Christmas Day, 1941.

May, 1942.—Dysentery.

July, 1942.—"Electric feet."

December, 1942.—Severe mental depression. Visual symptoms with central scotomata. Ankle reflexes absent: knee-jerks brisk. Numbness of legs, with anæsthesia of the shins and hyperæsthesia of the feet.

1945.—Depression unchanged. Visual acuity rt. 6/60, lt. 4/60. Absolute central scotomata (bilateral). Pigmented maculæ. Absent leg reflexes. Severe posterior-column loss. Rombergism present. Anæsthesia of shins unchanged.

1951.—Still depressed. Eyes unchanged. Macular atrophy persists. Left ankle reflex absent, otherwise leg reflexes normal. Posterior-column loss, rombergism, anæsthesia of shins, and hyperæsthesia of feet all unchanged.

Summary.—Persistent optic and macular atrophy. Gross persistent posterior-column changes.

Case 5.—Now aged 30, he was taken prisoner on Christmas Day, 1941.

April, 1942.—Failing vision.

August, 1942.—Dysentery.

December, 1943.—Scotomata noted. Absent corneal reflexes. Moderate deafness. Ataxia with bilateral foot-drop. Numbness of legs. Soreness of tongue and mouth.

1945.—Pallor of optic discs. Macular pigmentation. Visual acuity rt. 6/36, lt. 6/36. Small paracentral scotomata. Much left facial weakness (lower-motor-neurone type). Lateral nystagmus present. Limbs showed typical amyotrophic lateral sclerosis syndrome with wasting small muscles of hand and increased reflexes and spasticity in legs. Foot-drop present. Severe posterior-column loss. Micturition precipitate. Cerebrospinal fluid normal.

1951.—Visual acuity, scotomata, and macular pigmentation all unchanged. Hearing much better. Facial paresis persists. Nystagmus unchanged. Legs less spastic, but reflexes increased. Plantar responses invalid owing to complete (unchanged) foot-drop. Posterior-column loss in legs unchanged.

Summary.—Amyotrophic lateral sclerosis syndrome of nutritional origin. No regression. Slight improvement in gait.

Case 6.—Now aged 44, he was taken prisoner on Christmas day, 1941.

September, 1942.—Dysentery.

October, 1942.—Weakness of legs. Numbness of hands. No eye symptoms.

November, 1942.—Scrotal eczema. Much weakness of arms and legs. All tendon reflexes absent. Vibration sense absent in legs. Severe myotonia noted and myotonia atrophica diagnosed.

April, 1943.—Foot-drop reported.

1945.—True diagnosis missed, and findings in central nervous system thought to be result of malnutrition.

1951.—Classical dystrophia myotonica facies and typical findings in central nervous system. Slight testicular atrophy. Glossal myotonia. Congenital dot opacities of lenses. Severe foot-drop. Some posterior-column loss in legs. Family history gives no definite lead.

Summary.—Dystrophia myotonica possibly precipitated by malnutrition.

SUMMARY AND CONCLUSIONS

29 cases of severe nutritional neuropathy have been followed up after an interval of six years, and the various features of the condition assessed.

The visual signs (visual acuity, scotomata, and optic atrophy) have persisted largely unchanged irrespective of the degree of involvement.

The auditory nerve seems to have been less vulnerable in that some recovery took place in all the mild cases.

Severe posterior-column loss has remained unaltered, but, where it was slight, some improvement has taken place.

The most obvious improvement in the series was in patients with peripheral-nerve lesions.

The one case resembling amyotrophic lateral sclerosis has remained unchanged.

We acknowledge with thanks the great help given to us by the Medical Director-General of the Royal Navy in supplying us with the old case-sheets and for permission to publish. We are also grateful to Dr. F. T. Rees, C.B.E., M.C., T.D., for giving us access to the Ministry of Pensions records; to Mr. McKie Reid, M.C., T.D., and his staff for the scotoma records, and to the board of governors, United Liverpool Hospitals, for defraying the expenses of the follow-up.

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ISSEMINATED LUPUS ERYTHEMATOSUS COMPLICATED BY MILIARY TUBERCULOSIS DURING CORTISONE THERAPY

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THE increasing use of A.C.T.H. and cortisone has ttracted attention to the potential dangers of these ormones in the presence of known or unsuspected uberculosis (*British Medical Journal* 1951). The rôle of hese agents in the treatment of the collagen diseases as now been extensively investigated. It appears that hey have a limited value in the therapy of disseminated upus erythematosus (Soffer et al. 1950). The possible elation between tuberculosis and disseminated lupus rythematosus remains, for the present, controversial Keil 1933).

This case of disseminated lupus erythematosus compliated by miliary tuberculosis during cortisone therapy s therefore thought worthy of report.

CASE-REPORT

A 36-year-old spinster, who worked as a machinist, first ought advice early in 1946 for a maculopapular rash on the ace which later spread to the trunk and arms, and for loss of nergy and weight. In June, 1947, she was admitted to hospital with a diagnosis of lupus erythematosus. She improved n treatment with penicillin and bismuth.

During the next 18 months she continued to lose weight nd developed stiffness, pain, and swelling of her knees, nkles, elbows, and wrists. In April, 1949, she was readmitted with left-sided pleuritic pain and an exacerbation of her rash; this was thought to be an acute phase of disseminated lupus erythematosus. X-ray examination showed shadowing at the base of the left lung. There were no tubercle bacilli in the sputum, and the white-cell count was 5000 per c.mm. with a normal differential count. Both pulmonary and cutaneous lesions responded to penicillin, but she developed alopecia of the scalp. On discharge 6 weeks later her lungs were radiologically normal.

The disease appeared quiescent until June, 1950, when she relapsed with arthritis, loss of weight, and recurrence of the rash. In August she was again admitted and improved on streptomycin and penicillin, but loss of hair increased.

In April, 1951, she again relapsed and in June she was transferred to the Royal Hospital, Sheffield, for cortisone treatment.

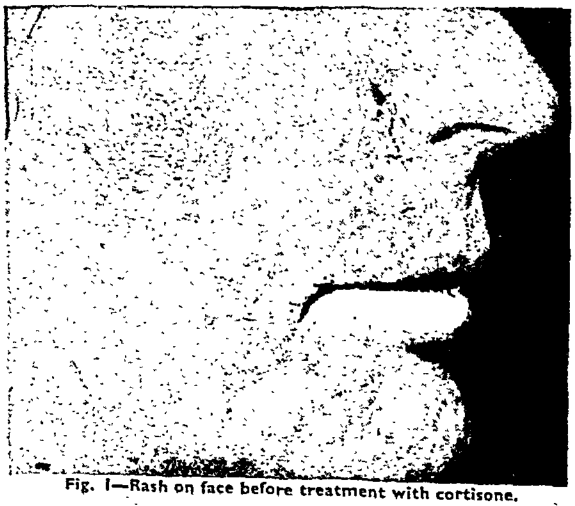


Fig. 1—Rash on face before treatment with cortisone.

She was seriously ill, with a temperature of 102°F, and a pulse-rate of 120. A rash was present over the face, scalp, suprasternal notch, and hands; it was deep red, and maculopapular over the malar regions of the face, becoming confluent toward the eyebrows, but there was no butterfly distribution. The eruption on the hands was less vascular, but over the scalp and suprasternal notch it resembled that on the face (fig. 1).

The blood-pressure was 108/48 mm. Hg. There was no clinical evidence of endocarditis. Slight periarticular thickening of both wrists and typical rheumatoid swelling of the fingers were present. The knees were similarly affected and movement of all these joints was painful and limited.

The blood picture was as follows: hæmoglobin 70% (10·5 g. per 100 ml.), red cells 3·5 million per c.mm., leucocytes 1000 per c.mm. (polymorphs 57%, lymphocytes 11%, monocytes 15%, band cells 17%), platelets 64,000 per c.mm. The erythrocyte-sedimentation rate was 101 mm. in 1 hour (Westergren); clotting-time 9 min. (Lee and White); and bleeding-time 9 min. (modified Ivy). At first the Haserick culture showed no clumping or lupus erythematosus cells, but these were later present. The urine repeatedly contained protein, granular casts, and red blood-cells. An X-ray film of the chest showed increased vascular markings at the left base, but no other abnormality (fig. 2).

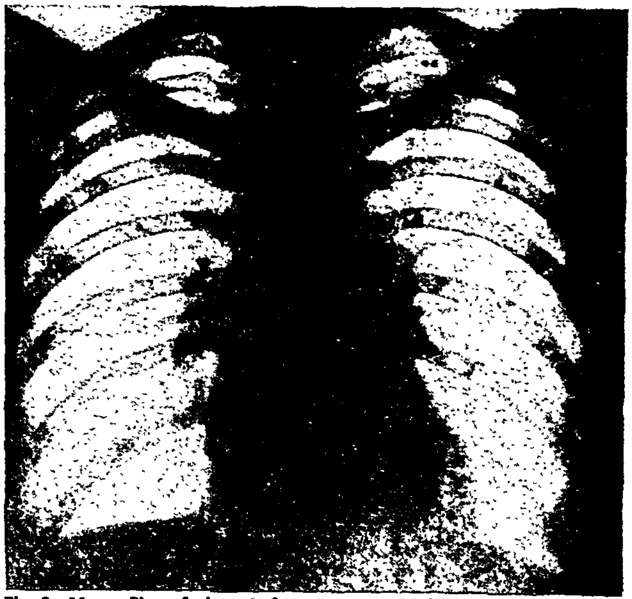


Fig. 2—X-ray film of chest before treatment with cortisone showing increased vascular markings only.

During an initial observation period of 10 days without treatment the rash faded slightly but the temperature remained elevated. But as no permanent improvement seemed likely a total of 2·35 g. of cortisone acetate (Merck) was given by intramuscular injection over a period of 21 days. Within the first 3 days the rash cleared and the joints became painless. After 8 days she was apyrexial, and all that remained of the rash was some residual staining (fig. 3). On the 17th day of treatment, when she was receiving 100 mg. on alternate days, joint pains returned and the pulse-rate and temperature rose. Dosage was increased to 100 mg. daily, but the pyrexia became even greater and cortisone was stopped. Although the rash did not return with its original severity, a diffuse solar dermatitis developed on exposure to direct sunlight, and there was further loss of hair.

The albumin/globulin ratio was reversed during the illness and gradually diminishing urea-clearance values suggested progressive renal damage. Other investigations were normal.

The patient had a slight and almost unproductive cough; fine scattered crepitations were heard over both lung fields. Although still febrile, she looked and felt quite well. An X-ray film showed miliary infiltration throughout both lungs (fig. 4).

Miliary tuberculosis was thought more likely than pulmonary lupus erythematosus; though the sputum, gastric washings, and urinary deposit showed no acid-fast bacilli on direct examination, guineapig inoculation was positive. Tubercle bacilli of human type were cultured from gastric washings.

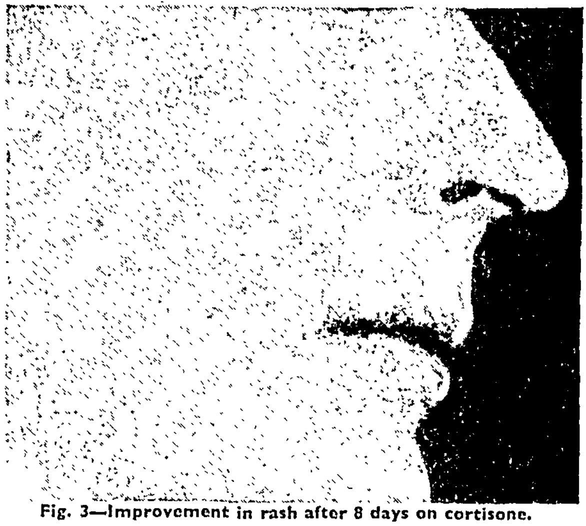


Fig. 3—Improvement in rash after 8 days on cortisone.

Streptomycin and p-aminosalicylic acid (P.A.S.) were given; she had 1 g. of streptomycin and 18 g. of P.A.S. daily for 3 months. Her temperature fell steadily and finally settled below 99°F. She became extremely well and gained 8 lb. in as many weeks, and her hair grew rapidly. There were now no abnormal physical signs in the lungs, but the miliary infiltration on the X-ray film did not change appreciably (fig. 4).

DISCUSSION

There is now good evidence that A.C.T.H. and cortisone control relapses in disseminated lupus erythematosus, but they do not seem to be curative.

Soffer et al. (1950) reported fourteen cases in an acute phase where the diagnosis seemed indisputable. Both A.C.T.H. and cortisone had effects; only 1 patient showed no response at all and died of a fungus pneumonia. The first response was usually a fall in temperature and then a fading of the rash. Withdrawal produced relapse, and a maintenance dose was necessary. Complications in this series were hypertension, striæ of the skin, œdema, mental depression, pigmentation, hirsutism, alkalosis, and diabetes. The only pulmonary complication was the fatal fungus pneumonia. Plotz et al. (1950) discussed three cases including one of Libman-Sach endocarditis. Initial response to A.C.T.H. was followed by fatal relapse in each case. Haserick et al. (1951) used the drugs in 16 cases of disseminated lupus erythematosus and found that doses of cortisone in the region of 100 mg. hourly for short periods were necessary in a crisis. Baehr and Soffer (1950) mention some well-known complications but no pulmonary ones. Brunsting et al. (1951) point out that the drugs may mask serious complications such as peritonitis, pancreatitis, and septicæmia.

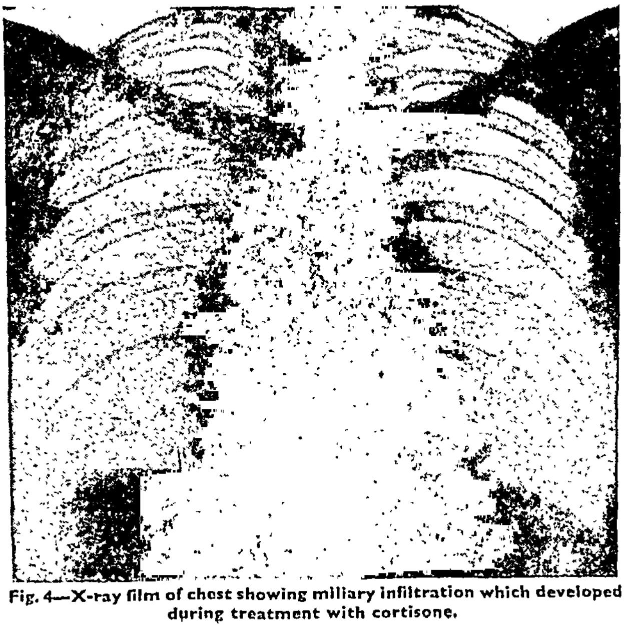


Fig. 4—X-ray film of chest showing miliary infiltration which developed during treatment with cortisone.

Keil (1933) thought that there was no conclusive evidence of a relation between disseminated lupus erythematosus and tuberculosis. Dittrich (1949) reported a case of disseminated lupus erythematosus in which pulmonary disease was demonstrated radiologically. This resolved and there was no lesion at necropsy; it was probably hæmorrhagic or allergic and not tuberculous.

There is experimental evidence that A.C.T.H. and cortisone facilitate the spread of tuberculosis in the lungs of susceptible animals by inhibiting fibroplasia (Cummings 1951, Hart and Rees 1950, Michael et al. 1950, Spain and Molomut 1950). Recent work shows that these hormones may sometimes have this effect in man.

A patient with rheumatoid arthritis and hepatic cirrhosis was given A.C.T.H. and cortisone by Fred et al. (1951). The arthritis improved, but he developed tuberculous bronchopneumonia and died. The sputum was positive, but there was no clear proof that he was free from tuberculosis before treatment began. King et al. (1951) reported rapidly progressive pulmonary tuberculosis following cortisone in a patient with rheumatoid arthritis, but there was no pathological proof that this complication was tuberculous. Popp et al. (1951) had a patient in whom cortisone probably activated a quiescent tuberculous focus known to exist before treatment. The sputum had been consistently negative for many years but it became bloodstained and acid-fast bacilli were found after cortisone therapy.

Our patient had been under observation for 4 years with no evidence of pulmonary tuberculosis. Lung changes were reported in 1949, but they resolved. The chest films immediately before cortisone treatment did not suggest active or latent tuberculosis. However, unequivocal signs of miliary tuberculosis followed a short course of cortisone; the radiological appearances were typical and tubercle bacilli were present in sputum and urine. This sequence may be explained in one of three ways:

(1) Miliary tuberculosis was in fact present before treatment began, but its presence was unrecognised.

(2) It developed after treatment began, but was not in any way attributable to cortisone.

(3) It developed from an unsuspected and latent focus as a direct result of cortisone therapy.

The first two possibilities cannot be excluded, but in the circumstances the third explanation seems to us the most likely. This case supports the belief that disseminated lupus erythematosus may have an affinity with tuberculosis, and confirms reports that these hormones are potentially dangerous in active or latent tuberculosis. A careful search for such foci should be made whenever A.C.T.H. or cortisone therapy is contemplated and this watch should be maintained during and after treatment.

SUMMARY

A woman of 36 was given cortisone for disseminated lupus erythematosus. She developed miliary tuberculosis with positive sputum and urine. She had previously been under observation for 4 years and no evidence of tuberculosis had been found at any time.

It seems likely that the disease spread from a latent and unsuspected focus directly activated by cortisone. Published reports are quoted in which the use of A.C.T.H. and cortisone was followed by lung disease, which in some cases was definitely proved to be tuberculous.

We should like to thank Dr. C. Gray Imrie for his kindly criticism and for permission to publish this article.

ADDENDUM

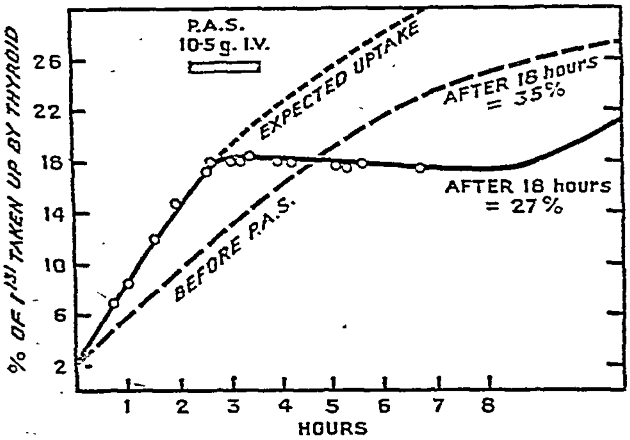
Since this article was submitted a similar case has been reported by Walker (1952).

References at foot of next column

Preliminary Communication

DETERMINATION OF THE ANTITHYROID ACTION OF PARA-AMINOSALICYLIC ACID USING RADIOACTIVE IODINE

MYXŒDEMA associated with *p*-aminosalicylic acid (P.A.S.) therapy was first described by Clausen and Kjerulf-Jensen[1] in 1951. They reported three patients in whom signs of myxœdema disappeared when P.A.S. was stopped. In England Komrower[2] has described a similar case of a child aged $8^{1}/_{2}$. Kjerulf-Jensen and Wolffbrandt[3] have since shown that rats fed with P.A.S. and *m*-aminophenol developed moderate cellular hyperplasia of the thyroid gland.



Inhibition of uptake of I^{131} in the thyroid gland after 10·5 g. of P.A.S.

Using radioactive iodine (I^{131}) according to the method of Astwood and Stanley,[4] I have studied the accumulation of iodine in the thyroid gland during P.A.S. therapy. The radioactive material in the gland was measured by direct external application of a Geiger-Müller counter.

In the accompanying figure the broken line shows the rate of iodine uptake after an oral dose of 0·1 millicurie of I^{131} in a patient with pulmonary tuberculosis who had had no chemotherapy. The curve reached a maximum after 24 hours, when in this case 35% of the dose given had been taken up by the thyroid. The first part of the unbroken line shows the uptake of radioactive iodine in the same patient after an identical dose, but after 3 weeks' P.A.S. therapy. After $2^{1}/_{2}$ hours a total of 300 ml. of sodium P.A.S. (1 ml. = 0·035 g. of P.A.S., the total dose being 10·5 g.) was given by intravenous infusion over a period of $1^{1}/_{2}$ hours. After about 45 minutes (when approximately 150 ml. had been given) the uptake of iodine in the gland stopped. The curve remained stationary for a further 4 hours. After 15 hours, however, the thyroid had regained some of its ability to take up iodine. The inhibitory action of P.A.S. ceased probably before the non-protein-bound iodine was excreted. This is in accordance with the findings in assays with propylthiouracil. The steeper rise of this curve compared with the first one may be the result of compensatory enlargement of the gland due to an increased formation of thyrotropic hormone in the pituitary gland. This increase is caused by a decrease of thyroid hormone in response to antithyroid substances.[5] If intravenous P.A.S. had not been given after $2^{1}/_{2}$ hours the dotted curve would have been obtained.

Similar curves were obtained in two other patients, although the time which elapsed before the inhibition of iodine uptake was variable. In one patient the iodine accumulation ceased as early as 20 minutes after the intravenous infusion of P.A.S. began, when only 2·1 g. had been given. This patient had been having 10 g. of P.A.S. by mouth daily for 14 days.

The concentration of P.A.S. in the blood after the intravenous infusion of 10·5 g. is about 25 mg. per 100 ml.; after 6 hours it falls to 3 mg. per 100 ml.

When P.A.S. is given therapeutically, a certain concentration in the blood will inhibit the synthesis of thyroxine in the same way as thiouracil. Therefore doses of P.A.S. in excess of the patient's thyroid sensitivity may give rise to myxœdema, and before P.A.S. is given the possibility of such individual sensitivity should be considered.

A detailed account of the antithyroid action of P.A.S. will be published later.

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Reviews of Books

The Sensations

Their Functions, Processes, and Mechanisms. HENRI PIÉRON, M.D., professor of the physiology of sensation, Collège de France, Paris. Translated by M. H. Pirenne and B. C. ABBOTT. London: Frederick Muller. 1952. Pp. 469. 42*s*.

THE first French edition of this book was published in 1944, and in this English translation much work which has since been done on the physiology of sensation has been incorporated. The object of the book is to survey facts which have been discovered about the physiology and psychology of the spinal senses and of cutaneous and proprioceptive sensation, and to review the many theories which have been proposed to account for them. It is based on lectures given at the Collège de France by the author, who has made many original contributions to the physiology of vision. Neither the subject nor the style makes this an easy book to read; but, though it is unlikely to be of great interest to clinicians, it should be valuable to physiologists and psychologists who are working on any aspect of sensation.

Handbook of Diseases of the Skin

HERBERT O. MACKEY, F.R.C.S.I., member of the dermatological section of the Royal Academy of Medicine, Dublin. Dublin: Fallon. 1952. Pp. 216. 7*s*. 6*d*.

AUTHORS of books intended primarily for students need to obey three essential rules: the content must be confined as far as possible to facts; the whole subject should be systematically covered, so that the student can form an impression of its scope; and there must be a sense of balance, so that common disorders are not omitted or rarities given too much attention. This book conforms fairly well to the first of these tenets but less well to the second and third.

Thus the chapter titles do not indicate what lies within them: the chapter headed "*Tinea Circinata*" includes all forms of ringworm, the chapter headed "Parapsoriasis" deals as well with three other conditions, while the chapter headed "Prurigo" covers also pruritus ani but not pruritus vulvæ or generalised pruritus. The earliest chapters adequately cover anatomy, embryology, physiology, and pathology; then follows symptomatology, and a useful list of diagnoses based on morphology. The list of common skin diseases based on their distribution cannot be recommended, however, because of the many exceptions. Diagnosis must be made on history, arrangement, and morphology as well as on distribution; and in any case a list of 22 different trunk lesions does not guide the student far towards diagnostic lucidity. Readers in Great Britain will hardly agree that "too much meat and fresh bread are common errors of diet"; and the injunction that "worry or anxiety should be forbidden" invites the riposte "How?" Many would disagree that Bowen's disease should be treated by surgery, diathermic destruction, or radium; and no mention is made of good results obtainable with carbon dioxide snow. Some 36 photographs are scattered indiscriminately through the book, without references in the text. Some are good—for example those of pemphigus and molluscum contagiosum—others very poor.

Vaccination par le B.C.G.

R. MANDE and A. HUËT, Station-Pilote B.C.G. du Centre International de l'Enfance, Paris. Paris: *Centre International de l'Enfance, Travaux et Documents*—III. 1952. Pp. 168. Fr. 750.

THIS book is a documentation of work done in the past three years at the Station-Pilote B.C.G. du Centre International de l'Enfance, founded in Paris by UNICEF in 1948. The investigators' purpose has been to compare and contrast the effects, on human beings, of several commonly used tuberculins and B.C.G. vaccines. The first part of the book records comparative studies of the intradermal Mantoux test (with different doses of tuberculins from France, Denmark, and Sweden), the Moro-patch, the *timbre tuberculinique*, the Pirquet with and without adrenaline, and the modified Trambusti as currently used in Finland. The intradermal, scarification, and multiple-puncture techniques of vaccination were compared in relation to tuberculin allergy, local lesions, and frequency of complications (ulcer, abscess, adenitis). The second part is concerned with the effects of variations in the batch, source, and concentration of the vaccine itself; the influence on fresh vaccine of time (up to 24 days) and temperature of storage (20°C for 3 days), and on dry vaccine of storage for 1–6 months at 4°–5°C or for 1–2 weeks at 20°C; and the comparison of fresh and dry B.C.G. prepared from the same culture.

The authors recognise that many relatively simple facts about B.C.G. are still unknown, and they have made so great an effort to answer important questions that it seems ungrateful to question the reliability of their data and conclusions. But insufficient information is given on some of the critical details of technique. Who were the subjects and how were they selected? How comparable were the studied groups? How uniform was the technique from series to series—and within each series? What precautions were taken to avoid biased observations?

Writing on the effect of storage temperature on fresh vaccine, for example, they say that "it is important that vaccine, after it is put in ampoules, should be kept at a low temperature (4°–5°C) in order to preserve a sufficient proportion of living bacilli." But the data which follow concern 76 subjects given B.C.G. kept for 10 days at 4°C, and 74 given a *different batch* of B.C.G. stored in the ice-box for 7 days, and then at 20°C for 3 additional days. Post-vaccination tests (time, test, and dose not stated) revealed 80·4% to be positive in the first group, 90·5% in the second. Such "paradoxical" results, the authors explain, do not justify concluding that there were sufficient living bacilli in the heated vaccine to sensitise the subjects, as "it is known that dead bacilli can produce allergy." They feel that no conclusion should be drawn from this study because "the circumstances, in fact, did not permit assembling homogeneous groups, of equal age, nor to use the same vaccine on the same day, nor to have all the vaccinations given by the same vaccinator. Many other variables than temperature [of storage of the vaccine] could have interfered, and as it is impossible for us to take each of them into consideration, it seems preferable for us not to decide the issue."

When, however, the results were not considered paradoxical, the authors often draw quite definite conclusions without indicating whether the "circumstances" in these cases allowed for assembling more comparable groups and/or for technique any less irregular.

It is difficult to imagine how some of the studies, as the example cited, could have been expected to provide reliable data; and unfortunately many of the results must therefore be considered inconclusive.

Child Psychiatric Techniques

LAURETTA BENDER, B.S., M.A., M.D., professor of clinical psychiatry, New York University College of Medicine. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 312. 60*s*.

THIS is neither a textbook of child psychiatry nor a manual for the therapy of maladjusted children. It might perhaps be likened to the working notebooks of a skilled and experienced team. The chapters, some of them taken from work already published in the journals, reveal the thrust of a number of highly intelligent minds, not the least being the chief author's late husband, Paul Schilder. He came to his original work with difficult children from the unusual background of organic neurology combined with Freudian psychoanalysis, and traces of both these disciplines show in his approach to the work.

After a general survey of the way in which child psychiatry became a clinical study in its own right—borrowing something from organic neurology, adult psychiatry, mental deficiency, and pædiatrics in medicine, and from pædagogics and delinquency in the educational and social fields—Professor Bender describes the range of techniques in use at the Bellevue Hospital in New York, with its ward for 50 problem children. Almost any kind of problem is accepted for short-term study, and some children remain resident for sustained therapy. A chapter, rather too far on in the book, describes succinctly some aspects of day-to-day routine in the ward. A later chapter describes various projects, some educative and most of them planned to reveal conflicts which are distorting the child's sense of reality. This picture of the interplay of emotion in a group of gravely disturbed children is so vivid that it makes painful reading. In describing the school, which is part of the regular programme of activity, the authors discuss the question of group activity and the reactions of the children themselves towards symptoms in others.

Another considerable part of the book is devoted to work on Bender's Gestalt test, both as a projection test and as a measure of distortion of the body image. This latter concept is given great weight as being a significant part of the inner disturbance especially in the schizophrenic child. In the Gestalt chapters the diagrammatic arrangements are tiresomely out of line with the text; and the one chapter dealing more fully with the interpreted material from a single child is a little disappointing.

The book, however, is full of matter, often controversial, and covers in a wide sweep all the techniques available for a very diverse group of troubled children. A further volume might well deal more fully with less material.

A Textbook of Midwifery (15th ed. London: A. & C. Black. 1952. Pp. 586. 30*s*.).—This fine standard work is in its fortieth year, and its fifteenth edition. We all mature, but not all of us reach middle age with a plastic and unprejudiced outlook. A good textbook, however, must keep this quality above all others; and that it can only do if it is regularly revised and scrutinised by its authors. To keep their book abreast of reliable recent observation and practice Prof. R. W. Johnstone and Prof. R. J. Kellar have each revised the entire text. It is as factually informative as ever, and written clearly and precisely, and without condescension. Changes have been made in the section on maternal metabolism during pregnancy (a subject on which knowledge is always growing). There is a very good new paragraph on the reassurance and instruction of the mother about the course of events in labour (which should be rehearsed) and on the value of teaching her to relax. A.C.T.H. is mentioned in the section on pre-eclampsia; and the chapter on radiology has been revised by Dr. J. Z. Walker.

THE LANCET

LONDON: SATURDAY, JULY 19, 1952

Delaying Action

IN the matter of pay and prospects for doctors in the Civil Service, the Treasury is fighting one of its characteristic delaying actions. The operations now in progress began nearly three years ago when in September, 1949, a deputation to the Chancellor's department pointed out that many of the abler young doctors were leaving the Ministry of Health because remuneration was insufficient, and that Government service could not hope to attract enough recruits of the proper calibre unless it offered salaries much closer to those obtainable in the National Health Service.[1] On behalf of the Joint Committee formed by the Institution of Professional Civil Servants, the Ministry of Health Medical Staff Association, and the British Medical Association, this deputation put forward a claim for pay on a scale that it thought appropriate to those at present in the service, and likely to secure suitable entrants for the future. After six months this claim was firmly rejected by Sir STAFFORD CRIPPS.[2] He fully recognised, he said, the need for maintaining the efficiency of medical establishments, and indeed of other important establishments which were at present below strength; but in his view it was then even more important to maintain the policy of wages stabilisation, which would be jeopardised if exceptions were made to the general rule. He added that a claim by Civil Service doctors must be regarded as a Civil Service claim "to be dealt with on the basis of the policy applied to the Civil Service generally." However, by way of concession, he proposed to appoint a committee to go into the question of "the remuneration and the general salary structure of Civil Service doctors" and advise the Government on what changes can be made "when economic conditions allow improvements to be made in remuneration generally."

The history of that committee is not a happy one. Originally it was to consist of four administrators and only two doctors: and, as we remarked at the time, it looked rather like a mechanism for repeating the Chancellor's own opinions after a decent interval. Medical protests led him to say that he would consider nominations by the Institution of Professional Civil Servants and by the British Medical Association, but he neither accepted the doctors nominated nor gave those bodies a chance to put forward other more acceptable names. As finally constituted, the Howitt Committee did indeed have four medical members, and they were all men much respected in the profession; but it nevertheless embodied the Treasury's decision not to have a representative committee making a fundamental inquiry. Its all too brief report, issued last autumn, reads like a departmental memorandum rather than the findings of a public commission; for in stating its own conclusions it neither summarises nor comments on the cogent contrary arguments submitted for its consideration. With much of what the committee said we are ourselves in agreement[3]; but neither its appointment nor its report has demonstrated to the profession or the public that the problem has had the full and judicial examination it deserves.

An impasse has now been reached. The Joint Committee, arguing that the Howitt scales are additionally unacceptable now that the Danckwerts award has improved remuneration for general practitioners, has asked for arbitration—which Civil Servants above a certain grade cannot claim as a right. To this Mr. BOYD-CARPENTER, for the Treasury, replied on April 17 that the Howitt Committee was a completely independent body, and to refer the question to an entirely fresh arbitration tribunal, before making any trial of the salaries which the committee recommended, would be a wholly unjustifiable reflection on its competence. "We shall," he said, "be very willing to give the matter further consideration if, after the rates recommended by the Howitt Committee have been given a fair trial, they are found insufficient to attract the doctors we require." The Treasury realises, he added, that it will be necessary to consider whether the effects of the Danckwerts award necessitate adjustment in the Howitt scales. So far, so bland. But unfortunately it now appears that the time arranged for this much-needed review of the success or otherwise of the Howitt salaries is "not later than December, 1953"—i.e., rather more than four years after the Joint Committee put forward its claim. The delaying action, in fact, is to continue. The Treasury, we cannot help thinking, does not really mind very much if Civil Service medicine deteriorates, just as it did not mind about general practice deteriorating. By resisting the claims of general practitioners for an equitable settlement it did quite incalculable harm to the National Health Service in the early formative years —without, in the long run, saving the nation a penny. Further harm has been done to the N.H.S. already, and much more will be done in future, because the Treasury does not enable the Ministry of Health to pick the best men for its work at the centre.

From the final exchange of letters described on p. 141, it will be seen that until such time as the Treasury feels able to discuss some alternative proposals, the British Medical Association is going to refuse to accept "any further advertisements for medical officer appointments in the Civil Service." When a similar decision was taken in May, 1950, in an earlier phase of these negotiations, we explained[4] that, as an independent journal, we differ from the B.M.A. on the constitutional propriety of rejecting advertisements as a means of inducing a Government to change its policy: we thought, and still think, that the professions should set an example by refraining from all measures that may be construed as "direct action" for political or semipolitical purposes, since this kind of pressure has inherent dangers for a democracy. On principle, therefore, we cannot refuse to publish advertisements of Civil Service appointments, unless or until the Government can be shown to have violated an agreement. On the other hand, like the Joint Committee, we have lost all confidence in the Treasury's intentions, and we wish to associate ourselves most strongly with the committee's request that the subject should be reconsidered much sooner and more objectively than is now proposed. Though we shall not deny the Government the right (if they wish) to advertise their medical posts in our columns, we think it would now be only proper that any such advertisements should be accompanied by an editorial statement of the present objections to their being filled. Accordingly, in the (perhaps unlikely) event of advertisements being submitted, we intend to add to each of them an indication to possible applicants that conditions of remuneration and promotion for doctors in the Civil Service have not yet been satisfactorily settled, and that the B.M.A. has made these posts the subject of an Important Notice.

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[1] *Lancet*, 1950, i, 75.
[2] *Ibid*, p. 772.
[3] *Ibid*, 1951, ii, 921.
[4] *Ibid*, 1950, i, 959.

Diagnosis of Infective Mononucleosis

THE clinical guises of infective mononucleosis (glandular fever) are diverse, as TIDY [1] showed many years ago. The form with enlargement of cervical glands predominates, and, especially in outbreaks, this form may cause no diagnostic difficulties; but in atypical forms, at least the early stages of the illness do not resemble the usual conception of the disease. Thus, meningeal,[2] encephalitic,[3] and other neurological syndromes common to a number of virus, or presumed virus, infections may so overshadow other clinical features that infective mononucleosis is not at first considered; or the illness may take the form of a generalised febrile and toxic state [1] (sometimes severe and possibly fatal from hepatic and renal failure [4]) which may precede adenopathy by many days; or adenopathy, if it appears early, may be so slight as to be overlooked. On the other hand, symptomless infections occur [5] [6] and are discovered only as the result of routine blood-counts, followed, if these are suggestive, by heterophil-antibody (Paul-Bunnell) tests, in patients admitted to hospital for other conditions. Again, the blood picture early in the attack may not reveal the characteristic atypical lymphocytes. Nor is the presence of these cells in the peripheral blood confined to infective mononucleosis. In a number of virus infections and in pertussis the blood picture is similar though, to the expert hæmatologist, not identical. Finally, even in a true case of infective mononucleosis the heterophil-antibody test may be negative or else positive only in a titre regarded by the serologist as insignificant. Nevertheless, it is generally accepted that, especially in sporadic cases, a characteristic blood picture and preferably a significantly positive Paul-Bunnell test are required for a positive diagnosis. BENDER [7] suggests that the atypical-lymphocyte count should be greater than 1000 per c.mm.; but this in itself is not diagnostic, and he recommends more precise differentiation of mononuclear cells by supravital staining [8] since this number of atypical lymphocytes "may indicate rubella, rubeola (measles), varicella or mumps." Supravital staining is not, apparently, generally used by hæmatologists; yet BENDER finds that in smears prepared for routine differential counts the atypical cells seldom present recognisable characteristics: "only a thin even spread makes these cells easy to identify."

As to the diagnostic *tertium quid*, the heterophil-antibody test, BENDER points out that if cases are classified as serologically negative on the basis of a single test during the first week of the illness, "the results are understandable." In his own experience of 146 patients in hospital and 194 ambulant patients, aged 17–32 years, who were followed up clinically and hæmatologically, "all patients with a positive blood smear have shown a diagnostic titre of heterophil antibodies provided serial tests were made through the second week of the disease." But what is a diagnostic titre? PAUL'S [9] opinion, in 1941, was that a titre of 1 : 64 was nearly always diagnostic, and one of 1 : 32 suggestive. BENDER selects a titre of 1 : 56 as positive; "but in very few hospitalised patients did a titre of 1 : 896 fail to develop," and he concludes that if the test is not positive at the beginning of the second week "other leads should be pursued." This time-limit may suffice in most cases; but in some forms of the disease—notably that commencing with a neurological syndrome and TIDY'S febrile type—heterophil antibodies may appear only in the later stages or even in convalescence. Probably, as with other agglutinin tests, a rising titre is more important than the initial absolute titre unless this is high. Some titre of heterophil antibodies may persist for quite a long time after a clinical attack; but in these circumstances, and in symptomless infections, the titre does not rise. BENDER reminds us that, despite numerous atypical clinical pictures, sore throat and adenopathy represent the clinical prototype of the disease; and when these are absent he calls for stricter laboratory checks, and especially repeated heterophil-antibody tests, on which he pins his faith.

Employment of Disabled Youth

THE Medical Research Council memorandum on Employment Problems of Disabled Youth [10] is a penetrating study of a matter of consequence to the whole nation. Professor FERGUSON and his colleagues examine the many difficulties which beset the handicapped adolescent, and conclude that much more could and should be done to help him in his effort to keep up with his more fortunate fellows. They think that "there can be few more promising fields for the practice of constructive medicine than those concerned with the problems of disabled youth . . . for the successful settlement in employment of a disabled young person provides him at once with a means of livelihood and a satisfying and constructive job, surely two of the greatest of human rights."

The investigators set out to discover to what extent disabled young people in Glasgow are unable to earn a living, what kinds of disability interfere most seriously with their working capacity, how far social and environmental factors contribute to their difficulties, and whether any amelioration is possible. The first study concerned 579 young people, under nineteen years of age, who had registered in Glasgow under the

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[1] Tidy, H. L. *Lancet*, 1934, ii, 180, 236.

[2] Tidy, H. L. *Ibid*, 1946, ii, 819.

[3] Crowther, J. S. *Brit. med. J.* 1951, ii, 775.

[4] Marshall, S., Millingen, K. S. *Ibid*, i, 1325.

[5] Halcrow, J. P. A., Owen, L. M., Rodger, H. O. *Ibid*, 1943, ii, 443.

[6] van der Meer, R., Lutterloh, C. H., Pilot, J. *Amer. J. med. Sci.* 1945, **210**, 765.

[7] Bender, C. E. *J. Amer. med. Ass.* 1952, **149**, 7, 65.

[8] Sabin, F. R. *Bull. Johns Hopk. Hosp.* 1923, **34**, 277.

[9] Paul, J. R. *Lancet*, 1941, i, 584.

[10] Ferguson, T., Macphail, A. N [illegible] Employment Problems of Disabled Youth [illegible] Research Council memorandum no. 28. Pp. 66. 3s.

Disabled Persons (Employment) Act, 1944, as "disabled persons" who were substantially handicapped in getting and keeping suitable work. The second study dealt with 408 physically handicapped young people who were pupils of the Glasgow special schools at the end of their school career, and who had mostly left school a full three years before the date of the survey. Control figures for these two complementary studies were provided by a similar survey, also made in Glasgow, by Ferguson and Cunnison,[11] of a large group of normal adolescents. Only 30% of those who attended special schools for the physically handicapped were registered under the Act, but it must be remembered that the reason for attending a special school is educational need, whereas a disabled person is likely to register because he has difficulty in obtaining and holding a suitable job. A considerable proportion of both groups had failed to avail themselves of necessary medical care—often because they had grown tired of doctors and hospitals—and 8% in the first group and 9% in the second required some form of medical appliance. In both groups unemployment was common; at the time of the survey 19% of the combined total were out of work. Those with organic diseases of the nervous system, particularly epilepsy and cerebral palsy, and the mentally retarded, found it especially hard to get work, while disabilities caused by respiratory disease, infantile paralysis, or deafness were less likely to cause unemployment. Not only is the unemployment-rate higher among the disabled, but the proportion engaged in non-manual work and in skilled or semi-skilled work is lower, while the proportion in unskilled manual work, often heavy in its physical demands, is twice as high as in normal youths. Many of these disabled people were therefore doing work far beyond their physical capacity, those with cardiac disease or tuberculosis, for instance, often undertaking heavy manual labour.

Each disabled person has his own problems, often intensified by his social background, and each requires careful individual consideration. Age, too, affects the employment picture:

> ". . . the proportion unemployed, for instance, is relatively low up to the age of 17 and rises steeply between 18 and 20. The proportion in non-manual work rises up to 19 years. The 16-year-old can easily find an unskilled job near his home; at first it may be within his physical compass and is often better paid in the initial stages than the job requiring special skill. It is only later, at 18, that he finds that the unemployment rate has doubled and that demands on his physical strength are steadily increasing. Such youths scramble through one exhausting job after another, and they are often hard put to it to avoid physical collapse and prolonged unemployment."

The way in which work was obtained was likewise important. When the young person found it himself he favoured office work; relatives or friends tended to guide him into skilled or semi-skilled manual work; and the employment exchange usually gave short-term unskilled work, largely because the exchanges had to find work when other means failed. When a disabled person registered on the advice of the authorities of special schools, the proportion in skilled and semi-skilled manual work was satisfactory. Those who were advised to register by their doctors were usually severely disabled, and their unemployment-rate was high, but when the stimulus came from their employers unemployment was rare. Much of the most stable and satisfying work was skilled office or skilled manual work. The survey also showed that 20% of the young people changed their jobs unusually often; unskilled workers and the mentally retarded did so most frequently, and the older the worker the less likely was he to change. Girls changed their jobs more light-heartedly than boys.

Deficient schooling adds greatly to the burden of the disabled child. If the deficiency is great, he may be denied the choice of office work, and he is usually forced into manual labour: should he be unfit for this he becomes either ill or unemployed. The educational standard was closely related to inability to perform non-manual work and to the unemployment-rate. Unfortunately education in special schools still carries a stigma of inferiority in the eyes of both the pupil and his potential employer. Professor Ferguson and his colleagues think it essential to secure the highest possible standard of education for disabled children, especially in the special schools, so that the disability of gross educational poverty shall not be added to that of physical impairment. The best time for a disabled youth to start work is when he leaves school, for then his attitude to employment is positive and full of enthusiasm. But

> ". . . constructive action is too often delayed and, as the months pass, the youth drifts into unskilled manual labour. At first it is comparatively well paid, and the youth, no longer a schoolboy, resents advice which urges him to take a job that may be skilled but which brings him in a smaller wage. Later still, when illness or idleness have opened his eyes to the hazards of unskilled labour and he sees his friends in skilled work now earning more than he can, disillusionment and bitterness often give way to cynicism or dissolve finally into apathy. The crisis of leaving school is never repeated. These surveys, which so often saw the hopes of fourteen turn to the cynicism of twenty-one, suggest that the striking success gained in resettling deaf young folk in Glasgow could be attained in many other disabilities if the same deep insight and interest in the special problems of youth were shown."

Other factors which have an important effect on employment include bad housing conditions, which make the task of reablement far harder; 30% of Ferguson's badly housed group were unemployed, and only 11% were doing skilled work. Unhappy homes made for more unemployment and frequent changes of job. The investigators conclude that the future of the disabled child is so precariously balanced that the parents' attitude is usually the decisive factor: where it is apathetic, unemployment is common and the general outlook unfavourable, but where the child is blessed by the security of a good home and enjoys real family life, even severe disabilities can be overcome.

This valuable report expresses disquiet at our failure to find these young people the right work. Of those registered under the Disabled Persons (Employment) Act only 26% were receiving suitable training; 22% were apprenticed in a variety of callings, non-manual and manual, and only 4% were attending training courses arranged by the Ministry of Labour and National Service. Many of the others bitterly resented the frustration of hopes which had been raised by the posters about training courses displayed in the employment exchanges. It is disappointing that, at a time of full employment, a greater effort has not been made to provide for disabled young people. Team-work is the key: each disabled person presents a personal problem which often can be solved only if all those concerned—parents, family doctor, school doctor, consultants, school teachers, social workers, employment officer, and sometimes potential employers—join in considering the facts and in making an appropriate individual policy by discussion. It is important for one member of the team, preferably the employment officer, to be given the responsibility of arranging training and employment without delay. Such is the logical approach advocated and practised by FERGUSON in Glasgow, and by others, with conspicuous success. Insufficient progress in helping disabled youth means a larger and harder core of unemployment in years to come, when it seems likely that the strain on the working population will in any case be great. FERGUSON and his associates point to four immediate needs: (1) improvement in education; (2) satisfactory settlement on leaving school; (3) more training courses; and (4) intensive medical and surgical treatment where this is required. All these needs can, and should, be met.

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[11] Ferguson, T., Cunnison, J. The Young Wage-Earner. London, 1951.

Annotations

CHLORAMPHENICOL AND THE BLOOD

PATIENTS receiving antibiotics have not escaped being troubled by side-effects; but these have been limited more or less to the occasional urticarial reaction, nausea, and, with streptomycin, deafness. Chloramphenicol, however, has been suspected of affecting the blood-forming tissues; and, as we reported last week,[1] the Food and Drug Administration has started a nation-wide survey in the U.S.A. after receiving reports of many cases of aplastic anæmia from this cause. Hitherto only six cases of bone-marrow depression following the use of chloramphenicol seem to have been published; but now Wilson et al.[2] have added to this list two cases of aplastic anæmia, in one of which the patient died.

Kracke and Parker[3] found that substances having in their chemical structure a benzene ring with an attached amino or nitro group were likely to affect the bone-marrow adversely. Chloramphenicol has this type of structure. Gill[4] described two cases of granulocytopenia, both in infants who were being treated for acute salmonella infection. One developed granulocytopenia after 12·3 g. of chloramphenicol had been given in twelve days, the other after only 1·75 g. in two days; in both the granulocyte-count promptly returned to normal when chloramphenicol was discontinued. Volini and co-workers[5] in the U.S.A. had three cases of neutropenia among patients treated with chloramphenicol for up to nineteen days, and one patient with typhoid fever had anæmia as well; in this patient the blood-count took three weeks to return to normal, but the others recovered very quickly. Rich et al.[6] reported the first fatal case. The patient was receiving chloramphenicol regularly for a urinary-tract infection; treatment had been continued for fifteen weeks, about 57 g. of the drug having been given. The first sign that something was wrong was the appearance of purpura; the patient eventually died and necropsy showed an aplastic bone-marrow.

The two cases reported by Wilson and his colleagues had also had long courses of chloramphenicol. These patients were members of a group of 62 who were receiving chloramphenicol regularly in a trial of the drug for the control of chronic bronchopulmonary suppuration; the dose was small—1 g. twice weekly. The first patient had been taking chloramphenicol for twenty-six weeks when the first unusual symptoms—epistaxis and purpura—appeared. Her hæmoglobin was reduced to 6 g. per 100 ml.; the white-cell count was 1110 per c.mm. with 8% neutrophils; platelets were 15,000 per c.mm. The bone-marrow was hypocellular; and most of the cells were lymphocytes and plasma and reticulum cells. It was clear that she had aplastic anæmia, and blood-transfusion was begun; but the hæmorrhages spread rapidly and became uncontrollable, and the patient died. Necropsy revealed generalised marrow aplasia. The second patient had severe epistaxis after receiving chloramphenicol for three months, but the significance of this symptom was not appreciated; the blood was not examined, and treatment with the drug was continued for another two months. At this stage, when the patient had received over 50 g. of chloramphenicol, she had severe epistaxis, and purpura appeared. Her hæmoglobin was reduced to 10 g. per 100 ml.; white cells were 9800 per c.mm. but there was only 33% of polymorphonuclears; platelets were greatly reduced to 9000 per c.mm. The bone-marrow was hypoplastic with unusual numbers of lymphocytes and eosinophil granulocytes. Treatment with chloramphenicol was stopped and cortisone was given, without effect. Without any further treatment the symptoms cleared, but the blood and bone-marrow pictures were still unaltered two months later.

The pattern of the toxic effect of chloramphenicol on the hæmopoietic tissues is one already familiar to us from the toxic effects of sulphonamides. These effects may appear quite quickly after a small dose in people whose blood-forming tissues are presumably exceptionally susceptible to the drug, or else after long-continued dosage when toxicity is more severe; reported deaths have, so far, been limited to this group. Now that we know that chloramphenicol may affect the blood-forming tissues, certain precautions should obviously be taken. Experience with many drugs that cause agranulocytosis has taught us that the onset of granulocytopenia is often so rapid that even regular blood-counts give us no warning; but if chloramphenicol is used for a long course of treatment, it would be sensible to have weekly blood-counts done. Any symptom suggesting affection of the blood-forming tissues—such as hæmorrhage from the nose or other mucous membranes, an unusually heavy menstrual loss, an unexplained sore throat, or purpura—should be the signal for discontinuing the drug and examining the blood. The experience of Wilson et al. suggests, too, that treatment with chloramphenicol should not be resumed in such patients.

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[1] See *Lancet*, July 12, 1952, p. 96.

[2] Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O., Kahn, J. *J. Amer. med. Ass.* 1952, **149**, 231.

[3] Kracke, R. R., Parker, F. P. *J. Lab. clin. Med.* 1934, **19**, 799.

[4] Gill, P. F. *Med. J. Aust.* 1950, i, 768.

[5] Volini, I. F., Greenspan, I., Ehrlich, L., Gonner, J. A., Felsenfeld, O., Schwartz, S. O. *J. Amer. med. Ass.* 1950, **142**, 1333.

[6] Rich, M. L., Ritterhoff, R. J., Hoffman, R. J. *Ann. intern. Med.* 1950, **33**, 1459.

DANGER FROM DRIED CULTURES AND VACCINES?

DRIED therapeutic products, such as antibiotics, are obviously free from serious risk to those who make and use them, though they may occasionally cause unpleasant effects.[1] But what of dried cultures and vaccines? In laboratories a rumour has been circulating that one worker contracted enteric fever by inhaling particles from a dried culture.

The risk is, of course, well known; and fluorescent tracers have been used to estimate the danger of airborne spread of the light particles of such dried material.[2] Fortunately the risk can be largely overcome by inserting a cotton-wool plug in the neck of an ampoule before it is sealed. Such a plug, however, can itself be a source of danger; for it is likely to contain fine particles of the dried material, and when it is grasped these particles may be diffused on to the skin or into the air. It is essential, therefore, that the plug should not be touched by the hand and that on withdrawal it should immediately be discarded into a container that can be sterilised.

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[1] Barker, A. N. *Lancet*, 1945, i, 177.

[2] Cowan, S. T. *In* Freezing and Drying. London, 1952; p. 127.

Living vaccines are used widely in veterinary practice and occasionally in human medicine. The organisms are non-pathogenic variants, which are presumably harmless; but there are technical problems in manufacture. During vacuum-drying, material may escape from the ampoules and reach the interior of the vacuum system; gales of 800 miles per hour occur in an efficient machine,[3] and cross-infection of ampoules is possible when two or more cultures are dried at the same time. Drying plants cannot be satisfactorily sterilised, and therefore the same machine cannot safely be used to dry two types of organism, even at different times.

STRUCTURE OF GROUND SUBSTANCE

To the naked eye interstitial connective tissue has a membranous appearance, but under the microscope this is replaced by a picture of a network of fibres, with occasional cells. In the last twenty years the nature of the apparently structureless mesenchymal ground substance lying between these collagen fibrils has been elucidated by numerous studies centring around the admirable work of Duran-Reynals[4] Meyer et al,[5] and Chain and Duthie[6] on spreading factors and mesodermal polysaccharides. The work of Hechter[7] has underlined the importance of the mechanical factors of pressure (e.g., œdema) and volume in determining hyaluronidase spreading action, but little attention has been paid to the structural aspects of the interfibrillary substance which may influence these factors. During the last five years Day[8] has presented a convincing structural conception of the ground substance, illustrated by simple and compelling experiments, which does much to explain both the membranous quality and the especial permeability of connective tissue.

In 1876 Flemming[9] described cementing substance in and around the fibre-bundles of connective tissue, and noted that weak acid caused coagulation and contraction of this substance, whereas the collagen fibres swelled. Day has re-stated and amplified this observation. He found that at about pH 4 lamellæ of connective tissue from rat fascia became opaque and shrunken, while increasing alkalinity caused increasing swelling; the collagen fibres themselves showed no microscopical change until the pH exceeded the range 4–11. The concentration of neutral salts causing swelling became proportionately less as the hydrogen ion concentration fell. In wet preparations of connective tissue he noted irreversible changes at a slightly more acid pH (3·6); the hitherto clear interfibrillary spaces became opaque under dark-ground illumination, owing to the appearance of exceedingly fine branching fibrils and refractile granules. 50–60% ethanol induced similar changes, and Day found the resulting microscopic appearance of a fine network lying in the same optical plane very strikingly similar to the membranous naked-eye appearance of connective tissue. The collagen and elastic fibres were embedded in the opaque membrane "like twigs in a frozen pond." Trypsin treatment disintegrated this membrane, but hyaluronidase left it structurally intact. Day concluded from this and other work on the hydration of connective tissue, that a main constituent of the interfibrillary substance was of a protein nature, precipitable at its isoelectric point, organised in structure, and not leached out by water.

Contemporary workers have been much preoccupied with the mucopolysaccharides in ground substance; and, while opinions have differed as to whether they are free or bound to the protein element, no clear picture has hitherto emerged of how the interfibrillary substance is organised within the meshes (often 50 μ or more across) of the fibril network. In electron micrographs, although the collagen structure is revealed with great clarity the ground substance remains amorphous.[10] More recently Day[11] has described experiments in which he measured the rate of flow of saline across a mouse-connective-tissue membrane occluding the end of a vertical tube immersed in saline. Hyaluronidase added to the perfusing fluid increased the rate of flow 10–20 times. Subsequent perfusion of starch solution reversed this effect, while the effect of ptyalin on the starch-perfused membrane mimicked that of hyaluronidase on untreated membrane. Histologically, iodine treatment of the starch-perfused membrane showed homogeneous blue staining extending across the interfibrillary spaces. The starch was not removed by prolonged subsequent re-perfusion with saline. Day established that these findings were not due to a mere viscosity effect of macromolecular substances; and he attributes them to a sieve-like action of the permanent protein trellis of ground substance which he previously described. He concludes that the structure of the interfibrillary substance is that of an organised protein network, whose meshes are "water-proofed" by molecules of polysaccharides susceptible to the action of hyaluronidase.

P.I.E. OR P.U.O.?

TWENTY years have passed since Loeffler[12] first described a symptom-complex comprising transient pulmonary infiltrations and eosinophil leucocytosis in the blood. His cases ran a brief and benign course, and in a high proportion there was a history of diseases of allergy. Since then many similar cases have been described, but in some the patients have been ill longer and more seriously. Reeder and Goodrich[13] suggest that the classical syndrome represents the benign end of a range of disorders extending by degrees to severe and irreversible disease, as in periarteritis nodosa. They propose the introduction of a new term—"P.I.E. syndrome" to denote pulmonary infiltration with eosinophilia.

Ruzic et al.[14] feel that Loeffler's syndrome should be understood to include transient infiltrations in other organs. They report a case with asthmatic symptoms, vomiting, and abdominal pain in which transient pulmonary shadows and blood and marrow eosinophilia were found. The abdominal symptoms led to suspicion of gastric carcinoma, but gastrotomy showed a purely submucosal mass lying along the lesser curve. Biopsy showed an inflammatory infiltrate containing a fairly large number of eosinophils. The mass resolved spontaneously within two months. Loeffler's syndrome has also been described in conjunction with eosinophilic infiltrations of lymph-glands, muscle, and epididymis,[15] and inflammation of serous membranes.[16] Lyon and Kleinhaus[17] reported this syndrome associated with skin eruptions resembling erythema multiforme, but unfortunately no biopsies were done. More recently, Argentinian workers[18] have described an erysipeloid-like skin lesion with blood eosinophilia and fleeting infiltrations of the lungs in a case of lymphoid leukæmia after treatment with urethane. Skin biopsy showed an infiltrate which, in the subcutaneous layers and the fat, contained numerous eosinophils. "Eosinophilic granuloma of the skin" is not an entity, but at least some of the lesions described under that name are probably allergic in origin. Lewis and Cormia[19] reported a case associated with tinea pedis: the lesions were aggravated by injection of trichophytin, and similar patches appeared where the injections were made. This resembles the experience of Dostrowsky and Sagher,[20] who described positive reactions to the antigen of *Dirofilaria immitis* in cases of "eosinophilic erythrœdema" of the skin, with in three instances recrudescence of the skin lesions. It would be interesting if Leoffler's syndrome could be shown to be present in endocarditis parietalis fibroplastica, where eosinophilia and residence in the tropics raises the suspicion of allergy to parasites—e.g., loa loa.[21]

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[3] Greaves, R. I. N. *Ibid*, p. 159.
[4] Duran-Reynals, F. *C.R. Soc. Biol. Paris*, 1928, 99, 6.
[5] Meyer, K., Dubos, R., Smyth, E. M. *Proc. Soc. exp. Biol., N.Y.* 1936, 34, 816.
[6] Chain, E., Duthie, E. S. *Nature, Lond.* 1939, 133, 977.
[7] Hechter, O. *J. exp. Med.* 1947, 85, 77.
[8] Day, T. D. *J. Path. Bact.* 1947, 59, 567; *Lancet*, 1947, ii, 945; *J. Physiol.* 1949, 109, 380.
[9] Flemming, W. *Arch. mikr. Anat.* 1876, 12, 391.
[10] Gross, J. *Ann. N.Y. Acad. Sci.* 1950, 52, 964.
[11] Day, T. D. *Nature, Lond.* 1950, 166, 785; *J. Physiol.* 1952, 117, 1.
[12] Loeffler, W. *Beitr. Klin. Tuberk.* 1932, 79, 368.
[13] Reeder, W. H., Goodrich, B. E. *Ann. intern. Med.* 1952, 36, 1217.
[14] Ruzic, J. P., Dorsey, J. H., Huber, H. L., Armstrong, S. H. *J. Amer. med. Ass.* 1952, 149, 534.
[15] Maier, C. *Helv. med. Acta*, 1943, 10, 95.
[16] Harkavy, J. *J. Allergy*, 1943, 14, 507.
[17] Lyon, E., Kleinhaus, E. M. *Acta med. orient.* 1945, 4, 144.

How pertinent is the eosinophilia in these cases? Over-emphasis on its importance has led to grouping of quite dissimilar lesions—e.g., the eosinophilic granulomas of the skin. We do not know the function of the eosinophil leucocyte; but clearly an allergic reaction is only one of many processes that can evoke eosinophilia, just as allergy is only one cause of fibrinoid degeneration. Perhaps we are dazzled by these mysterious beauties, whose presence may be more ornamental than significant. Several notable histopathologists are colour-blind.

TUBERCULOSIS IN THE COMMONWEALTH

THE third Commonwealth Health and Tuberculosis Conference of the National Association for the Prevention of Tuberculosis (N.A.P.T.), held in London this month, has brought visitors and views from many parts of the world. Representatives from Mauritius, Singapore, British Guiana, and the Colonial African Territories reported great advances in the use of tuberculin-testing and X-ray surveys to measure infectivity and find new cases. Africans, it seems, cannot stomach bed rest or isolation in hospital; but chemotherapy has given us the means to combat their diseases in spite of these prejudices, and fortunately results are as good with them as with white men. Moreover the old notion that Africans and Asians cannot withstand tuberculosis appears to be ill founded; or perhaps their resistance is improving. At all events speakers from many tropical regions agreed that, provided the environment was satisfactory, their patients resisted well enough. B.C.G. vaccination is now widely used, and plans are on foot in Jamaica and Trinidad to immunise all susceptible children within the next two years. An annual X-ray examination is proposed for the 300,000 African miners of the Witwatersrand gold mines, among whom an incidence of 4 active cases of tuberculosis per 1000 radiographed has already been found. India has already made history with a record of 8 million people tuberculin-tested and $2^1/_2$ million vaccinated with B.C.G.—yet this is a mere beginning in that vast population of 356 million. Pakistan, estimated to have 2 million cases, is mainly agricultural, and has meagre resources to deal with its problem. Progress is slow and at present depends largely on the help of the World Health Organisation. This may be contrasted with the enviable position of Canada, where there are 18,000 sanatorium beds—a ratio of 5 beds to 1 annual death from tuberculosis. There Koch's bacillus is pursued in mobile mass X-ray units of the bus type, augmented by equipment carried in railway coaches.

News of isoniazid was much the same as we have had already from the British Tuberculosis Association,[22] but Prof. Ralph Tomsett, from the Cornell Medical centre, warned his hearers against the possibility of florid fatal relapses in patients who have developed resistant mutants.

At a joint meeting of the N.A.P.T. with the B.T.A. to discuss childbearing and tuberculosis, Dr. C. J. Stewart surprised some of his hearers by concluding that whether the disease is minimal, moderately advanced, far advanced, or quiescent, its progress is uninfluenced by pregnancy, parturition, or the puerperium. He based this opinion on the five years' after-history of a large series of lung cases, comparing it with a control group who were not pregnant. He averred, too, that there are no medical indications for terminating pregnancy on account of tuberculosis. Nevertheless he counselled against a woman with active or unstable disease having a baby within two years of quiescence, and held of course that a mother with active disease should not breast-feed her baby (who, incidentally, should be vaccinated with B.C.G.). Dr. Raymond C. Cohen confirmed these main conclusions from a study of 400 mothers in his own maternity unit at Black Notley Sanatorium, and emphasised the need to avoid hæmorrhages and fatigue during labour in the more anæmic tuberculous women. He suspends pneumoperitoneum refills for two months before the confinement, and counsels against resuming them too soon afterwards. In all acute cases, he thinks, lactation should be suppressed by the use of concentrated œstrogens. Dr. Geoffrey Beven, however, reported enlargement of cavities in 17 out of 41 puerperal cases, and moreover, in a group of 150 women sputum-negative before pregnancy, he had seen 10 become sputum-positive after delivery. Mr. Camac Wilkinson drew attention to the spontaneous improvement often seen, during pregnancy, in patches of cutaneous lupus, with relapse after childbirth. This, he suggested, might be due to the temporary increase in plasma sterols during pregnancy. A useful suggestion for case-finding was made by Dr. Cohen: if all pregnant women were given a routine X-ray examination of the chest, he said, we might expect to find 4 or 5 cases of pulmonary tuberculosis in every 1000, and hence some 3000 new cases in England and Wales each year.

The social aspects of the disease are changing with the change in methods of treatment. The Australian government have introduced a scheme by which the unfit tuberculous worker, if a married man, can be paid £8 5*s*. a week, and may also retain £4 a week additional income from other sources. Our own scales, of course, fall short of this. Our tuberculous patients are not housed as well as they should be. Dr. W. Hartston mentioned that while only 3% of all London's families, and 5% of its tuberculous adults, are believed to live under conditions of overcrowding, as defined in the Housing Act of 1936, yet barely half of the 30,000 tuberculous adults in the metropolis have a bedroom to themselves. Priority is given to tuberculous London families for rehousing outside the county; but this has caused some misgivings because the proportion of tuberculous in the rehoused communities may sometimes be as much as 3 or 4 times the proportion in London as a whole. Dr. Hartston, however, has found an incidence of new cases, in these rehoused communities, of only about a third of what might reasonably have been expected from the numerical prevalence. This applies not only to the tuberculous families but also to their neighbours. Nor has he been able to find evidence of an increased incidence among the—often rural—populations of the districts where the new estates are established.

ON July 14 Lord Tedder opened the International Congress of Physical Medicine which is being held in London this week under the presidency of Lord Horder. Mr. Iain Macleod, the Minister of Health, welcomed the delegates, who have come from 23 countries.

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[18] [illegible] Caballero, H. J., Bosq, P. *Rev. argent.* [illegible] 6.

[19] [illegible] E. *Arch. Derm. Syph.* 1947, 55, 176.

[20] [illegible] *J. Palestine Jewish Ass.* 1946, 30, 33.

[21] [illegible] 1951, 13, 387.

[22] [illegible] 9.

Public Health

PEOPLE, JOBS, AND HOUSES

New light on the social structure of Britain

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THE volume of advance tabulations of the results of the 1951 Census in Great Britain,[1] published last week, is of considerable importance to medicine. The structure of the population in age and in its manifold social characteristics, such as occupation, are essential ingredients of the vital statistics to which medical officers of health turn for measurement of trends in public health. To clinicians population statistics may have a less immediate appeal. A new influence has been at work, however; for the tendency is, more and more, to contemplate the patient as a member of a community. The smallest unit of this is the family; at a higher level are the workshop or factory group, and ultimately the population at large. Close statistical study of the population is being taken up as a tool in the elucidation of the ætiology of disease. The approach to disease is now macroscopic no less than microscopic; and thus the contributions of human diathesis and environmental influences can be distinguished.

TABLE I—ENGLAND AND WALES: AGE AND SEX DISTRIBUTION IN 1931 AND 1951
(Numbers in thousands)

Age (yr.)	1931				1951			
	Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%
0–4	1510	7·9	1480	7·1	1896	9·1	1823	8·0
5–14	3298	17·2	3232	15·5	3065	14·6	2949	13·0
15–34	6471	33·8	6870	33·0	5850	27·9	6087	26·7
35–64	6581	34·4	7547	36·3	8211	39·1	9075	39·9
65 and over	1273	6·7	1690	8·1	1957	9·3	2832	12·4
Total	19,133	100·0	20,819	100·0	20,979	100·0	22,766	100·0

A first requirement in all these studies is a classified enumeration of the population. Apart from specialised and local surveys, this is obtainable only from a national census. Though power was given in the Census Act of 1920 to conduct enumerations more often, no intercensal interval has yet been less than 10 years and the census of 1951 was divided from the preceding enumeration by a long space of twenty turbulent years with only the national registration of 1939 as a stop-gap. The 1951 tabulations have therefore been eagerly awaited. This time the normal interval of several years between the date of the census and the publication of the results has been shortened to just over one year by taking a 1% sample of the records for advance analysis, leaving the full results to be obtained later from the whole body of records. The census tables cover the whole of Great Britain; but the figures cited here relate to England and Wales only.

The Ageing Population

The decline in the birth-rate since the latter part of the 19th century and the increased longevity brought about mainly by the conquest of the infections formerly causing tragic waste of life in infancy and youth have increased the proportion of people with degenerative disease and infirmity of old age. The general death-rate, even when analysed by cause, tells us little about this since it is an average of the mortality at all ages. When the effect of the higher fertility of earlier years in inflating the present middle age-groups is worn out by the passage of time, and the bulge in the age pyramid of the population has passed up to older ages, then we may expect the general death-rate, which has been falling, to rise again. Meanwhile we look to death-rates in narrow age-groups, and here in the census tabulations we have a precise measure of the denominators for present use and as a new base-line for estimations in the years until the next census. How do the new figures compare with those of 1931? How far has the ageing progressed? The figures are shown in table I.

The population of young adult men (15–34) has fallen from 33·8% of all men to 27·9%. The percentage of all men over the age of 65 has increased from 6·7 to 9·3. For women the percentage in the 15–34 age-group has fallen from 33·0 to 26·7, while at ages over 65 the proportion has risen from 8·1 to 12·4. The improved survival of women (not only an absolute improvement but also an improvement relative to that of men) has accentuated the old-age weighting of their population structure. The effect of the temporary post-war boom in births can be seen at ages 0–4.

The need for attention to age-distribution is further illustrated in table II, showing the changing pattern of mortality from age to age.

Sex Differences in Disease

Apart from the obvious differences in the occupational risks as between the two sexes, giving rise to differing morbidity experience, and the special risks of women in pregnancy and childbirth, there is evidence of consti-

TABLE II—PRINCIPAL CAUSES OF DEATH IN AGE-GROUPS: ENGLAND AND WALES 1948–49

Age-group (yr.)	Cause of death	5th Revision International List	Deaths	Death-rate
				Per 1000 related births:
Under 1	Congenital malformations Birth injury, and Other diseases of early infancy	157 158 160, 161	17,859	11·79
	Prematurity	159	12,081	8·00
	Respiratory diseases	104–114	9542	6·17
	Enteritis and diarrhœa	119, 120	4267	2·76
	Infective diseases (excl. tuberculosis)	1–12 23–44	1835	1·18
	Other causes	—	5065	3·27
				Per 1,000,000 in age-group:
1–14	Violence	163–198	3740	216
	Tuberculosis	13–22	2301	133
	Infective diseases	1–12 23–44	2040	118
	Pneumonia	107–109	1789	103
	Other causes	—	7255	419
15–44	Tuberculosis	13–22	21,236	571
	Cancer	45–55	10,304	277
	Violence	163–198	9204	247
	Heart-disease	90–95	8574	230
	Diseases of the digestive system	115–129	3520	95
	Nephritis	130–132	2729	73
	Other causes	—	19,418	522
45–64	Cancer	45–55	60,084	2935
	Heart-disease	90–95	55,322	2702
	Intracranial lesions of vascular origin	83	22,239	1086
	Bronchitis	106	13,922	680
	Tuberculosis	13–22	13,171	643
	Diseases of the digestive system	115–129	10,265	501
	Pneumonia	107–109	6984	341
	Other causes	—	46,907	2291
65 and over	Heart-disease	90–95	224,656	24,004
	Intracranial lesions of vascular origin	83	89,127	9523
	Cancer	45–55	88,982	9508
	Bronchitis	106	38,344	4097
	Other circulatory diseases	96–103	32,961	3522
	Pneumonia	107–109	19,524	2086
	Other causes	—	113,372	12,114

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[1] Census, 1951, Great Britain. One per cent. Sample Tables. Part 1: Ages and Marital Condition, Occupations, Industries, Housing of Private Households. H.M. Stationery Office. Pp. 159. 17*s.* 6*d.*

TABLE III—RATIO OF FEMALE TO MALE DEATH-RATES (ALL AGES): ENGLAND AND WALES, 1949

Cause of death	International List	Death-rate per million		Ratio F : M
		Males	Females	
Cancer	45–55	1981	1771	0·89
Diabetes	61	54	104	1·93
Respiratory diseases ..	104–114	1635	1095	0·67
Peptic ulcer	117	185	50	0·27
Disease of gall-bladder ..	126,127	20	48	2·40

tutional (as distinct from environmental) causes of variation in susceptibility to certain diseases. Table III illustrates the type of variation.

The ratios fluctuate from disease to disease even more violently when narrow age-ranges are taken. Martin (1951) has drawn attention to the faster decline in mortality in females compared with that in males during the past hundred years; he finds that it is difficult to separate the effects of social class or occupation from other factors.

Clearly, then, there will be considerable interest in the sex ratios in the general population, since these are likely to influence the total volume of disease. The changes since 1931 are indicated in table IV.

At very young ages the higher (male to female) sex ratios at birth in war and post-war years have slightly increased the male superiority in numbers. At middle ages males are less deficient in numbers relative to females than formerly. At ages over 65 the still further relative improvement in the longevity of women gives them an enormous numerical advantage—much greater still than in 1931. The medical effects of this change are reflected in health service statistics. Of all cases, other than pregnancy and childbirth, discharged from hospitals covered by the General Register Office survey in 1949 (Mackay 1951) 10·4% were females aged 55 and over, compared with 11·6% of males in this age-group. Of all cases nursed at home by the L.C.C. home nursing service in 1950 (Benjamin and MacGregor 1950), however, 32·5% were females over the age of 60, and only 15·8% were males over 60. The effect is therefore mainly on the volume of chronic sickness which is nursed at home and is not treated in hospital.

Marriage

There was a tendency during and after the war of 1939–45 for spinsters to marry earlier, thus tending to increase the average period of exposure of married women to the risk of childbearing and bringing to the care of antenatal clinics, maternity departments, or domiciliary midwives, mothers of a younger average age. In addition we have the effect of the higher marriage-rates in the early years of the late war and after. (Some of these were not extra marriages but marriages which, if there had been no war, would have occurred sooner or later; the war merely affected their timing.) In this context it is only necessary to look at the proportion married at younger ages to see that there have been large changes; at 25–34, for example, the proportion has risen from 67·0 to 81·9% (see table V).

TABLE IV—SEX RATIOS IN THE POPULATION OF ENGLAND AND WALES

Age (yr.)	Sex ratio (i.e., females per 1000 males living in each age-group)	
	1931	1951
0–4	980	961
5–14	980	962
15–34	1062	1041
35–64	1147	1105
65 and over ..	1328	1447
Total	1088	1085

The proportion of women who are married is of interest, too, in any general measure of morbidity, since often marriage means the removal of a woman from the environment of the office, shop, or factory to the environment of the home where the stresses and strains are different. The bearing of this factor on, for example, the shape of the age-curve of tuberculosis mortality in women has seemed important in the light of evidence of higher morbidity in those who married and remained at work (Benjamin and Nash 1950), though a more important factor may be the more acute form of the disease in females (Springett 1952).

Occupation and Social Class

The importance in the ætiology of disease of nutrition, cleanliness, fresh air, the comforts of living, congenial employment, and all the intuitively recognised but vaguely defined elements which make up that complex connoted by "social conditions" has already been cited as a reason for expecting heightened medical interest in the results of the census. In addition there is the demand for more up-to-date information for the continuing and more intensified studies of direct occupational hazard. Much work has been done in recent years perforce on the basis of 1931 figures of occupational and social class-distribution, though it has been realised that since that year the preparation for war and the rehabilitation of the national economy in peace have possibly involved profound disturbance of the industrial and occupational distribution of man-power.

TABLE V—PROPORTION OF WOMEN MARRIED: ENGLAND AND WALES

Age (yr.)	Proportion of women ever married (*% of all women*)	
	1931	1951
15–19	1·8	4·5
20–24	25·8	48·4
25–34	67·0	81·9
35–44	80·6	86·6

In looking at table VI two important changes must be borne in mind: (1) 1931 was a year of economic depression and heavy unemployment, and men may have recorded occupations representing not their normal skill and practice but temporary employment governed by opportunity rather than choice; and (2) the school-leaving age has been raised and National Service instituted since 1931, resulting in later entry into trades and professions. Furthermore, changes in the occupational classification between 1931 and 1951 render it impossible to make precise comparisons without lengthy explanations. In table VI an attempt has been made to adapt the 1931 figures to the 1951 classification; the adaptation is approximate only, but the general nature of changes indicated may be accepted as reliable.

Thus comment on the 1951 figures shown in this table must necessarily be cautious. It does seem clear that the drift from agriculture, from village to town, may have continued. There are far fewer miners now than twenty years ago. Increases in the chemical and engineering occupations reflect the higher level of armament production, as well as the export drive in motor-cars and other post-war needs for machinery. There are fewer textile workers but more builders; more clerks and fewer women in domestic service; more professional workers (and some new professions); many more soldiers, sailors, and airmen.

The effect of these changes of occupation on the social-class gradient is indicated in table VII for men aged 20–64. A personal impression is that the change, though significant, is slight and amounts to a small general shift upward, mostly from unskilled workers to skilled workers. (Doubtless *within* social classes there have been changes in distribution, as is evidenced in table vi; and there have also been small changes in the actual classification, which have been ignored.) If this observation appears out of accord with common impressions based on contemporary income-levels, it must be remembered that the allocation of occupation to social class is related not solely to current income but to a broader view of the general standing of the occupation in the community. For this reason some occupations occupy a higher social class than other occupations with larger incomes. The various elements of the social complex to which reference has been made are closely correlated, though perhaps less than formerly; income and housing and education are still dependent on each other, and it is impossible to separate their effect on health. Indeed, if this were not so the composite measure of social class would not be needed, for direct association with more objective variables would be preferred.

In the London boroughs in 1931–33 (Benjamin 1952) the mortality-rate from pulmonary tuberculosis was correlated with the percentage of the borough population in social classes iv and v (coefficient of correlation +·73) and with the percentage living at a density of more than 1½ persons per room (+·69); but social class and housing density were correlated (+·72); and while the partial coefficient of correlation of tuberculosis mortality with social class (holding the housing effect constant) was +·45, the correlation with housing (holding social class constant) was slightly less at +·35.

In the circumstances, and for medical purposes, the social-class grading is probably as realistic a measure as any of the environmental and educational influences as a whole. (Those who are unfamiliar with the grading will find details in the Classification of Occupations 1950 (General Register Office 1951). The social-class allocations are also shown in table ii. 1 of the 1% sample.)

TABLE VI—OCCUPATIONS OF MALES AND FEMALES IN 1931 AND 1951: ENGLAND AND WALES
(Numbers in thousands)

Occupations	Males 1931 (14 +)	Males 1951 (15 +)	Females 1931 (14 +)	Females 1951 (15 +)
Fisherman	27	17	—	—
Agricultural, forestry, &c. ..	1117	953	57	91
Mining and quarrying	960	602	3	2
Non-metal mining products (excl. coal)	77	84	44	47
Coal gas, coke, chemical, and allied trades	47	94	4	11
Metal manufacture, engineering, &c.	1556	2272	142	215
Textile workers	298	201	583	363
Tanners, leather, fur dressing ..	167	110	63	69
Makers of textile goods and dresses	151	124	506	433
Food, drink, tobacco	139	146	70	83
Wood, cane, cork	442	437	7	16
Paper, board, printing	159	167	93	90
Other products	60	86	33	43
Building	646	818	—	—
Painters, decorators	242	307	13	12
Administrators, managers not included elsewhere	355	420	27	43
Transport and communications..	1566	1403	69	129
Commercial, finance, and insurance (excl. clerical)	1470	1240	605	762
Professional and technical (excl. clerical)	404	726	394	523
Defence Services	282	689	—	19
Entertainment and sport ..	91	83	22	23
Personal service (domestic, waiters, &c.)	473	463	1934	1427
Clerks, typists, &c.)	711	846	571	1278
Warehousemen, storekeepers, packers, bottlers	245	342	147	189
Stationary-engine drivers, tractor-drivers, stokers, &c.	162	235	—	2
Other unskilled occupations .. Other and undefined ..	1401	1214	219	362
Total occupied	13,247	14,079	5606	6230
Retired or not gainfully occupied	1386	1940	10,805	11,763
Total	14,633	16,019	16,411	17,993

TABLE VII—SOCIAL CLASS IN MALES AGE 20–64: ENGLAND AND WALES
(Numbers in thousands)

Social class	1931		1951	
	No.	%	No.	%
I. Professional and managerial	278	2·4	432	3·4
II. Intermediate between I and III	1569	13·8	1939	15·2
III. Skilled workers ..	5499	48·5	6609	51·9
IV. Intermediate between III and V	1993	17·6	2004	15·7
V. Unskilled workers ..	1845	16·3	1572	12·3
Unoccupied *	158	1·4	190	1·5
Total	11,342	100·0	12,746	100·0

* These are not normally gainfully employed; this group does *not* include those workers who were, at the census, unemployed and who are classed to their customary occupation.

Of the many diseases in which social-class gradients of mortality are striking, coronary heart-disease, owing to the heavy increase in deaths assigned to it, has been the subject of much discussion (Morris 1951, Logan 1952). In giving advance social-class allocations for deaths in 1949 from heart-disease Logan was justified in what was then an assumption—that the social-class distribution of the population exposed to risk had not suffered sufficiently large changes since 1931 to invalidate his comparisons. It appears therefore that the social-class gradient of coronary disease (formerly decreasing from i to v) has in fact become less evident, though the opposite gradient of myocardial disease has been maintained. Peptic ulcer is another disease in relation to which social class is important. Comment has been made (Benjamin 1949) on the variation of the relationship between gastric and duodenal ulcer with social grading. Within the peptic-ulcer group of deaths gastric ulcers become more preponderant with descent in the social scale. The suggestion is that the type of mental distress and intensity of living associated with duodenal ulcer is more within the experience of higher "social classes," while it is in the lower "social classes" that there is more likelihood of feeding habits which produce injury of the gastric mucosa associated with gastric, as distinct from duodenal, ulcer (Nicol 1941).

Housing

In 1951 the proportion of structurally separate dwellings in England and Wales shared by more than one household was 7·0%, compared with 9·1% in 1931. In terms of families 15% of private households were sharing occupation of a dwelling in 1951 compared with 19% in 1931. For epidemiologists this is an important fact, for households in shared occupation may maintain an economic independence but are bound to be in more frequent contact with each other than if each occupied structurally separate dwellings. It has been shown (Stein 1952) that in Glasgow tuberculosis mortality is more highly correlated with persons per dwelling than with persons per room—i.e., the total number exposed to risk in the small community of households in the dwelling may be more important than their actual density of occupation.

It is doubtful whether anyone has ever separated the effect of housing on health or even satisfactorily defined what is meant by "housing effect." Correlation of disease incidence may merely reflect correlation with income, as has been illustrated already. If a tuberculous person has to share a bedroom with a non-tuberculous contact, that would probably be regarded as a real effect of overcrowding on health. A Bristol investigation suggested a relationship between basement rooms and rheumatic fever (Daniel 1942), but it was not statistically significant; and other stronger relationships with social factors were operating. Dampness, lack of fresh air, lack of light, or lack of warmth must all take their toll; but it would be difficult to carry out controlled experiments to measure the precise effects. Housing conditions cannot be interfered with for the sake of experiment.

Persons per household in England and Wales decreased from 3·72 in 1931 to 3·19 in 1951—a product of the recent high marriage-rates and also of a significant rise in "one-person" households. There has been, too, a very large rise in the number of dwellings from 9,123,000 in 1931 to 11,934,000 in 1952. Persons per room fell from 0·83 to 0·73, and the percentage of persons living in overcrowded conditions (more than 2 per room) fell from 6·94 to 2·16. The average housing density of 1951 is not as bad as in 1931, however many people may still be waiting for better accommodation. The figures will of course repay more detailed examination. For example, for families of the same size the average number of rooms available is the same in 1951 as in 1931 and the improvement in density seems to arise from an increase in small households with low density and a reduction in large households with high density.

Household Arrangements

While there has been a considerable reduction in the mortality from—and indeed in the incidence of—enteritis and diarrhœa, notified cases of dysentery have been more frequent in recent years. This increase is not entirely confined to institutional outbreaks; nor is it wholly due to improved pathological services and better diagnosis. Food-poisoning has become so much more prevalent, and has aroused so much more public concern, as to have been included among the notifiable diseases. This greater prevalence is symptomatic of an era of extended resort to communal feeding, but the handling of food in private homes often leaves something to be desired. The development of detergents may have outpaced improvement in personal habits. There is still need to remind ourselves of the simple truths of hygiene which our forefathers learned only from the tragedies of cholera and other pestilences. Much depends, however, on the means of cleanliness. The results of the census indicate that out of 13,043,500 households in England and Wales 5,817,400 (44·6%) are without exclusive use of a fixed bath (1,008,200 households are sharing a bath and 4,809,200 households are entirely without a fixed bath)—i.e., it is not easy for these households to take a bath, though presumably most have portable baths and access to public baths. There are 21·4% of households without exclusive use of water-closets (7·9% entirely without). There are 13·8% of households without exclusive use of both sink and stove (6·3% are entirely without a kitchen sink). There are 1,541,900 households sharing a piped water-supply within the house and 735,400 entirely without, making a total percentage of 17·5 without exclusive use of piped water in the house.

Such figures provide essential comparative information when local epidemiological inquiries involving these factors are carried out. It is not enough to know the facilities available to those in whom disease is observed; it is equally important to know as much about those who have escaped. One example is recent study of enteritis in the London area in which factors of cleanliness were recorded.

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Paratyphoid-B Fever in Cardiff

An outbreak of paratyphoid-B infection occurred at Cardiff in 1939, and since then there have been sporadic infections at the rate of one or two cases each year.

An outbreak began on May 6 this year when a Cardiff resident, who was employed outside the city in one of the coal-mining areas, sickened. He was not notified as a case of paratyphoid-B fever until May 23, some 17 days after his first symptoms. Dr. W. Powell Phillips, the deputy medical officer of health, to whom we are indebted for these notes, says that by this time it was known that other cases of paratyphoid fever were occurring in the mining district where he was employed and where he had food in the daytime. The onset of these cases coincided with the Cardiff case.

The next patient—an infant, aged 10 months—sickened on May 10. This case was notified on May 17. With such a small child and the restricted dietary it was possible to pin-point the likely source of infection, and it was found that the child had been given some cream trifle. This was also taken by 3 adults and 1 other child, aged 3 years, in the family. On routine investigation it was found that they were excreting paratyphoid-B bacillus, type I. The child aged 3 sickened on May 28, but the adults remained symptomless excretors. The cream trifles were manufactured outside Cardiff, and investigations at the source of supply provided no clue to the infection.

A further case was notified on June 6; this was in a woman who had been ill for 10 days before notification. Synthetic cream confectionery was the most suspicious article of food and in 14 subsequent cases the same kind of food came under suspicion. This was traced back to a large confectionery establishment, and on routine fæcal investigations it was found that there was an excretor among the staff. This excretor also had mild symptoms, and as the agglutination titre rose considerably it is considered that he was a case rather than a symptomless carrier. There is absolutely no evidence to link these cases with the first cases notified in Cardiff, although every effort was made to detect a common source of infection. A further 8 cases have been notified in Cardiff, and again the most suspicious article of diet has been cream confectionery; but the source of supply has not, so far as can be ascertained, been common manufacturing or sales establishments.

An interesting feature of this outbreak has been that there have been some 100 cases of paratyphoid-B, type I, infection within a radius of about 50 miles, mainly in the mining valleys which radiate from Cardiff. Confectionery seems to have played a prominent part in the history of most of the cases, and many bakeries have come into the picture. A detailed study of the commodities used in the industry has revealed how intricate are the sources of supply for the various articles which go to make up modern confectionery. The primary manufacture of these products, such as synthetic cream, dried egg, and liquid egg, is outside the Cardiff area, and they have a nation-wide distribution. Viewing this epidemic as a whole, it seems that some wholesale establishment supplying bakeries in this area may be a source of infection. Furthermore, Cardiff serves as a distribution centre for the greater part of the area in which cases have occurred.

Bacteriological investigations have been carried out on the staff of such suppliers and also on samples of synthetic creams, dried egg-white, frozen egg, custard-powders, pastry and cake margarines, and marshmallow, with negative results so far.

Most of the patients have not been severely ill, but among the 25 cases up to July 2 there have been 2 deaths. It is noteworthy that in 2 cases the organism was isolated from the fæces 24 hours before symptoms developed.

The Public Health Laboratory Service has been responsible for the enormous amount of bacteriological investigations involved, and they have also been advising on, and taking part in, the epidemiological investigations. The Welsh Board of Health has been actively engaged in coordinating the investigations throughout the whole affected area.

BRITISH MEDICAL ASSOCIATION

The joint annual meeting of the British Medical Association and the Irish Medical Association was concluded in Dublin last week. Three plenary scientific sessions were held, and the various scientific sections met during the second half of the week.

The annual dinner of the two associations was held in the Pavilion of the Royal Dublin Society on July 10. The minister for health of Ireland, Dr. James Ryan, proposed the toast of the associations. He forecast an extension of the health services in Ireland in the near future, but he would not be drawn into any details. He did, however, declare that whatever was done would be based on "the solid foundation that has stood the test of time—the family doctor." Dr. E. A. Gregg responded for the B.M.A. and Prof. T. G. Moorhead for the I.M.A. Professor Moorhead thought that the medical schools were turning out too many doctors. Their energies would be better concentrated on turning out really healthy patients suitable for the lists of doctors practising under a national health service. The Guests was proposed by Dr. I. D. Grant who hoped that the lessons learnt from the National Health Service would be of value to those who were planning the medical affairs of Ireland. Senator Andrew Clarkin (lord mayor of Dublin), Dr. P. P. Lynch (New Zealand), and Prof. E. Grzegorzewski (World Health Organisation) replied. Mr. T. C. J. O'Connell proposed the toast of the new President of the B.M.A., Dr. P. T. J. O'Farrell, who, he said, had done so much to build up the I.M.A. into a strong and representative body. Dr. O'Farrell made a brief reply.

On July 10 Dublin University conferred honorary degrees on Dr. H. A. Clegg, editor of the *British Medical Journal*, Dr. Gregg, chairman of the council of the B.M.A., and Dr. O'Farrell. The honorary degrees conferred by the National University of Ireland are given on p. 151.

A scientific exhibition was arranged in University College. Here Prof. K. H. Digby demonstrated a new nasopharyngoscope for the early detection of carcinoma. A model of the nasopharynx was available for surgeons to try the instrument by identifying 'Plasticine' tumours and taking "specimens" for biopsy. Mr. O'Connell's exhibit illustrated the pathology and surgery of mitral stenosis, using specimens, models, and diagrams. A colour film of the operation of valvulotomy was shown. Dr. J. J. Stevenson illustrated the value of a new contrast medium for bronchography. This is an ester of diodone, suspended in water with carboxymethylcellulose. Its particular virtues are the ease and evenness of its spread through the bronchi and the absence of alveolar filling, which is uncommon even after coughing. It is much more rapidly absorbed than iodised oil and usually disappears in from one to four days. Dr. D. A. Darcy had brought a number of excellent enlargements of photomicrographs to show what happens after tissue transplantation. The histological disintegration of the homograft was contrasted with the successful consolidation of the autograft. The most interesting pictures were those of an adrenal-gland homograft which had apparently taken in a rabbit—an observation which may lead to a better understanding of grafting phenomena. There were 26 exhibits in all, and the exhibition's popularity was evident from the brisk business at every stand.

The manufacturers of 'Ethicon' sutures had arranged showings of a three-dimensional colour film made at the Lahey Clinic, Boston, Mass. Through polarising spectacles, the audience saw with remarkable clarity the operation of radical gastrectomy for carcinoma of the stomach. The depth of focus achieved was amazing, and the effect was like looking through a window directly on to the operating-table.

Plenary Sessions

THE RELIEF OF PAIN

Chairman : Dr. O. C. Carter

Prof. V. M. Synge (Dublin) introduced the subject with some general ideas about pain. He thought that most people fell into one of two groups: (1) those who recognised three types of pain—upper abdominal, lower abdominal, and extra-abdominal—for which the appropriate treatments were respectively bicarbonate of soda, salts, and aspirin with or without a rub; and (2) those to whom pain was more complex and its significance more alarming. We do not really know how pain is produced; for though the nervous pathways carrying pain sense can be traced readily enough to the thalamus, matters become confused and uncertain above that level. Visceral pain is particularly puzzling; it is satisfying to attribute the pain of a duodenal ulcer to the passage of acid over a raw surface, but that cannot be the complete explanation. Professor Synge hoped that the doctor who had never experienced real pain would be cautious in estimating the impact of pain on his patients. When no organic disease is found, the pain is all too often said to be imaginary or trivial. When a doctor says: "Your pain is only muscular," it is clear that the doctor has never had lumbago. *Dolor animi gravior est quam corporis*, he summed up, or, in other words, it is worse to give the patient a pain in the neck than to tread on his toe.

Dr. E. T. Freeman (Dublin) emphasised the physical deterioration which can result from unrelieved pain—e.g., in thrombo-angiitis obliterans. He thought that town-dwellers complained more readily of pain than country folk; one of the features of modern civilisation was the demand for the relief of the transient pain, a demand met by the enormous growth in popular analgesics containing what are almost homœopathic doses of codeine. Turning to pain as an aid to diagnosis, Dr. Freeman regretted that more attention was often focused on relieving a pain than on determining its cause. It could not be repeated too often that a pain should only be suppressed after the diagnosis had been made. Negative findings on clinical examination and on investigation were not conclusive. If the patient sensed that his pain was being underestimated, he often developed hysterical overlay in an attempt to convince the doctor of its reality, and he thus obscured still further its true physical basis. The ideal means of relieving chronic pain had not yet been achieved. A drug that will suppress pain without affecting consciousness or muscular power and without producing the euphoria that leads to addiction awaits discovery. Dr. Freeman was guarded in his estimate of surgery as a means of relieving pain. Was the patient with angina of effort any better off because his cardiac anoxæmia passed unnoticed? Leucotomy was of undoubted value in some cases, but if used unwisely it might be even more destructive to the patient's personality than morphine addiction.

Prof. D. M. Dunlop (Edinburgh) described the pharmacology and uses of the pain-killing drugs. He made a particular point about pethidine; it is insufficiently realised that this drug causes spasm of the sphincter of Oddi and, though it is useful in intestinal and ureteric colic, it should not be used in biliary colic. Pethidine has no action on the cough reflex, a property which recommends it for postoperative use, and little action on the respiratory centre, an advantage in obstetrical analgesia. Amidone has no effect on the sphincter of Oddi and is a good choice for biliary colic. Given intramuscularly, it is less nauseating than morphine, but given by mouth to ambulant patients it seems just as likely to cause vomiting. Professor Dunlop's recommendations in brief were:

In the late stages of hopeless disease: Heroin.

For pre-anæsthetic narcosis and for acute cardiac disease: Morphine.

For intestinal and ureteric colic, in obstetrics, and for postoperative pain: Pethidine.
For biliary colic: Amidone (intramuscularly).

He had found phenadoxone unreliable. In answer to a question, Professor Dunlop said that there was a strong case for stopping the legal use of heroin altogether, and thereby easing the task of those who are trying to stamp out its illegal production. Heroin addiction was not a serious matter in this country, but, in his own view, the dangers of its use outweighed the advantages. In another reply, he said that there was no evidence that injections of liver extract relieved the pain of herpes zoster.

Speaking about the surgical relief of pain, Sir GEOFFREY JEFFERSON, F.R.S. (Manchester), recalled a remark of Wilfred Trotter: "Pain is relievable in proportion to the presence of recognisable cause." When an inoperable cancer caused relentless pain by involvement of bone or nerve-plexuses, cordotomy or neurectomy could bring relief. When cordotomy failed to stop the pain, it did so, not because it was a bad operation, but because section of the cord had not been carried far enough. Recent work suggested that the spinal-cord pathways are arranged in laminæ, and to cut off all painful stimuli below a certain level it may be necessary to divide almost the whole of the anterior half of the cord. Cutting the posterior nerve-roots was useless in postherpetic neuralgia, for the virus often attacked the cord itself, as could be seen from the milky stains visible upon it at operation. He agreed with Dr. Freeman about the need for caution in advising leucotomy; he never pressed reluctant patients to undergo the operation. Asked if all forms of pain could be relieved surgically, Sir Geoffrey said that it was theoretically possible, but that theory could be defeated in practice. He had treated a man whose paralysed and painful arm had been amputated after a brachial-plexus injury. Phantom-limb pain was severe and cervical cordotomy was performed. The pain returned within 3 months, and finally the sensory cortex was exposed under local anæsthesia. The area corresponding to the pain was localised by electrical stimulation, and this area was then removed. The more agonising element of the pain was relieved, but some pain still persisted. It would be easy, said Sir Geoffrey, to say that this was an imaginary pain, but he thought that in cases like this there might be some unexplained spread of painful stimuli throughout the whole cortex. The destruction of nuclei in the thalamus was another line of attack, but results so far had not been as good as had been hoped.

Mr. F. N. REYNOLDS (London) considered that the methods of relieving pain in childbirth were unsatisfactory, especially in domiciliary midwifery. There were, he admitted, inherent difficulties in the way of providing the best method of analgesia for the mother in her home, but he thought that lack of interest and of determined exploration were contributing more to this unnecessary distress than any practical considerations. Midwives are often brought up to feel that the relief of pain is to be discouraged, and consequently those methods that were available were not used as fully as possible. The Minnitt apparatus was bulky and difficult to carry around, and the mother confined at home had usually to be content with a mild sedative. She was very lucky if she got gas and oxygen. Pethidine has made matters rather better, but there was still much to be done. We must give up the idea that the best midwifery is that of the midwife, Mr. Reynolds said. He appreciated and admired her work no less than anybody else, but his heart would fail him if he had to set out to a confinement as poorly equipped as she usually was. He suggested that an obstetrician or anæsthetist should be appointed in each district to advise midwives and mothers on methods of analgesia. This had been done in Hertfordshire with encouraging results. By this means he thought that a sense of coöperation could replace that of competition, and that the disinclination of the midwife to seek the doctor's advice could be overcome. He said that the 'Trilene' inhaler would probably provide the efficient and portable apparatus that was needed, but it had not yet been accepted as safe by the Central Midwives' Board. Many women did not realise that analgesia existed, and it was most important that prejudices should be discarded if all mothers were to be spared unnecessary distress. Mr. Reynolds was asked what could be done for the pain of severe dysmenorrhœa. He said that thyroid extract was the only drug offering hope of cure. Its effects were often good if it was started early enough—at 16 or 17. Otherwise medical treatment was palliative. The most stubborn cases usually improved after the first pregnancy.

Dr. S. WAND gave some reflections from the point of view of the general practitioner. He urged the necessity to regard all pain as organic until it had become reasonably certain that an organic cause had been eliminated, if necessary by more than one investigation. Much distress to patient and relatives and embarrassment to the doctor at the later discovery of such a cause could be avoided by this attitude. The elimination of anxiety, the doctor's encouragement, and his understanding of the patient and his background were important considerations in relieving distress. Talking of useful drugs, he said that he had found amidone to be the most effective drug for the relief of cough in pulmonary tuberculosis. Aspirin had lost favour as a gargle in the face of newer remedies, but he still thought it brought the quickest relief. Intravenous procaine might be more widely used by the practitioner—e.g., as an anæsthetic for the dressing of burns. He thought that pain-killing drugs administered by inhalation might be one of the advances of the near future that would improve our ways of relieving suffering.

DERANGEMENTS OF THE BODY-FLUIDS

Chairman: Prof. D. M. DUNLOP

Like the other plenary sessions, that devoted to Derangements of the Body-fluids was designed to give specialists an opportunity of presenting their case to the medical public, and of submitting to whatever questions might be asked. It is surprising how little attention one need pay to what constitutes the greater part of our bodies; and our mental aloofness can be condoned only by the efficiency with which our so-called lower centres order this matter for us. In disease, however, the wisdom of the body may fail, and the opening speakers addressed themselves to describing the consequent derangements of body-fluid, and the practical steps required to restore euhydria.

In his chairman's remarks, Professor DUNLOP, a veteran of the previous day's plenary session on the Relief of Pain, commended the subject, deplored its complexity, and promised to ensure that speakers kept within their allotted span—an instruction which was admirably honoured by those who spoke.

Dr. D. A. K. BLACK (Manchester) discussed some physiological principles underlying the distribution of body-fluid. It was possible experimentally to produce syndromes of water, sodium, and potassium deficiency, although in clinical practice these were often blended with one another and further confused by alterations in the acid-base balance. In the assessment of clinical derangement of body-fluid, the history and clinical examination gave information on the changes in volume of body-fluid. Biochemical estimations were of value in defining changes in the composition of body-fluid, and also in assessing the quantities of water and electrolyte required for repair of existing deficiencies. In treating dehydration it was important at an early stage to give sufficient saline fluid to restore any deficit in plasma volume; given a normal circulation to the kidneys, the patient was in a much better position to resist inappropriate fluid therapy This principle was illustrated in the treatment of diabetic coma, where the sodium and water deficit should be corrected early, and the concurrent potassium deficit could be left until later. On admission serum-potassium levels were often high, through concentration of the plasma and extracellular fluid volume; later, with adequate saline therapy the plasma volume increased and the potassium deficit could then be corrected without risk of inducing toxic effects due to a high serum-potassium.

Mr. A. W. Wilkinson (Edinburgh) gave a thoughtful and well-documented paper on the surgical aspects of body-fluid depletion. He described metabolic studies in the postoperative period, which showed that in addition to nitrogen-loss the organism laboured under some difficulty in disposing of administered salt and water. There was, however, a considerable loss of potassium, and this might be augmented by intestinal aspiration or by the injudicious administration of saline fluid. In fact, the majority of patients after operation did not require intravenous infusion, but when they showed clear symptoms of potassium depletion intravenous therapy, including potassium salts, was of great value. Mr. Wilkinson described the clinical syndrome of potassium deficiency, and showed a telling picture of a patient slumped in bed and patently careless of what was going on around her. Volume-for-volume replacement of fluid-loss by normal saline was inadequate, and might be dangerous; it was much better to use a replacement fluid whose ionic composition resembled that of the fluid which was being lost from the body.

Dr. S. P. Dundon (Dublin) then dealt with the important applications to pædiatrics of knowledge of electrolytes. The severe effects of dehydration on infants could be accounted for by the fact that fluid exchange in the infant was much more rapid than in the adult, so that an infant deprived of water would die twice as quickly as an adult. Infants had much more extracellular fluid in proportion to their body-weight, and somewhat less intracellular fluid. Normally, the infant's diet contained more water and electrolyte than was needed for its minimum requirement, so there was some reserve to deal with moderate abnormal fluid-loss, provided that intake was maintained. Serious dehydration could, however, come on rapidly if the fluid intake was interfered with, as often happened in gastro-intestinal disease. Treatment of dehydration was complicated by the less efficient regulation of electrolyte excretion by the infant kidney. The commonest cause of fluid depletion in infants was vomiting and diarrhœa. Usually dehydration in infants was fairly mild and could be treated by oral administration of dilute milk, with added sodium and potassium salts. Severe dehydration demanded parenteral treatment with dilute saline solution, either subcutaneously with hyaluronidase or intravenously. Dr. Dundon concluded with the aphorism of Talbot and Butler that "therapy must reflect common sense and careful clinical observation, and a tolerance indicative of an enlightened awareness of ignorance."

Dr. W. E. R. Hackett (Dublin) reminded the meeting that a symposium was literally a drinking together, and as his own contribution to this bottle-party he proposed a bottle of blood. He thought that analysis in the field of fluid therapy had perhaps run riot, and commended synthesis of the type achieved by Marriott in his Croonian lectures. Dr. Hackett went on to discuss wound shock, which he regarded as essentially related to blood-loss, for which rapid transfusion was a sovereign remedy. Following Grant and Reeve, he recommended as guides to the severity of blood-loss observations on the blood-pressure, pulse-rate, temperature, and facial colour. Even in syndromes of primary electrolyte depletion, it was important to correct anæmia, as defective blood-flow to the kidneys would greatly interfere with the correction of electrolyte imbalance. When anuria interrupted a transfusion, it was still important to correct anæmia with accurately matched blood.

During an interval, members had the opportunity of studying a comprehensive and effective demonstration arranged by Dr. Hackett on body-fluid depletion and replacement.

In the general discussion, Dr. Paul Fourman rescued the adrenal glands from the oblivion to which the opening speakers had unwittingly consigned them. He commented on the varying clinical pictures of potassium deficiency, and suggested that lack of potassium might account in part for the malaise of convalescence from operation or illness.

Mr. John Bruce (Edinburgh) expressed his pleasure at seeing a surgeon as one of the openers in a discussion on electrolytes. He emphasised the difficulty of picking the right time for operation in patients with pyloric stenosis or ulcerative colitis; and as a Parthian shot he exposed the ignorance of our profession on the real nature of "hepatic coma."

Dr. T. Parkinson (Luton) mentioned the value of electrocardiography in the clinical assessment of potassium deficiency. He pointed out how closely the apathy of potassium deficiency resembled neurasthenia, and he had seen symptoms attributed to neurosis disappear when the patient was treated with potassium.

Dr. W. N. Leak (Winsford) gently reminded members of the existence of the cell wall, suggesting that further work might be profitable on its relation to electrolyte exchanges.

Major-General J. C. A. Dowse described his tropical experience with heat exhaustion and cramps. He had found a mixture of gin, ginger-beer, and salt very useful in treating cramp.

Mr. Wilkinson and Dr. Black replied briefly to points raised in the discussion, and the meeting dispersed for fluid and electrolyte replacement.

DEATH IN EARLY ADULT LIFE

Chairman: Prof. J. McGrath

Dr. R. C. Geary (Dublin) said that the elimination of all but a few of the deaths at young adult ages was a reasonable objective of preventive and curative medicine; and the trend in death-rates of young adults in the European countries encouraged such a hope. In the past half-century the decline in death-rates ranged from 40% for Portugal to 78% for Norway; yet there was still a conspicuous difference between the countries of Europe, with Spain and Portugal showing young-adult mortality-rates more than twice those of the Scandinavian countries, the Netherlands, and England and Wales. The countries which started the century with the lowest death-rates had shown the biggest declines in mortality.

The secular trends in the tuberculosis death-rates had closely followed the general death-rates and there was a close correlation between the standard of living of a country and its tuberculosis death-rate for young adults. On the basis of national income, England and Wales and Ireland (the 26 counties) had more deaths from tuberculosis than they should have. Ireland showed up badly for deaths from non-respiratory tuberculosis, with a rate for this age-group of four or five times that for England and Wales.

Most countries, Dr. Geary said, had well-developed systems for analysing mortality-rates, but for those in the prime of life, morbidity statistics would be much more valuable as an indicator of medical and social problems. It was one of the iniquities of this time that undue emphasis was laid on problems which could be analysed statistically, whereas those with inadequate statistics, or none, were overlooked.

Dr. Ninian Falkiner (Dublin) quoted figures from the reports of the Rotunda Hospital. Between 1925 and 1937, he said, the maternal mortality was 6·2 per 1000, and in the period 1938–50 it had fallen to 2·8. Hyperemesis showed the most striking fall, from 0·29 per 1000 deliveries to 0·02. But the main improvement was due to the reduction in deaths from sepsis. Lives were still lost because adequate treatment was not readily available for difficult confinements. The death-rates from hæmorrhage and the late toxæmias were now the highest and more should be done to elucidate their causes. In comparing these two periods it could be said that deaths from cardiac disease as a complication of pregnancy had been reduced, but the mortality from tuberculosis had not changed.

Dr. Donald Teare (London) spoke as a pathologist who had since the war done more than 2000 necropsies on young adults—mostly coroners' cases and therefore highly selected material. But the outstanding feature in both men and women was the high number of suicides (183 men and 131 women), higher than any other single cause except coronary atheroma and hypertension. As a means of self-destruction, the most usual choice, for both sexes, was coal-gas poisoning; but men shot and hanged themselves more often than women, who chose the more dramatic methods of throwing themselves from buildings or under trains. The availability of coal gas played some part in its popularity, and a small number of these suicides seemed to be accidents in that the victims' intention was to excite sympathy rather than to destroy themselves. The inclusion of barbiturates on schedule IV of the Dangerous Drugs Act did not appear to have reduced the suicide-rate from this cause. Improved techniques in psychiatry and a more widely available mental-health service offered the best prospect of reducing these deaths.

Of the deaths from traffic accidents, 39 were motor-cyclists, of whom 30 died from fractures of the skull. Dr. Teare advocated legislation to make protective headgear for motor-cyclists compulsory. Another speaker, Major-General J. C. A. Dowse, suggested that crash-helmets should be sold as a necessary part of the motor-cycle.

Dr. Teare had had 44 cases where patients had died as the direct result of medical treatment. More than a third of these were due to air embolism, caused mainly by puncturing the lung with a needle during the treatment of tuberculosis. Drugs producing agranulocytosis were another potent cause of these misfortunes.* As soon as one drug fell into disuse because of its dangerous side-effects, another took its place and in time produced a further series of deaths. These deaths served to remind the medical profession of the need to review the value of certain types of treatment. He was horrified to read a recent article advocating puncture of the lung to induce pneumothorax. But with the great advances made in anæsthesia and surgery, there was not much difference for the general population, between the chances of being murdered and of dying under an anæsthetic.

Dr. Richard Schilling (Manchester) said that in the civilian population of England and Wales approximately 230,000 men and 223,000 women in this age-group died between 1940 and 1949; but only about 11,000 of these deaths could be ascribed to direct occupational causes such as accidents and industrial diseases. Most of these deaths were due to accidents, and though the general death-rates had declined in this period, the fatal-accident rate was the same now as it was before the war. Medical responsibility for preventing accidents extended beyond the limited scope of selection of workers and providing good early treatment in industry and hospitals. Doctors in industry could prevent biological stupidity in plant design and safety practices, and were in a favourable position to encourage industrial communities to take more interest in health and safety. In many different ways work undoubtedly influenced some of the common causes of death in this age-group—namely, respiratory tuberculosis, cardiovascular disease, and cancer. It was now recognised that factories could be a source of infection in tuberculosis, and the training of younger men with valvular heart-disease for suitable work could do much to prolong their lives. The death-rates for coronary disease were rising rapidly in the younger men, and the recent work by J. N. Morris and his associates had shown a high incidence of this disease in general practitioners compared with other doctors. There were probably occupational influences in its ætiology and it might be worth studying the histories of the younger men who suffered from it for clues to its social pathology. In the same way, the men who died early of cancer might give pointers to undetected carcinogens.

Industrial medicine was something more than a specialty dealing with industrial diseases. It was a discipline which took into consideration the many different ways in which work could influence health, and it could therefore help to elucidate the social causes of disease in individual patients and in groups.

Mr. Dickson Wright (London) said that the surgeon had done much to save life in young adults. The surgical treatment of acute appendicitis, perforated ulcers, and intestinal obstructions had become commonplace and successful, whereas not so many years ago 90% of sufferers perished. Those who died today did so from delay in diagnosis. The most usual mistake was to discount the patient's description of the pain, which after the first violent onset was followed by a lull. He strongly favoured resection in all cases of gastric ulcer because of the risks of malignancy, hæmorrhage, and perforation. While surgery had not yet provided any real help for coronary disease, there seemed good reason to hope that it might be possible to induce vascularisation by hormone therapy. Cerebral hæmorrhage, particularly from congenital aneurysms of the larger arteries of the base of the brain, was not uncommon in the younger people, and there was now no reason for depriving these cases of surgical help. He thought that not enough was done for head injuries. It was impossible for the cranial surgeon to look after them all. Some were left and died from failure to remove the hæmatomata which Dr. Teare found so often in the young men killed on the roads and elsewhere. He had in his lifetime saved ten patients who had attempted suicide. None had been reproachful of being saved, and some had subsequently lived very useful lives.

In reply to a question from Dr. Miller, Mr. Dickson Wright said that the American practice of reopening the abdomen at six-monthly intervals to look for recurrences of malignant disease after surgical treatment had not yet, as far as he knew, reached these islands.

Prof. Leonard Abrahamson (Dublin) said that not many years ago this discussion would have been largely concerned with puerperal and postoperative sepsis, acute generalised tuberculosis, and bacterial endocarditis. The advent of the antibiotics had changed the picture, and the optimism of Dr. Geary for the future rested on recent achievements.

In his experience in Ireland there had been a curious change in the symptomatology of rheumatic carditis, which was responsible for many of the deaths in early adult life. Rheumatic arthritis was now comparatively rare, but there had not been a corresponding reduction in the incidence of patients with valvular lesions. These patients had now, at the most, only minor manifestations of joint disease. It was too early to speak categorically of the benefits of cortisone and surgery. Time alone would provide the true perspective. Coronary heart-disease was now a disease of this age-group, and malignant hypertension continued to exact its toll; but the ætiology remained obscure and treatment was unsatisfactory. The tuberculosis death-rate in early adult life was still tragically high, but was now getting more attention in both medicine and surgery. Collapse therapy, employed so long with and without discrimination, had been largely replaced by chemotherapy and a variety of new surgical operations; but the enthusiasm for new surgical procedures was following an all-too-familiar pattern and for the moment the pendulum had swung too far in this direction. Bright's disease continued to take a substantial toll of life, and methods of treatment had gained little of real value from a vast amount of research. Ten years ago there was a most virulent type, in epidemic form, in Ireland. Though few patients died during the acute phase, few left hospital unscathed and many were dead within five years.

A survey of the past fifty years, said Prof. Abrahamson, offered a curious contrast between the most melancholy period in the history of mankind and the most illustrious era of medical progress. No doubt in the next half-century many of the diseases discussed in this symposium would have been prevented.

Scientific Sections

PATHOLOGY AND BACTERIOLOGY

President: Prof. M. H. O'Connor

Recent Advances in Active Immunisation

Dr. H. J. **Parish** (London), opening this discussion, quoted figures to show the success of the campaign for immunisation against diphtheria; in 1901 the disease had caused 10,000 deaths, but by 1951 this terrible total had fallen to 32. The question of what was the best antigen to use remained undecided. Formolised toxin was the basis of all prophylactics, and the alum-precipitated toxoid (A.P.T.), selected in 1940 for the Ministry of Health's immunisation scheme, had been the most widely used. Some recent work suggested that it might give a greater degree of protection if three injections were given at 3, 6, and 18 months of age. The new prophylactic, purified toxoid aluminium phosphate (P.T.A.P.), was a purified antigen with the advantage of containing much less bacillary protein than A.P.T. Whooping-cough had caused over 9000 deaths in England and Wales in the past ten years, and though a successful method of vaccination was available there was no reliable test of antigenicity. In a M.R.C. trial over 7000 children between the ages of 6 and 18 months were divided into two groups. Half of them received three doses of pertussis vaccine at monthly intervals, and the others were given an anticatarrhal vaccine. The attack-rate per 1000 child-months was 1·45 in the pertussis-vaccinated and 6·72 in the control group. Those in the first group who did develop whooping-cough had a mild and short form of the disease. Five kinds of vaccine are available, and the two prepared by Dr. Kendrick in Michigan seem to be the best. Early vaccination was desirable—at 2–3 months or even earlier. Three doses were given at monthly intervals, and a yearly boosting dose was probably justified. Some very recent work had suggested that a living vaccine was best in mouse-protection tests, and human trials were being carried out. On the whole, reactions after pertussis vaccination were more severe than after diphtheria immunisation, but Dr. Parish thought that too much emphasis had been placed on the risk of encephalopathies. The hope of the future lay in combined prophylaxis, which meant less injections and an enhanced antigenic response. The diphtheria-pertussis combination might carry an exceptional risk of poliomyelitis, and Dr. Parish considered that during epidemics all preventive inoculation should be discontinued. Turning to tuberculosis, he said that the effect of B.C.G. inoculation in man remained uncertain, but that it was certainly a valuable adjunct to fundamental control measures. The work reported by Palmer[1] had suggested that it was much easier to make a good vaccine than had been realised, and that it was not necessary to have large numbers of living bacilli. Wells's vole-bacillus vaccine had given encouraging results. The virulence of this organism, which is very high in the vole, was already stabilised for man and cattle, a situation which was reached with B.C.G. only after years of subculture. Dr. Parish felt, however, that the vole bacillus was unlikely to oust B.C.G.

Dr. J. **Ungar** (London) described work which demonstrated how the combination of a vaccine with diphtheria toxoid could safely enhance the antigenicity of the toxoid. Various vaccines were being used, and he thought that the mouse-protection test would enable the value of each vaccine to be assessed. Combination with a plain bacterial suspension in saline produced a rapid rise in antibody formation, but a vaccine precipitated with aluminium phosphate gave a better, if slower, response.

The virus diseases were dealt with by Dr. P. N. **Meenan** (Dublin). Influenza, he said, made its own epidemiological rules, and the A-prime virus which appeared in 1947 resisted the vaccines then available. The timing of the prophylactic inoculation may be critical, and the strain of vaccine used must be antigenically related to the organism causing the epidemic if protection was to be given. To be effective, a vaccine must evoke a high antibody response. Emulsification of the vaccine with heavy or light mineral oil to act as an adjuvant had improved its protective powers, but it then had to be given intramuscularly. Dr. Meenan thought that the trend of results was disquieting; the F.M.1 vaccine now in use would probably be less effective in future epidemics, and new vaccines would have to be tried. In poliomyelitis active immunisation was coming within the range of possibility. Inoculation with a living attenuated virus produced antibodies to the Lansing strain, and the risks could probably be minimised by an umbrella of gamma-globulin.

Clinical and Laboratory Aspects of Vitamin B_{12}

Prof. A. C. P. **Campbell** (Manchester), a vice-president of the section, took the chair for this discussion. Mr. W. F. J. **Cuthbertson**, PH.D., described his experiments, carried out in collaboration with Dr. J. N. M. Chalmers, into the excretion of the vitamin. Urinary output reached a peak about four hours after an intramuscular injection of 200 µg., and very little was excreted after seven hours. When 1000 µg. was injected, half the dose was eliminated by a normal person and about 60% by patients with pernicious anæmia. When the anæmia was in remission less of the vitamin was excreted than in relapse, but the results were not statistically significant. A dose of 50–100 µg. probably gave the maximum economical retention. After oral doses of from 3000 to 9000 μg., the excretion was much less than expected. It may be that the vitamin was taken up by the intestinal mucosa, into the abdominal lymphatics, or in the liver. Lymphatic absorption seemed unlikely because the excretion following intramesenteric injections at laparotomy was much the same as that after intramuscular injection.

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[1] Palmer, C. E. *Lancet*, 1952, i, 935.

Dr. G. I. M. Ross (London) said that a method of microbiological assay of vitamin B_{12} was now available. The green alga, *Euglena gracilis*, required about 6000 molecules of the vitamin for each of its cells, and could be used to estimate amounts down to 1 μμg. The normal serum concentration of vitamin B_{12} was about 30 μμg. per ml. A deficiency of the vitamin occurred in megaloblastic anæmias other than pernicious anæmia—e.g., those associated with pregnancy, steatorrhœa, and total gastrectomy. It was found that those patients with a normal serum level responded to folic acid but not to vitamin B_{12}. Repeated daily injections of vitamin B_{12} produced a saturation effect; the serum level became higher as excretion diminished. Folic acid had been shown to have no effect on the concentration of the vitamin in the serum.

Taking up the clinical side of the story, Dr. C. C. Ungley (Newcastle upon Tyne) said that the value of the vitamin was confined to the megaloblastic anæmias. He had found that the megaloblastic anæmias of pregnancy and the puerperium seldom responded to vitamin B_{12}, but whole liver or folic acid were usually effective. In these anæmias, dietary deficiency was unusual. In the tropical megaloblastic anæmias dietary deficiency was the rule, and therefore B_{12} was effective. He had had a patient whose anæmia followed total gastrectomy, and who had responded well to 1000 μg. of B_{12} by mouth. The fish-tapeworm anæmia of Finland had often been attributed to some toxin in the worm, but the dried worm itself was curative by mouth, suggesting that the living worm took up vitamin B_{12} in the intestine. The response in idiopathic steatorrhœa was variable; and the megaloblastic anæmia associated with thyrotoxicosis did not respond to B_{12} but did so to folic acid. Dr. Ungley thought that the anæmia which may develop after an intestinal anastomosis was the result of bacterial activity in a stagnant loop of bowel. The bacteria may spread to the rest of the small intestine where the *Bact. coli* absorb vitamin B_{12}, leaving less for the patient.

MEDICINE

President: Prof. Henry Moore

Clinical Use of Cortisone

Professor Moore described the arrangements under which supplies of cortisone became available in Ireland in the summer of 1950. The work was carried out by a team selected by the Medical Research Council of Ireland; and 70 patients with rheumatoid arthritis had been treated with cortisone. Its effect in 500 ophthalmological cases, and in several other conditions—e.g., Simmonds's disease, rheumatic fever and carditis, status asthmaticus, and anuria—had also been studied. Though he regarded the discovery of cortisone as one of the most important advances in medicine in his time, no doctor, he said, should use this potent hormone without first mastering the literature on the subject and without strict supervision in order to detect unfavourable side-effects.

Prof. D. K. O'Donovan (Dublin) surveyed the results achieved with 1100 g. used in two years by the cortisone committee of the Medical Research Council of Ireland. 52 cases of rheumatoid arthritis were treated: and he considered that this disease was the first choice for cortisone in medicine; severe or rapidly recurring asthma, and particularly status asthmaticus, not amenable to other treatment, was his second choice; and early rheumatic carditis his third. The side-effects of cortisone included psychotic changes (which developed in 5 cases), local sepsis (3), and water retention, diabetes mellitus, subarachnoid hæmorrhage, "moon-face," epilepsy, angina pectoris, and hypertension (1 each). Dying patients were, he thought, resistant to the beneficial action of the drug.

Prof. E. J. Conway, F.R.S. (Dublin), described experiments with deoxycortone acetate and cortisone at the department of biochemistry, University College, Dublin.

Adrenalectomy in rats produced pronounced changes in the level of glucose-6-phosphate and fructose-6-phosphate in muscle with some increase in adenosine triphosphate and phosphocreatine. Cortisone and deoxycortone acetate restored these levels, but cortisone did so more effectively than deoxycortone. Both substances were given in 2 mg. injections daily. Cortisone increased nitrogen excretion in young rats, and inhibited their growth, whereas deoxycortone had little or no such effect.

The action of cortisone and deoxycortone on the sodium and potassium levels of plasma and muscle depended on the amount of sodium in the diet. On a low-sodium diet, cortisone and deoxycortone both increased the sodium and decreased the potassium levels of plasma, but the effect of cortisone was somewhat greater than that of deoxycortone. With a high-sodium intake, the effect on the plasma-sodium level disappeared. The plasma-potassium level was still reduced, but here deoxycortone was more effective than cortisone. The muscle levels generally followed those of the plasma, but it was noteworthy that an appreciable decrease in plasma-potassium was associated with distinct increases in muscle sodium, even when a fall in plasma-potassium was produced by a potassium-free diet. Such changes would appear to be secondary to those in the plasma. The final control lay in the nephrons of the kidney.

In yeast large-scale active transports of sodium and potassium could be demonstrated and interpreted in terms of a "redox pump" mechanism. The effect of deoxycortone, cortisone, compound F, and eight other steroids (other than adrenal) on the active extrusion of sodium and active absorption of K ions in yeast was examined. Deoxycortone, even in *M*/40,000 strength, had a definite inhibitory action on the active sodium and potassium transport. Cortisone had some effect, but not so great, and compound F gave a small but definite stimulus to the active potassium transport. No effect was produced by the various other steroids. This fundamental action of the adrenal hormones on a primitive cell such as yeast could be used to interpret the mechanism of action in the animal organism.

Professor Conway hoped that this and subsequent work would clarify the mode of action of cortisone in the human body.

Dr. Bernard Schlesinger (London) gave an account of his experiences with A.C.T.H. and cortisone in rheumatic fever. He thought it was too early to draw any definite conclusions as to their value. Pyrexia and arthritis disappeared within a day or two, but chorea was uninfluenced. Only a long follow-up would elucidate finally whether serious permanent valvular lesions could be prevented.

Dr. C. J. McSweeney (Dublin) described cases of early rheumatic carditis in which cortisone had been given. Pyrexia and arthritis had quickly subsided and the heart had remained normal; but in one late case, with an old-standing mitral lesion, the subsidence of acute symptoms during a recrudescence had not been accompanied by improvement in the heart clinically or electrographically.

Prof. R. H. Micks (Dublin) referred to a series of cases treated by Dr. J. A. Wallace and himself. He thought that cortisone hastened the recovery of patients with acute rheumatic carditis. Chronic rheumatic patients did not appear to respond to cortisone.

Dr. W. S. C. COPEMAN (London) described his results with 20 selected cases of rheumatoid arthritis treated over a period of two years. In only 1 of these was it possible to omit cortisone after five months' continuous treatment. This patient had now remained well for a year without cortisone. Of the 20 patients 17 had been able to return to work, but they were still on treatment. Dr. Copeman stressed the value, in deciding dosage, of clinical assessment by methods he had already published—e.g., occurrence of spontaneous pain, measurement of joint tenderness, and muscular strength as shown by grip—rather than by the estimation of erythrocyte-sedimentation rates and urinary ketosteroids or corticoids. He placed the optimum dosage for these cases at 75 mg. a day or less. Major side-effects were not seen in any of his patients.

Dr. JOHN MOWBRAY (Dublin) gave an account of 5 children with rheumatoid arthritis, and emphasised the value of low dosage. The criterion should be the lowest dose which would allow painless movement of the affected joints. The average dosage was 50 mg. daily for a few weeks, followed by a maintenance dose of 25 mg.

Dr. F. J. LAVERY (Dublin) discussed local use of cortisone in 650 ophthalmological cases, and its systemic use in 10 others. In those conditions which benefited from cortisone, local application had been found satisfactory when the anterior segment of the eye alone was involved. The conditions which responded best to cortisone in his experience were phlyctenular ophthalmia, interstitial keratitis, iridocyclitis, and sympathetic ophthalmia. Cortisone should be used with caution in virus infections of the eye.

Sir JOHN MCNEE (Glasgow), summing up, said he regarded cortisone as an empirical remedy, because there was no exact knowledge as to how it worked. He thought its use in rheumatoid arthritis and in certain eye conditions was indicated; but he deprecated, as did many other speakers, its indiscriminate use without proper control in hospital.

CHILD HEALTH

President: Prof. ALAN MONCRIEFF

Subdural Hæmatoma

Dr. C. M. SAUNDERS (Dublin) described the various types of cerebral hæmorrhage encountered in the newborn baby. Cerebral hæmorrhage, he said, is one of the main causes of neonatal mortality and affects premature babies more often than mature babies, in a ratio of about 20 to 1. In premature babies some 60% of the hæmorrhages occurred after a short second stage, whereas in mature babies they occurred when labour was long or difficult. In these circumstances, sedation of the mother, anæsthesia, episiotomy, and a low forceps delivery might prevent hæmorrhage.

Dr. A. P. BARRY (Dublin) pointed out that natal causes such as trauma, anoxia, or precipitate labour account for about 60% of cases of cerebral hæmorrhage, but in the remaining 40% obstetric factors were not responsible. Prenatal factors, such as fœtal anoxia due to maternal anæmia, toxæmia, direct uterine trauma, or genetic causes, might predispose to hæmorrhage, and postnatal factors such as anoxia and infections might also play a part. By ensuring that during pregnancy the mother received a suitable diet, with iron and vitamins, the frequency of prematurity might be diminished and the susceptibility to hæmorrhage might be lessened.

Dr. W. R. F. COLLIS (Dublin) described some of the clinical features of subdural hæmatoma seen in 5 babies (4 of them breech deliveries) at the Rotunda Hospital during the past eighteen months. Separation of the cranial sutures was often striking, and it might develop within a few days. Facial asymmetry resulting from rapid increase in skull circumference might persist after the subdural hæmatoma had been treated. The clinical suspicion of subdural hæmatoma could be confirmed by subdural tap, and in some cases up to 10 ml. of blood was found. The residual encapsulated hæmatoma may require surgical removal, and Mr. J. P. LANIGAN (Dublin) described the routine surgical procedure in these cases. A subdural effusion of clear fluid with a high protein content might arise after the blood from a subdural hæmatoma had been absorbed, and unless this was removed surgically damage to the underlying brain would follow.

Dr. AGNES MACGREGOR (Edinburgh), who described the pathological features, based her remarks on 101 cases of subdural hæmatoma seen post mortem at the Royal Hospital for Sick Children, Edinburgh, over a period of four years, during which 1000 necropsies on stillbirths and infants were performed. A quarter of the hæmorrhages were in stillbirths and most of the remainder in babies dying within two days of birth. In these fatal cases a tentorial tear was usually present and blood had accumulated below the tentorium. In the infants surviving for a time, the hæmorrhage usually accumulated over the vertex and arose from a tear of the small veins which drain from the surface of the brain into the superior sagittal sinus. Organisation of the blood-clot took place almost entirely from the dural surface and the arachnoid played little or no part. This process was often rapid and vascular granulation tissue might develop within ten days. The complications encountered included damage to the underlying brain by pressure, hydrocephalus, and ossification. This latter condition might cause irritation of the cerebral cortex.

Dr. J. P. M. TIZARD (London) discussed the prognosis in a series of 169 patients treated by the accepted methods. The immediate mortality was 3%, and in over two-thirds of the survivors the mentality appeared to be normal. In some of these, more detailed assessment by intelligence tests and other means showed that mental development was somewhat retarded. Hemiplegia and convulsions also developed in some of the cases.

Treatment of Primary Tuberculosis

Dr. F. J. W. MILLER (Newcastle upon Tyne) described a series of 2567 children suffering from primary tuberculosis who had been followed up for at least two years. 41 of them had developed miliary tuberculosis or tuberculous meningitis. In view of the infrequent occurrence of complications he considered that streptomycin and *p*-aminosalicylic acid (P.A.S.) should not be given to children with uncomplicated primary tuberculosis. There were, however, special indications for giving these drugs. They were of value (1) in children in whom the primary complex was associated with an acute febrile illness but in whom radiography did not reveal miliary spread; (2) in children with aspiration bronchopneumonia from a primary complex; (3) when a lymph-gland had penetrated the bronchial wall and had been expectorated; (4) in primary tuberculosis of the tonsil with large cervical glands; and (5) in those cases of primary skin tuberculosis which failed to heal.

Dr. M. HALL (London) outlined the routine treatment for children with primary tuberculosis. They were best treated at home, but if there was danger of further infection at home they should be admitted to a hospital where education could be provided. The children were on bed rest, adequate diet, and vitamin D and calcium gluconate. Streptomycin and P.A.S. were given to children under one year of age or if there was ulceration of the bronchial mucosa. The diagnosis of endobronchial disease was made by bronchoscopy—a procedure also indicated for collapse of a lobe, to relieve symptoms of compression such as stridor, and as a preliminary to surgery in the few cases in which this was necessary. A persistent infection of the upper respiratory tract was present in a number of cases and could be relieved by giving streptomycin nose drops, but sometimes removal of tonsils and adenoids was necessary.

Mr. Denis Browne (London) said that the tonsil infected with tuberculosis was pale, small, and often thought to be harmless. In 50 children with active pulmonary tuberculosis the tonsils and adenoids were removed, and in about a third of them virulent tubercle bacilli were isolated. In 50 control cases with a positive tuberculin reaction, but in whom the disease was inactive, no tubercle bacilli were found in the tonsils and adenoids.

Dr. R. McL. Todd (Liverpool) described a controlled trial designed to assess the value of P.A.S. in primary tuberculosis. Alternate cases of primary pulmonary tuberculosis in four age-groups, admitted to Alder Hey Children's Hospital during 1951, were given P.A.S., while the remainder did not receive any specific therapy. All cases were at rest in bed for three months and were given a diet adequate in protein, calories, and vitamins. The progress of the "trial" and "control" groups was judged by the clinical response (appetite, vitality, temperature, pulse-rate), serial white-cell counts, serial sedimentation-rates, weight gain, and serial chest radiographs, and by development of complications, and was found to be similar in both groups. Complications, such as miliary tuberculosis, tuberculous meningitis, and spread of the tuberculous process locally in the lungs, occurred in both groups but only in children under the age of three. It was felt that the use of streptomycin and P.A.S. was justified in children under three years of age suffering from primary tuberculosis. Preliminary results with isonicotinyl hydrazine were encouraging.

Dr. B. M. Dunlevy (Dublin) described the work of the public-health department in Dublin during the past five years. During this period there had been a fall in the mortality-rate from tuberculosis of 44% in adults and 74% in children. This achievement had resulted from the adoption of a number of measures. B.C.G. vaccination was introduced in 1948 for babies born to tuberculous mothers, and it was later offered for all newborn babies. At the present time 35–40% of all babies born in the maternity hospitals were vaccinated with B.C.G. No case of miliary tuberculosis or tuberculous meningitis had occurred in the vaccinated children despite continued contact with cases of active adult phthisis. Mass radiography of expectant mothers was also undertaken, and when several cases of primary tuberculosis were notified in children from a particular school, all pupils in that school were submitted to radiography. The number of beds for adults in sanatoria had been increased so that shortly there should be no waiting-list for admission. This would considerably reduce the risk to children in their homes.

CARDIOLOGY

President: Prof. Leonard Abrahamson

Rheumatic Heart-disease

Dr. William Evans (London), *opening the discussion*, concerned himself chiefly with diagnosis. One of the main errors, he thought, was caused by the combination of an innocent systolic murmur and a history of rheumatic fever. Just as a large proportion of patients with rheumatic heart-disease gave no history of acute rheumatism, so also many had acute rheumatism with no permanent cardiac lesion. It might therefore be a good idea for students to form their opinion about a murmur before they inquired about the history. Another source of error was the physiological third heart-sound which was often misinterpreted in various ways, though if heard as a clear sound in a child it was to be regarded as a sign against mitral disease. A trivial systolic murmur was nearly always innocent, and it was a good thing for the cardiologist to be a little deaf so far as this type of murmur was concerned. Whether loud or soft, this murmur should not lead to the use of the term mitral incompetence, the existence of which could only be certain when there was mitral stenosis. As rheumatic carditis must be regarded as the most important form of heart-disease from the social point of view, Dr. Evans felt that a long-term plan for its prevention was urgently necessary; this would include compulsory certification and special hospitals with teams of research-workers.

Valvulotomy for mitral stenosis figured prominently in the discussion; *and* Dr. Charles Baker (London) dealt particularly with this. Among contra-indications to the operation, he mentioned active rheumatism (of which he did not think the erythrocyte-sedimentation rate was a reliable index), and the lack of sufficiently severe symptoms. In reply to a question, he said that the youngest age at which the operation could be contemplated was automatically determined by the presence of the valve lesion and its pulmonary effects.

Sir John Parkinson (London) pointed out that the operation was palliative rather than curative, and that many patients with rheumatic heart-disease lived long and active lives. Both he and Dr. Evans acknowledged the great contribution of the Guy's workers on mitral valvulotomy.

Dr. Gerald Thomas (Taplow) spoke on the clinical diagnosis of latent active carditis, and the need for careful heart examination in a child with vague limb pains and poor general health. It was occasionally difficult to differentiate rheumatic valve lesions from congenital defects, particularly atrial septal defects. In acute carditis, the diastolic murmur, which could appear in a matter of days, was of course very important; but the systolic murmur was hard to assess, though if it increased or appeared first when pyrexia and tachycardia were regressing it was more significant. Pericardial friction and subcutaneous nodules were strong evidence of activity. At Taplow the corrected Q–T interval and the heparin resistance were no longer thought to be reliable guides. Remarkable recovery could often follow acute rheumatic carditis; and Dr. Thomas described instances in which considerable cardiac enlargement and diastolic murmurs had disappeared within a few weeks.

Dr. Walter Somerville (London), discussing the treatment of chronic rheumatic carditis, thought that there was little new or dramatic to be said. He noted, as all cardiologists have done, a general reluctance to use digitalis in heart-failure with normal rhythm and, more rarely, its excessive use with the production of toxic effects. Such effects included abnormal rhythms, and if these prompted a further increase in dosage things went from bad to worse. Severe salt restriction could be harmful, especially if combined with mercurial diuretics. The method of restricting sodium absorption by means of resins could also have unfavourable effects, and until more was known about these resins they were perhaps best left in the hands of those investigating them.

Dr. Paul Fourman (Oxford) described the mechanisms by which low-salt diets and mercurial diuresis produced adverse symptoms; and Mr. T. C. J. O'Connell (Dublin) spoke of his experience in mitral valvulotomy. He thought that, so far from increasing mitral regurgitation, the operation often lessened it.

Summing up, Professor Abrahamson thought it remarkable that infective endocarditis had not once been mentioned in the discussion. Perhaps this reflected a tendency to regard this problem as more completely solved than it really was.

CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The first International Congress of the International Diabetes Federation was held on July 7–12 in the delightful setting of the old university town of Leiden, with the hospitable Dutch as hosts. It was attended by some 250 delegates from 19 different countries, including such honoured names as Dr. Elliott P. Joslin, Prof. Charles H. Best, Dr. R. D. Lawrence, and Dr. H. C. Hagedorn. This congress was a success despite the many language and other difficulties which beset such international meetings.

HYPERGLYCÆMIC FACTOR OF THE PANCREAS

In the Banting lecture, sponsored by the British Diabetic Association, Prof. Christian de Duve recalled that Bürger had originally described the hyperglycæmic factor of the pancreas under the name of glucagon; and he suggested that this word should be generally adopted. Bürger had described its glycogenolytic action on dog's liver, but this knowledge was only later associated with the transient hyperglycæmia observed after the administration of relatively crude insulin preparations. Fresh interest was aroused in the subject when Abel's method of crystallising insulin was superseded by that of Scott and Fisher, which, nevertheless, allowed noticeable amounts of the glycogenolytic factor to contaminate the insulin crystals. Glucagon assays were performed on rabbits which received 30 units of insulin intravenously and in whom the amount of glucose required to maintain the blood-sugar was then measured. Glucagon preparations freed of insulin acted as strongly when administered subcutaneously as intravenously, although on subcutaneous administration the effect of glucagon was masked in the presence of insulin. Sutherland and Cori demonstrated the glycogenolytic effect of glucagon on liver slices in vitro, even in association with insulin.

Glucagon was presumably a protein since it was destroyed by proteases. In many ways the glycogenolysis initiated by glucagon simulated that due to adrenaline, both apparently acting on the same hepatic enzymes. Like adrenaline, glucagon depressed the level of circulating eosinophils, although this action might be mediated through the hyperglycæmia. That glucagon was distinct from adrenaline was shown by its lack of action on the heart, blood-pressure, and muscle-glycogen. Fœtal pancreas was relatively rich in glucagon and also in islet tissue, and the same was true of dog pancreas after ligature of the duct. These facts suggested that glucagon was probably present in the pancreatic islets; but from the observation of a nearly normal glucagon content in the pancreas of alloxan-diabetic rabbits in which no insulin could be demonstrated, it seemed likely that the α cells were the source of glucagon. Van Campenhout and Cornelis had found that cobalt chloride caused extensive selective but transient injury to the pancreatic α cells of guineapigs, and the glucagon content of the pancreas was reduced by about 60%.

With regard to the clinical importance of glucagon, it might be possible to define two types of pancreatic diabetes: (1) with deficiency of both the α and β cells, and (2) with deficiency of the β cells only. It was well known that totally pancreatectomised (type 1) patients required less insulin than many spontaneous (? type 2) diabetics: and experimentally metahypophyseal and alloxan diabetes needed more insulin than the diabetes of completely pancreatectomised animals. These differences had been attributed to the absence of the exocrine secretions of the pancreas in the pancreatectomised animals, with consequent malabsorption of food: but the work of Candela and his team tended to discount this suggestion. Tying off the pancreatic duct of alloxan-diabetic dogs did not reduce their insulin requirement, but removal of the sclerosed pancreas did do so. This work had received further support from Cavellero and Malandra in Italy, who raised the insulin requirement of a pancreatectomised rat by grafting into it the pancreas from an alloxan-diabetic rat.

The function of glucagon in the intact animal remained an enigma. Bornstein et al. found a hyperglycæmic principle in the pancreatic venous blood of diabetic animals treated with growth hormone. This suggested that at least some of the diabetogenic activity of growth hormone might be mediated by glucagon, especially since purified growth hormone was not a powerful peripheral inhibitor of insulin. Glucagon remained indeed the most effective natural insulin antagonist, and the recent work of Tyberghein had shown that anti-insulin activity might occur without any net loss of liver-glycogen. Possible clinical applications of our knowledge of glucagon were now being recorded. McQuarrie, for instance, had described two cases of spontaneous hypoglycæmia where no α cells were demonstrable in the pancreas.

INSULIN

Dr. D. R. Drury (Los Angeles) presented isotope data which indicated that, although insulin has an immediate effect in transferring glucose into cells, this may be separated from its rôle as catalyst for the oxidation of glucose, this latter effect being inhibited by the simultaneous administration of β-hydroxy-butyrate.

Dr. J. J. Groen (Amsterdam) presented the latest information on his assay of blood insulin by the rat-diaphragm method. While there was reason to believe that this test was specific for insulin, its main drawback was the wide variation in response of different rat diaphragms and the extremely small differences of glucose content which had to be measured in the fluid bathing each quarter rat diaphragm.

Dr. K. Hallas-Møller and Dr. M. Jersild (Copenhagen) presented laboratory and clinical data bearing on the new crystalline and amorphous insulin-zinc compounds with long action. These products of the Novo Terapeutisk Laboratories are prepared with thrice-crystallised insulin and have not so far produced any sensitivity reactions in patients. They offer similar advantages to N.P.H. insulin but are more accommodating, as by the use of judicious mixtures most patients' requirements can be met by a single daily injection.

RAPID BLOOD-SUGAR TESTS

Any gap in the proceedings was ably filled by Dr. H. L. C. Wilkerson, of the U.S. Public Health Service. He demonstrated his machine for performing screening blood-sugar tests at the rate of 120 an hour, and described the results of his extensive surveys for new diabetics in the U.S.A.

ALLOXAN DIABETES

The session on alloxan diabetes opened with a stimulating review by Prof. M. G. Goldner (New York). Dr. J. L. Rodriguez-Miñon (Madrid) suggested that in chronic alloxan diabetes in dogs progressive damage to the pancreatic β-cells might be due to hyperglycæmia, for there was a latent interval of up to 3 months from the last dose of alloxan before diabetes became apparent. Dr. F. D. W. Lukens (Philadelphia), however, doubted whether the hyperglycæmia had been sufficient to cause this delayed onset of diabetes. Dr. A. Lazarow (Cleveland) described the spontaneous disappearance of hyperglycæmia and glycosuria in alloxan diabetic rats after 12–18 months of the disease, but much work remains to be done on the mechanism of this recovery.

CHOLESTEROL METABOLISM

The congress shared two sessions in Amsterdam with members of the 1st International Dietetic Congress.

At one of these Prof. Ancel Keys (Minneapolis) suggested that the incidence and severity of atherosclerosis could be correlated as well with total serum-cholesterol values as with any of the other more detailed results of fat studies. Furthermore the serum-cholesterol level depended more on total fat intake or the proportion of dietary calories derived from fat, than on the actual cholesterol content of the diet.

Dr. Groen then described his group's well-controlled studies on 60 normal volunteers who ate in turn each of three diets. The first had a high fat and animal-protein content, while the second consisted mainly of vegetables and contained only 1·5 mg. cholesterol per day; the third was a normal frugal Dutch diet. The results showed a significant difference in serum-cholesterol values between the dietary periods, but a great individual variation was also apparent. Any form of stress also seemed important in lowering the serum-cholesterol with a subsequent, often pronounced, rise in the convalescent period. Dr. Groen concluded that these findings helped to bridge the gap between those who maintain that atherosclerosis is mainly of metabolic origin and those who point to its common occurrence in individuals who live a stressful life.

BLOOD LIPIDS

Back in Leiden, Dr. J. Möllerström (Stockholm) described his group's work on the blood lipids in diabetes. The postprandial chylomicron count rose significantly more steeply in ketotic diabetics than in balanced diabetics; and in diabetics as a group there was some correlation of increased lipæmia with diabetic complications, particularly neuropathies. Studies on urinary choline established a direct relationship between its level and that of blood phospholipids.

DIABETES AND SEX

Dr. T. Brakier-Zelkowicz (Louvain) suggested that the increased incidence of diabetes in middle-aged women might possibly be due to their excessive caloric intake; but Dr. Joslin pointed out the relatively smaller diabetic incidence in single women than in married women with children. It was clearly important to consider these classes separately when studying the incidence of diabetes.

Dr. Wilfrid Oakley read a most useful paper on the prognosis in diabetic pregnancy, based on an analysis of over 700 cases, nearly 300 of which he had observed personally. Maternal mortality, he said, had been reduced to 1·4% at King's College Hospital, London, but the fœtal mortality remained at 20-25% even when the maternal diabetes was well controlled. This high residual mortality could not be ascribed to duration of the diabetes, its severity, or the presence of moderate complications at the time of conception. Even the toxæmic mothers had only a slightly greater fœtal mortality than that of the whole series. The cause of the high fœtal mortality remained unknown. Dr. Oakley described the reasons for performing cæsarean section at the 36th week, which, although it raises the neonatal death-rate, more than compensates for this by lowering the intra-uterine death-rate.

Dr. C. van Beek (Leiden) reviewed her extensive experiences of necropsy findings in stillbirths and neonates of diabetic mothers. The moral, she thought, was that benign renal glycosuria should not be diagnosed lightly, especially where there was a history of previous stillbirths or of large babies, because in her experience this had not uncommonly included true diabetics.

DIABETES AND THYROID DISEASE

Dr. Frank Allan (New York) reviewed the experience of the Lahey Clinic on coexistent diabetes and thyroid disease, and emphasised how the presence of one of these could mask the other.

RÔLE OF KIDNEY

Interesting experimental work on the part played by the kidney in the production of alloxan diabetes was reported from Professor Jimenez-Diaz's institute in Madrid: but at the close of the discussion there were at least two factions; one believing the kidney to be potentially diabetogenic, and another ascribing the results to possible adrenaline activity.

DIABETIC NEUROPATHY

Dr. M. M. Martin (London) suggested that autonomic nerve damage constituted the earliest phase of diabetic peripheral neuropathy, and this would explain its diverse manifestations.

ELECTROLYTE STUDIES

Dr. John Stowers (London) gave an account of electrolyte studies performed during glucose and glucose-insulin tests. The decrease in serum and urinary phosphorus was interpreted as evidence of utilisation and storage of glucose in the periphery, and corresponding changes in potassium were thought to parallel glycogen formation in the liver.

DIABETIC KETOSIS

Dr. G. A. Wrenshall (Toronto) gave the results of his work on the acetone content of exhaled air in normal and diabetic subjects. Parallel chemical and mass-spectrometric determinations agreed well, and showed that even balanced diabetics exhaled more acetone than normals and that young diabetics exhaled more than older ones. In young, but not in older, diabetics increasing blood-sugar was associated with increasing acetone content of the breath.

Dr. J. D. Nabarro gave a commendably clear account of metabolic studies at University College Hospital, London, on patients with severe diabetic ketosis. He drew useful conclusions with regard to replacement therapy and in particular to the importance of potassium in the fluid recommended for the intracellular repair phase.

COCARBOXYLASE

Results were reported by Prof. R. Boulin's team in Paris on the value of cocarboxylase in the treatment of diabetic coma. They claimed that significantly less insulin was needed by the cases receiving cocarboxylase, in comparison with cases treated similarly but without cocarboxylase.

UTILISATION OF PENTOSES

Considerable interest was aroused by the report of Dr. M. Loos (Hamburg) on the utilisation of pentoses by diabetics. Xylose caused depression of the serum-phosphorus in diabetics without insulin, reduced glycosuria and ketosis when substituted for glucose in the diet, and caused no undesirable side-effects. He felt that pentoses deserved further investigation with regard to their utilisation in diabetics and their use in diabetic diets.

CONCLUSION

Dr. Lawrence, as the pioneer of the first national diabetic association to be formed, had a leading rôle in the congress. This was of great value in bringing together workers from many lands; but possible small improvements for the next such meeting also suggested themselves. One need is for clearer and properly labelled slides rather than illegible tables, to be projected on the screen; and a single definition should be adopted for "diabetic coma."

Special Articles

MEDICAL RESEARCH COUNCIL

THE latest annual report of the Medical Research Council[1] contains, in its introduction, a brief account of the ways in which the council is fostering the training of research-workers.

Far and away the best training for a research-worker is to engage in actual investigations under the eye of an acknowledged expert. This is easy to arrange when the chosen field of research has been the subject of his undergraduate studies. But a new graduate may wish to be trained for research in a sphere with which he is unfamiliar —for example, in one of the several important biological subjects that are judged unsuitable for the undergraduate curriculum—or he may wish to enter a field which spans more than one subject, or to refresh or extend his knowledge of one of the basic sciences after some years spent in purely clinical practice.

> "Problems of this kind arise to-day in connexion with practically every branch of biological or medical research. In catering for the training of research workers in medical science it is necessary therefore to provide opportunities not only for those who need a further period of training in their own subject but also for those whose training is lacking in some important particular or who wish to work in a subject suitable only for postgraduate study. With these considerations in mind the Council have recently reviewed their arrangements for training research workers and now have three special schemes for this purpose: postgraduate studentships (to be known in future as postgraduate scholarships); clinical fellowships tenable in this country; and travelling fellowships."

The council now covers a wider field than ever before; and the following passages, abstracted from the report, refer to only a little of the work completed or in progress.

PROTEINS

To acquire information about the size and shape of the molecules of purified proteins various physical methods have been used. The ultracentrifuge provided accurate knowledge about molecular weights. The electron microscope is being used at the National Institute, and the council's Biophysics Research Unit at King's College, London, to discover the molecular shape of some of the larger proteins or protein-complexes such as viruses. Many proteins have approximately spherical molecules and can often be obtained in the form of crystals, whilst others, such as the contractile protein of muscle, have long fibrous molecules. Both types of protein have been examined by X rays. Although the discovery of the exact position of each atom is a goal that will probably be attained only in the distant future, considerable progress has been made in defining the general shapes of certain protein molecules. It has been clearly shown that the amino-acids are arranged in chains of a regular geometrical form, parallel to the main axis of the molecule, and that the chains are arranged in a regular pattern relative to one another. The chains are folded to give a compact molecule; and recently it has been suggested that they are in the form of a spiral containing eighteen amino-acids to every five turns.

On the building up and breaking down of proteins our knowledge has advanced greatly, partly because of chromatography but even more because of the introduction into biological research of stable and radioactive isotopes, with which the changes undergone by different substances in the body can be traced in detail. From isotope work it is now known that the proteins of the blood-plasma, the liver, the kidney, and the intestinal tract are almost completely renewed every fifteen or twenty days, which makes the relative constancy of composition of these tissues most remarkable. However, this rapid turnover does not apply to all body proteins. Collagen remains practically unchanged once it is formed.

It is becoming evident that the metabolism of some amino-acids is closely connected with the formation or action of certain vitamins. It has been found that animals need a supply of labile methyl groups, and do not grow unless the diet includes choline or the amino-acid methionine, both of them sources of such groups. On the other hand, it has been shown that the rat can to a very limited extent synthesise methyl groups from other components of the diet. Preformed methyl groups can much more readily be dispensed with if the diet contains vitamin B_{12}. Similarly, a deficiency of vitamin B_{12} leads to a disturbance of the metabolism of tryptophan.

PRESERVATION OF LIVING CELLS

Among the lower forms of life certain cells, tissues, and organisms may survive freezing at very low temperatures, such as can be obtained with "dry ice" (—79°C) or liquid air (about —192°C). Thus, successful experiments have been carried out with certain bacteria, moulds, protozoa, minute worms, rotifers, and the like. Little work has been done on vertebrates, and the functional survival of normal cells of birds or mammals after exposure to low temperatures has rarely been recorded. From recent work, however, it may prove possible to verify the theoretical expectation that if a cell can be frozen to very low temperatures the arrest of biochemical processes will confer a virtual immortality on the cell while it is maintained at these temperatures. This work has important practical applications in that it will make it possible to store various cells and tissues for clinical use. In trials of the fertilising capacity of frozen bull spermatozoa, a pregnancy-rate of nearly 80% followed insemination with semen stored at —79°C for periods varying from two hours to eight days. Since then pregnancies have been obtained by the use of semen stored for several months. Similarly, it seems that endocrine tissues may survive protracted freezing; and methods are being developed for storing red blood-cells in this way.

STATISTICS IN MEDICAL RESEARCH

Nowhere in medicine has the application of the statistical method had a more salutary effect than in the testing of new agents for the treatment or prevention of disease. The council's Whooping Cough Immunisation Committee found it necessary for its trials of different whooping-cough vaccines to recruit nearly 10,000 children; since less than one in five were in the next two years in contact with a known case of whooping-cough, the incidence of attack was inevitably low; and it was only the large numbers used that enabled the positive value of the best vaccines to be decisively shown. Often, however, a carefully designed inquiry can give an answer with relatively few observations. The council's trial of the value of streptomycin in the treatment of tuberculosis in young adults used only 50 treated cases and 50 controls and gave a clear result. Similar numbers sufficed to demonstrate the improved effect when *p*-aminosalicylic acid (P.A.S.) was given in conjunction with streptomycin.

INFECTIOUS DISEASES

Whooping-cough

Nearly 10,000 children under two years old have been inoculated; half were given one or other of three whooping-cough vaccines, the other half a fluid superficially indistinguishable from the vaccines. All the inoculated children were visited once a month for two years. At the end of this period the proportion attacked by whooping-cough was five times as high in the unvaccinated children as in the vaccinated. Efforts are now being made to find the factors responsible for differences in potency between the vaccines.

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[1] Report of the Medical Research Council for the Year 1950–51. H.M. Stationery Office. Pp. 214.

Work is also in progress to find a method by which the effectiveness of a particular vaccine can be tested in the laboratory instead of in the field. If satisfactory methods can be evolved, protection against this disease may in the near future be made available on the same scale as protection against diphtheria.

Infantile Gastro-enteritis

Further work has strengthened the conclusion that the "alpha" type of coliform organism is associated with this disease. In some outbreaks another type, "beta," has been found; and there is reason to believe that the few in which neither has been found may have been caused by another type not yet recognised. The alpha type at least is very susceptible in the laboratory to chloramphenicol, aureomycin, and terramycin, though not to penicillin.

Tuberculosis

The trials of B.C.G. and vole-bacillus vaccines are making progress; over 40,000 children of school-leaving age have entered the scheme, and the follow-up has started and will be carried on until the end of 1955. A national survey of tuberculin-sensitivity at various ages has been completed, 95,000 children and young people having been examined in twenty-two representative areas of England and Wales.

Certain non-ionic surface-active agents have been found to produce a striking antituberculous effect in the mouse and guineapig. Unlike previously known antituberculous agents, these substances have no action against the bacillus in the test-tube but seem to act on the body itself, by stimulating or accelerating the ordinary defence mechanism. The present compounds are too toxic to be used in treatment, but new methods are being developed in the hope of preparing more active and less toxic products.

A Tuberculosis Chemotherapy Trials Committee has been formed, and at its first meeting in March recommended that extensive controlled clinical trials be conducted under the auspices of the council to compare the effects of isonicotinic acid hydrazide with those of streptomycin and P.A.S. It was essential for the trials to be organised rapidly and in such a way as to provide an answer as soon as possible. By the end of April thirty-five hospitals were already coöperating, and over 200 patients had been accepted. Analyses of the results will be made as the trial progresses, so that any striking effect may be reported without delay.

ANTIBIOTICS

The Antibiotics Clinical Trials Committee has made a study of pneumonia in which all cases, regardless of their causal nature (which was, however, subsequently ascertained), were allocated to one of three groups, which were treated with chloramphenicol, aureomycin, or "standard" treatment—that is, penicillin with or without sulphonamides. Terramycin was not available when this study was begun but was included at a later date.

> "Standard treatment is so effective in the majority of cases of pneumonia that a significant difference in mortality was not to be expected in any but a very large series; there were, however, slightly fewer deaths in patients treated with penicillin, and by other criteria there was little to choose between the three groups except that penicillin produced fewer undesirable side effects than either chloramphenicol or aureomycin."

DISEASES OF THE EYE

Much of the Ophthalmological Research Unit's time during the past year has been spent in studying the effects of cortisone. Largely because of its ready absorption on local application, diseases of the anterior segment of the eye are pre-eminently suitable for treatment with cortisone. Diseases of the posterior segment, for which cortisone must be given by injection or mouth, are in general much less responsive. It has been shown that cortisone is effective in controlling the acute phases of ocular inflammatory disease whether bacterial, allergic, or traumatic in origin. So dramatic is its action that in many such cases, where the life history of the disease is short or an infecting organism can be attacked by other means such as antibiotics, the results of treatment are excellent. Typical conditions wherein this occurs are acute iridocyclitis, sympathetic ophthalmitis, and infective keratitis. The effect, however, on chronic infective diseases and on the later consequences of inflammatory conditions is difficult to assess and is much less distinct. Cortisone is similarly ineffective in degenerative conditions affecting the eye. Its value in ophthalmic conditions is thus limited, but within its restrictions is great, particularly when it is remembered that the functional effects of acute or even subacute inflammatory changes may be disastrous.

SKIN DISEASE

The arms of volunteers were soaked in acetone to extract the sebum, which was found to be present in amounts equivalent to a surface film about $^1/_{1000}$ mm. thick. Some 40% consisted of free long-chain fatty acids, about half of which contained unsaturated carbon atoms and so were potentially active chemicals. Oleic acid was proved by X-ray crystallography to be a major constituent, and its disinfectant action, and that of sebum itself, on streptococci and other pathogenic micro-organisms was confirmed. Some bacteria are apparently but little affected by sebum, but these are mostly destroyed by drying; so very few harmful organisms can multiply or even survive for long on the healthy, intact skin surface. Even the staphylococcus, which is one of the most resistant organisms, has been shown to survive for only about three days. If the skin is injured, however, and serum exudes, not only does the moisture enable certain organisms to multiply but the disinfectant action of sebum is neutralised.

Skin grafts, it has now been found, can be stored in the refrigerator and used successfully several weeks later if any injured areas remain unhealed. Even more remarkable is the capacity of such isolated skin to withstand being frozen solid by liquid air, provided this is done gradually.

CORTISONE AND A.C.T.H.

The council's clinical and experimental work on cortisone and A.C.T.H. began towards the end of 1949, but its scope was at first severely limited by the extreme scarcity of the two hormones. The manufacture of both hormones continues to be difficult and this country is still almost entirely dependent on supplies from the United States. Cortisone is not manufactured here at all; but several commercial firms have become interested in the manufacture of A.C.T.H., and the first home-produced samples have already been delivered under contract to the Ministry of Health and approved on the basis of provisional specifications laid down by a specially appointed committee of the council. One obstacle to expanding production has been the scarcity of the animal pituitary glands from which A.C.T.H. has to be extracted, but it is hoped that this difficulty may gradually be overcome as a result of recent steps by the National Research Development Corporation to encourage their collection and arrange for their distribution. Another serious obstacle is the difficulty of standardising the potency and purity of the finished product, the method in use at present requiring laborious and uncertain tests on a large number of rats. Continuous, but so far unsuccessful, work in search of less complicated and more reliable methods has been in progress at several different centres.

The raw material for the commercial synthesis of cortisone has so far been deoxycholic acid, obtained from animal (mainly ox) bile, which must always remain inconveniently scarce. Every effort is therefore being made to find some more plentiful alternative of vegetable origin, amongst those first considered being sarmentogenin, which can be extracted from the seeds of a particular strain of *Strophanthus sarmentosus*, a climbing plant growing in certain areas of Africa. The possibilities were recently investigated on the spot by a team sent out by the council to Nigeria and the Cameroons; but supplies of the seed proved so inaccessible, and the best yield of sarmentogenin so small, that no immediate contribution can be expected from this source. One of the most promising naturally occurring compounds from the point of view of cortisone synthesis is a sapogenin called hecogenin, which was already known to occur in small quantities in agave species in the Southern United States and Central America. It has now been discovered by a team of council workers that hecogenin occurs also in sisal waste and in still higher concentration in the juice of the sisal plant. Investigation of this matter by a member of the team in Kenya has shown that hecogenin can be easily and cheaply extracted from the sisal juice, so that this source material for cortisone synthesis becomes potentially available in a large amount and at low cost.

SALARIES OF CIVIL SERVICE DOCTORS

Discussions arising out of the report of the Howitt Committee[1] have been continued by the Civil Service Medical Officers Joint Committee, formed by the Institution of Professional Civil Servants, the Ministry of Health Medical Staff Association, and the British Medical Association. On June 27 the Government's decision was given in the following letter from the Financial Secretary to the Treasury:

> "In the course of the discussion with the deputation from your Committee who came to see me on 13th June I promised to consider what undertaking we should give you about a future review of the salaries recommended by the Howitt Committee for Civil Service Medical Officers.
>
> "As I explained to the deputation, we do need to go ahead as soon as possible with the recruitment of Medical Officers in the Civil Service and for the reasons that I have already explained we think that the rates recommended by the Howitt Committee should first be given a fair trial. In this we should naturally hope to receive the usual facilities to advertise in the medical journals.
>
> "On this understanding I should be willing to agree that there should be a further review of the salaries of Civil Service Medical Officers not later than December, 1953, and that this review should take account not only of the results of the competitions held in the meantime but also should have regard to the general principles enunciated by the Tomlin Commission and any other relevant factors.
>
> J. A. Boyd-Carpenter."

At an emergency meeting of the Joint Committee held on July 1, it was agreed that no useful purpose would be served by continuing the negotiations with the Treasury or by seeking a further interview with the Financial Secretary. A letter later sent to the council of the B.M.A. on behalf of the Joint Committee recalls that the council last January regarded the Howitt Committee's proposals as unacceptable, and points out that "quite apart from the preliminary period of preparation and discussion the claim of the Joint Committee has been before the Treasury since August, 1949, and no progress has been made."

After a meeting of the B.M.A. council in Dublin on July 5, Dr. A. Macrae, secretary of the B.M.A., wrote to the Financial Secretary of the Treasury in the following terms:

> "I have been asked to say that the Council is disturbed to learn that you feel unable either to refer the matter to arbitration or to review the recommendations of the Howitt Committee in the light of the Danckwerts Award until after the results of the competitions are known and then not until a considerable time has elapsed.
>
> "The Council has therefore decided that in all the circumstances it will not be possible to accept any further advertisements for medical officer appointments in the Civil Service until such time as you feel able to discuss with us some alternative proposals which offer more acceptable opportunities for the officers concerned."

CENTRAL HEALTH SERVICES COUNCIL

The Minister of Health has made the following appointments to the Central Health Services Council and standing advisory committees for the period ending March 31, 1955:

CENTRAL HEALTH SERVICES COUNCIL

Medical Practitioners.—J. A. Brown, M.D. (Birmingham); Sir Ernest Rock Carling, F.R.C.P., F.R.C.S. (London); Sir Henry Cohen, F.R.C.P. (Liverpool); Prof. A. J. Lewis, F.R.C.P. (London); Wilfrid Sheldon, F.R.C.P. (London).

Persons with Experience in Hospital Management.—P. H Constable, M.A., F.H.A. (London); N. A. Ball, F.H.A. (Carmarthen).

Person with Experience in Local Government.—Fred Messer, M.P., J.P. (London).

Dental Practitioner.—J. Ballard (London).

Person with Experience in Mental Health Service.—C. F. Comer, R.M.N. (Manchester).

Registered Nurse.—Miss Eleanor J. Merry, S.R.N. (London).

Registered Pharmacist.—Alderman W. J. Tristram, M.P.S., J.P. (Cheshire).

The Central Health Services Council has re-elected Mr. Messer as their chairman and Sir Henry Cohen as their vice-chairman for the current year.

STANDING ADVISORY COMMITTEES

Medical

J. A. Brown; Sir Ernest Rock Carling; Sir Henry Cohen; Prof. A. J. Lewis; H. Kenneth Cowan, M.D. (Chelmsford); H. M. C. Macaulay, M.D. (London); S. Wand, M.B. (Birmingham); one vacancy.

Dental

F. J. Ballard; Thomas Hindle (Blackburn); Prof. Martin Rushton, M.D., F.D.S. R.C.S. (London); Clement Spiridion, L.D.S. R.C.S. (Cardiff); Prof. F. C. Wilkinson, M.D., F.D.S. R.C.S. (London).

Pharmaceutical

Alderman Tristram; P. J. Gibbons, M.B. (Liverpool); J. B. Hough, M.P.S. (Newport, Mon.); Harry Noble. B.PHARM., PH.C. (London); D. E. Sparsholt, M.P.S. (Nottingham).

Ophthalmic

Macdonald Critchley, F.R.C.P. (London); G. H. Giles, F.B.O.A. (London); O. Gayer Morgan, F.R.C.S. (London); A. E. Turville, F.B.O.A. (Northampton).

Nursing

P. H. Constable; Miss Merry; Miss Muriel Edwards, S.R.N. (London); Miss Frances Goodall, S.R.N. (London); Miss Margaret J. Smyth, S.R.N. (London); Miss May E. A. Squibbs, S.R.N. (Leeds); Miss Bertha F. H. Townsend, S.R.N. (Enfield, Middx.).

Maternity and Midwifery

Miss Merry; Miss Joyce M. Akester, S.C.M. (Chichester); Miss Lois Beaulah, S.C.M. (Surrey); Miss Zita M. Goodall, S.C.M. (Surrey); one vacancy.

Mental Health

C. F. Comer; Prof. A. J. Lewis; N. H. M. Burke, M.R.C.S., J.P. (St. Albans); K. K. Drury, M.B. (Leicester); Denis Williams, F.R.C.P. (London); Prof. O. L. Zangwill (Oxford).

Tuberculosis

Sir Brunel Cohen (London); P. M. D'Arcy Hart, F.R.C.P. (London); Peter Kerley, F.R.C.P. (London); Miss Doris Lambert, S.R.N. (London).

Cancer and Radiotherapy

Sir Ernest Rock Carling; Sir Henry Cohen; Prof. E. C. Dodds, F.R.C.P., F.R.S. (London); Sir Ernest Finch, F.R.C.S. (Sheffield); K. I. Julian (London); Prof. J. S. Mitchell, M.B. (Cambridge); V. E. Negus, F.R.C.S. (London).

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[1] See *Lancet*, 1951, ii, 921.

In England Now

A Running Commentary by Peripatetic Correspondents

AT every meeting of the pædiatricians someone is bound to get up and say how enjoyable such meetings are because we still have so much of the child in us. Looking round the faces at our last local gathering I found this rather hard to believe and I fell to wondering what appropriate remarks are made when other specialists forgather. Do obstetricians congratulate themselves on their pregnant discussions or their speakers for their excellent delivery? Do dermatologists agree that they always get beneath the skin of their subjects and ophthalmologists that they always see eye to eye? Chest physicians, I suppose, pat each other on the back and maintain that they breathe more freely in each other's company. And cardiologists probably have heart-to-heart talks and listen to the lecturer without a murmur.

* * *

As a peripatetic electrocardiographer I have gradually learnt my way through the maze of electrical London, and I have marked on my map the islands of 110-volt, the treacherous swamps of D.C. and the deserts of gas and oil lamps. My bag resembles a museum of varied and curious fittings so that I can only be defeated by the occasional individualist who either makes his own plugs and sockets or imports them from the Continent—"I'll bet you've never seen one like this before."

Last week I had to mark a new danger area. Strangled noises from the instrument and a fantasticated base-line revealed that not only was it obliging with a rendering of "Woman's Hour," but was also trying, bless it, to write it down. "An ectopic beat?"—"No, entry of the brass, I think." On my second visit to the neighbourhood of the broadcasting station there was an additional distraction from a battery of hairdriers in the "Coiffeur des Dames" below the flat. The effort to make a simultaneous one-channel recording of a recipe for marmalade, lead one, and a realistic frizz of A.C. from the driers was too much for the machine. Or perhaps it was overcome by misogyny, for it sulkily wrote a few complexes upside-down and then clicked off in an electrical huff.

* * *

The other day, with a slight drizzle and a boisterous wind blowing, I saw half a dozen oddly assorted people sitting along the front-garden party wall between two houses in a pleasant residential district. They looked as pathetic as wet birds on a telegraph-line, each with his shoulders humped against the wind and nobody saying a word to his neighbour. Along came a housewife with a battered basket of shopping and an even more battered child, and turned in at the gate. "Full up inside?" she said to the last man, at which he and his five companions looked up, nodded, then relapsed into immobility again. They were queueing to get into the doctor's waiting-room.

Waiting-rooms have become fantastic places since my youth, when patients were received as friends of the family in the doctor's drawing-room, and fuel restrictions did not prevent a blazing fire and open windows. Since then the waiting-room has come down in the world. I remember in the Midlands during the war a doctor showing me his surgery with a rueful wave of the hand. About sixty patients sat on rows of forms in a bare gaunt room looking for all the world like a village treat waiting for the magic-lantern show to begin. Then there are those terrible surgeries in London where the doctor has acquired an old shop, with the windows perhaps still boarded up and the chairs salvaged from goodness knows what murky past. A third type is nothing more than the passage, usually graced with the title of entrance-hall, of a small suburban house, with a couple of forms against the wall, where patients sit, almost knee to knee, as though in an old-fashioned diligence, and which is as draughty, stuffy, and unwarmed as a diligence.

To make the best room of a small house do double duty for patients and family sets a housekeeper a problem, and nowadays the doctor will probably be wise, by hook or by crook, to provide a separate room. The number of his patients has risen and with it the cost of cleaning and wear-and-tear, and a room furnished for its special purpose and traffic can be at once more attractive and less expensive to maintain.

An ideal waiting-room should be easily cleared for cleaning. It should have gay washable walls and floor, some of the comfortable stacking-chairs now on the market, and magazine-racks to save space and chaos. A slow-burning combustion stove would keep it warm in winter. And I'd like to put in something to amuse the children; toys might lead to jealous outbreaks, but a dado on one wall with farmyard animals or an alphabet series would be a boon to mothers. Probably only a doctor who is building his own surgery can offer his patients the waiting-room he would like, but access to a lavatory would be a godsend to many, especially those who have to bring their children.

The patient spends perhaps seven or eight times as long in the waiting-room as he does in the consulting-room. Small wonder if he starts judging his doctor's character and professional ability by the thoughtfulness and hospitality shown.

* * *

Like many Scotsmen, my friend James is a collector of general information, on the principle that somewhere at some time it may come in useful. On the boat home somebody pointed out to him Mr. X, the working owner of a fishing fleet, watching his haddock and whiting being stored in the hold. It took James about thirty seconds to make the mæstro's acquaintance, and in another ten seconds questions were being asked and answered about the kinds of fish caught, the best places and time of year to go after them, and so forth. This pursuit of knowledge for its own sake seemed to me wholly admirable. Presently the conversation turned to the merits of various types of net. "I expect," said James, "that your nets get a good deal damaged in the course of the season?" The mæstro agreed that the net repair service was a large part of the business. "And how," asked James, "do you set about repairing a rent?" Bits of string, paper, and pencils were produced. Notes were made and practical demonstrations given. "Ah, thank you," said James at last, "that will be very useful. I have two or three small holes in my strawberry netting at home. . . ." So much for the pursuit of knowledge for its own sake.

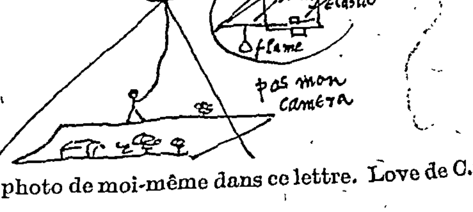
* * *

As I was passing through the outpatient waiting-hall of an East End hospital one morning about 11 o'clock, I saw a well-known figure, an elderly man, sitting on the bench. As the medical clinic did not start before 2 P.M. I suggested to him that he might go out for a meal and return later. But he replied "I insist on being seen first, as I refuse to be kept waiting."

I expect this proves something, but I don't know just what.

* * *

News from School.—"The balloon I want you to send could be in (*a*) the bread oven (most likely), (*b*) the shed, (*c*) the nursery cupboard, (*d*) the attic (not likely), (*e*) the other bread oven, (*f*) same as (*a*), (*g*) same as (*a*). I think I told you that I sent off two gas balloons. One of them came back from a place in Suffolk called Stansfield (near Sudbury) and would have gone nearly 80 miles if it went dead straight, and the second one only went about 30 miles, to Great Missenden, Bucks, where someone found it in the High Street. The two aren't on a straight line and they were sent off within about 15 min., so the first must have reached about 11,000 ft. because the winds were more westerly up there. The Sudbury one was found by a farmer while he was cutting hay. When and if you send my big balloon, I shall take an aerial photo of the School, comme ça:



J'ai mis un photo de moi-même dans ce lettre. Love de C."

Letters to the Editor

MATERNITY AND CHILD-WELFARE SERVICES

SIR,—Prof. Leslie Banks at the meeting of the British Medical Association in Dublin on July 10 made the remarkable statement that the maternity and child-welfare services, having fulfilled their main purpose, should now be merged with the hospital services, and that the "vast army of workers" engaged should be demobilised.

It will be generally accepted that these services, especially the infant-welfare services, are purely educational, and that they have never sunk to the position of mere outpatient departments for the patch-repair of bodies. It has also (up to July 10) been generally accepted that women are not born into the world with an inheritance through their chromosomes of all the knowledge necessary in this complicated civilisation to enable them to bear and rear their children in health and comfort. They have not been born, I suggest, with an understanding of the biological values of the various foods, nor of their availability.

Consequently, one would have thought that education would still be as necessary in 1952 as in 1902. But no, Professor Banks says that this education has been mainly performed, and would disband the teachers. Does this ecologist suggest that quite suddenly babies are now being born with their genetic characteristics so mutated that they now have, in addition to their normal instincts, a detailed knowledge of their nature and nurture? Does he suggest that from birth a baby can supervise the making up of his own feeds, can decide automatically the precise amount of orange-juice needed, and can guide his mother on her psychological approach, and the careful observance of those practices which can so materially affect his mental and psychological health? Can the New Baby (from July 10) ensure that his parents will not allow him to become maladjusted? Should this be Professor Banks's claim, then his name should be linked with that of the eminent Russian geneticist, Lysenko, who discovered that genetics was merely atom-fissured environment modified by an enlightened proletariat; and I would suggest that this theory might well be called, using a musical idiom, the theory of Lysenko, arranged by Leslie Banks.

There are, however, remnants, though Professor Banks does not indicate what residue the hospitals would deal with. These infants are *healthy*, and number 3,725,000. Would he admit the lot to the hospital, and if so would he send them to the wards or to the outpatient departments? It cannot be denied that either course would involve the hospital boards in some building costs, and might even interfere with the rearmament programme.

What would the medical staff do with these children? Their mothers have been "mainly educated," and so we must assume that Professor Banks does not consider they need the education they have received up to now in local-authority clinics. The hospital doctors will need guidance; will Professor Banks supply it? The hospitals (up to July 10) have only been willing to accept patients requiring treatment, but these 3¾ million kids are healthy! It is admitted that when they mix with the ill children in the germ-laden atmosphere of children's outpatient departments, a substantial number of them will be able to contract infection, and so qualify for attention; but at the most this would only involve a million or two. What about the others; and anyway, what material advantage would it be to the community, to the hospitals, or to the children to swamp the available accommodation?

Ecologists all over the world have pointed out the terrific problem confronting the world of a rapidly increasing population, and an almost stationary food-supply. The professor of human ecology at Cambridge would appear to have the answer!

Smethwick. HUGH PAUL.

SORE THROAT AND RHEUMATIC FEVER

SIR,—A report will shortly be published [1] of an inquiry into some epidemiological aspects of rheumatic fever conducted under the auspices of the Rheumatic Fever Committee of the Royal College of Physicians. May we anticipate the publication of this by commenting on a statement in your leading article last week which is in conflict with the findings of this recent inquiry?

A group of 31 rheumatic children, for whom a history of tonsillitis had been recorded before the onset of their rheumatism, was compared with a control group of 70 children who had also suffered from tonsillitis but had not subsequently developed rheumatism. It was found that 36 (51%) of the control group, but only 6 (19%) of the rheumatic group, had undergone tonsillectomy. This difference was far too great to be attributed to chance, and implied that the liability to rheumatic fever of children with tonsillitis may be reduced by about two-thirds when the tonsils are removed (i.e., 42% of the unoperated but only 14% of the operated cases of tonsillitis belonged to the rheumatic group of children). We were not, however, able with the records at our disposal to exclude the possibility that there might have been some cases in which rheumatic fever intervened between a decision to perform tonsillectomy and a suitable occasion for operating. If this were the case the advantage of tonsillectomy would have been overestimated to some extent.

The Medical Research Council Report of 1927,[2] which you cite, does not contain any direct evidence on the value of tonsillectomy: it records 60 cases in which tonsillectomy had failed to prevent rheumatic fever, but makes no comparison between operated and unoperated cases. The authors of the report concluded that "complete removal of the tonsils does not appear to afford absolute protection from attack by rheumatism," but this conclusion is compatible with the view that tonsillectomy is an effective means of reducing the incidence of rheumatic fever after tonsillitis.

Institute of Social Medicine,
Oxford.

ALICE STEWART
DAVID HEWITT.

B.C.G. VACCINATION AND TUBERCULIN ALLERGY

SIR,—I have read with great interest Dr. Palmer's paper.[3] As one responsible for the production and supply of B.C.G. vaccine for the mass-vaccination programmes in India, Ceylon, Burma, Malaya, and Thailand, I must sound a note of warning to B.C.G. workers in mass-vaccination campaigns against interpreting Dr. Palmer's observations to imply that fresh liquid B.C.G. vaccine can be handled without any refrigeration, that the age or the dose of the vaccine does not matter, that there is a wide margin of safety, and that satisfactory tuberculin-sensitivity will follow vaccination and that there is no question of a "positive" or "negative" reactor to tuberculin as almost all vaccinated children show some degree of tuberculin allergy.

All the field investigations were carried out on Danish school-children. This seems a pity because Danish children are known to develop a very high degree of tuberculin-sensitivity after B.C.G. vaccination.

Their capacity to develop tuberculin-sensitivity is best illustrated by the observations reported by Dr. Palmer himself. "When only heat-killed vaccine was used, the average size of tuberculin reactions among them was 5 mm., about the same as that found in Egyptian children vaccinated with standard (and presumably) living vaccine in the mass campaign! More interesting still is the fact that the average reaction of children receiving standard vaccine, which had been heated to 80°C for two hours, increased from about 5 mm. at ten weeks to more than 9 mm. at one year." Were these not Danish children, the question of superinfection would have been brought in as an aid to explain this very extraordinary phenomenon.

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[1] Hewitt, D., Stewart, A. M. *Brit. J. soc. Med.* (in the press).
[2] Social Conditions and Acute Rheumatism. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 114, 1927.
[3] Palmer, C. E. *Lancet*, 1952, i, 935.

We have therefore to assess the results of the investigations against the background, if I may say so, of a comparatively exaggerated tendency of Danish children to develop tuberculin allergy after B.C.G. vaccination; and this is bound to reflect itself in the results.

It would be interesting to speculate on the results had the field investigations been duplicated in Greece or Egypt. It is quite probable that the low tuberculin-sensitivity after B.C.G. vaccination observed in the children in Greece and Egypt would have adversely influenced the size of the tuberculin reactions in these countries, in much the same way as the high tuberculin-sensitivity of the Danish children has favourably influenced the tuberculin reactions in Denmark.

It would, therefore, seem that the observations made in Denmark are of purely local interest inasmuch as the same results cannot be reproduced in Greece or Egypt. In other words, the allergenic potency of the vaccine appears to depend not only on the vaccine but also on the capacity of the children of the particular country to develop hypersensitivity to tuberculin. Dr. Palmer has presented data from three countries to show that such variations in capacity do exist. In the circumstances, the inferences drawn from the results obtained in one country—Denmark—cannot be considered to apply to other countries.

Dr. Palmer mentions "standard preparations" from other laboratories.

So far as I know, there is no international, but only a national, standard for B.C.G. vaccine. I sent a sample of vaccine for comparative study of the potency to the W.H.O. Tuberculosis Research Office in February, 1951. I was requested to send a sample of our "usual" vaccine, and our "usual" vaccine contained at that time 0·5 mg. of semi-dry B.C.G. mass per ml., while the Danish "standard" vaccine contained 0·75 mg. per ml. Unless the Indian vaccine was excluded from the studies, the different vaccines cannot have been of the same labelled strength—not to mention the other possible variations.

It is clear that Dr. Palmer does not like the use of the terms "positive" or "negative" tuberculin reaction after B.C.G. vaccination, but prefers to measure the average size of the reactions as a convenient index of post-vaccination allergy.

Many would agree with him. But we need an expression to indicate whether B.C.G. vaccination has been successful or not. In this connection the terms "reactor" and "non-reactor" have been used by some investigators. In the case of smallpox vaccination, we speak of a successful "take." Is there no need for re-vaccination with B.C.G. even in a country like Egypt where the children are apt to develop only a low degree of tuberculin sensitivity? From the size of the tuberculin reaction how may one differentiate between a child that requires re-vaccination and one that does not?

Dr. Palmer thinks that many of our traditional concepts regarding B.C.G. vaccine may have to be discarded, as it seems they are ill-founded. Before they are discarded, it has to be convincingly shown that they are irrational or harmful. I should like to ask Dr. Palmer which of the two vaccines—one that is fresh, contains a fairly high concentration of B.C.G., and has been constantly refrigerated, or another, a month or more old, stored at 2–30°C, and containing only a small fraction of the strength of the first vaccine—he would recommend for mass vaccination in a country such as Egypt. The traditional concepts reflect great credit on the vision of the pioneers, which has made universal expansion of B.C.G. vaccination possible.

It would, in my opinion, be most undesirable for the impression to gain ground that strict refrigeration of B.C.G. vaccine is not essential or that the age or dose of vaccine does not matter, because slackness in attention to details of technique would inevitably result. I would make a strong plea that until a satisfactory dry vaccine is developed and made available for mass-vaccination programmes, there should be no relaxation of the present high standard of technique. The conditions in some remote areas in under-developed countries are already sufficiently adverse to B.C.G. vaccination; and it is undesirable to worsen them by lowering the standards.

B.C.G. Vaccine Laboratory,
King Institute, Guindy,
Madras, India.

K. S. RANGANATHAN
Director.

SURGERY OF PEPTIC ULCER

SIR,—There can be little to criticise in Sir Heneage Ogilvie's thoughtful paper on this subject (May 31). I wonder, however, whether his ingenious explanation of the lesser-curve site of ulceration is the right one? May it not be that it is the mucus, always in considerable quantity in the more dependent part of the stomach, that is responsible for its freedom from ulceration? When Lintott and I carried out our gastroscopic studies of the effect of aspirin on the stomach that conclusion seemed to us to be the obvious one.

Mr. Michael Smyth (July 5) thinks but little of the value of milk drip, and is good enough to quote a contribution of mine in support of an antacid mixture. I would like to make it clear, however, that although the effect of milk drip on gastric acidity is very variable, yet this treatment is the most certain means of abolishing pain *due to chronic peptic ulcer, and the most effective method* of treatment of duodenal ulcer during the night hours.

London, W.1.

A. H. DOUTHWAITE.

EFFECT OF VITAMIN B_{12} ON ICHTHYOSIS

SIR,—Ichthyosis is a distressing condition, so I should like to report a chance observation.

A man, aged 69, recovering from a slight cerebral vascular accident, received injections of vitamin B_{12} ('Cytamen 50'), 50 µg. twice weekly, as a "tonic." He has had ichthyosis all his life. After about four injections the scaling appeared to be much reduced, and after ten injections few scales are left.

Is this a natural remission?

London, N.W.6.

W. LEVY.

PHARMACOLOGY OF ANTABUS

SIR,—The findings of Hine et al.,[1] quoted in your annotation of June 21, give, we feel, too simple an explanation of the pharmacological action of tetraethylthiuram disulphide ('Antabus').

In a similar investigation of 36 male patients recently *carried out at this hospital*, mild toxic side-effects of the drug have been repeatedly observed before any alcohol was given; in no case was there a corresponding increase of the acetaldehyde content of the blood. When a test dose of alcohol was given after the patient had had 1 g. of antabus daily for four days, the *severity* of symptoms corresponded with the blood-*acetaldehyde* level in three-quarters of the cases only. Slight reaction (flushing and tachycardia) was associated with an acetaldehyde level under 0·3 mg. per 100 ml.; moderate reaction (dizziness, nausea, headache, and fall in diastolic blood-pressure) with a level of 0·3–0·5 mg. per 100 ml.; severe reaction (fall in systolic and diastolic pressure and other signs of vasomotor collapse) with a level above 0·5 mg. per 100 ml.

No fewer than 9 patients behaved anomalously. In these, only slight reactions were associated with acetaldehyde levels of 0·4–0·8 mg. per 100 ml., suggesting that the production of acetaldehyde is not the only factor concerned. In our patients attempts to correlate these atypical reactions with age, body-weight, general

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1. Hine, C. H., Burbridge, T. H., Macklin, E. A., Anderson, H. H., Simon, A. *J. clin. Invest.* 1952, 31, 317.

physical condition, and duration of addiction have been unsuccessful. Similarly, despite standardisation of the test procedure, we found the individual reaction unpredictable. The pharmacology of the drug being thus uncertain, the risk of accidents remains and must be guarded against.

J. HARPER
J. W. WALKER
W. MAYER-GROSS.
Department of Clinical Research,
Crichton Royal, Dumfries.

HEXAMETHONIUM COMPOUNDS IN HYPERTENSION

SIR,—Dr. Blainey[1] concludes that "the hexamethonium compounds had not greatly lowered the basal blood-pressures," the basal blood-pressure being defined earlier on as that recorded in the morning before the patient rose. Moreover we are told that no night treatment was given.

It has been my experience, and that of others, that the hypotensive effect of hexamethonium lasts but a few hours (3–6), and it is only to be expected that no effect on the morning blood-pressure would be detectable.

Although it appears scientifically neat to put patients to bed for some time to assess the "true" level of their blood-pressure, what exactly are we proving? Merely that most hypertensives until a fairly late stage have labile blood-pressures. Surely we must regard as their real blood-pressure the figure with which they meet their daily problems, including a visit to the doctor, and not try to determine what nadir can be reached by subanæsthetic doses of drugs, as this figure gives us a false low level on which to base our studies. A few minutes' rest and reassurance in the consulting-room should be the basis for estimating pressures before and during treatment. It is important that at each visit the reading should be taken at the same time relative to the taking of the hexamethonium.

Bondi Junction,
New South Wales, Australia.
Z. FREEMAN.

SUCCINYLCHOLINE

SIR,—After reading the article by Dr. Evans and his colleagues (June 21) I should like to report on a case of protracted paralysis following the use of succinylcholine for closing the abdomen after an appendicectomy.

The patient was a woman, aged 56, weight 12 st., with no history of previous illness and who appeared to be perfectly healthy on preoperative examination. Pulse-rate 86 per min. Blood-pressure 140/85 mm. Hg.

11 A.M.—Anæsthesia was induced with 0·5 g. sodium thiopentone and 2 ml. gallamine triethiodide and continued with nitrous oxide, oxygen, and trichlorethylene. There was only momentary apnœa following the administration of the gallamine triethiodide.

11.25 A.M.—The appendix had been removed and for closing the abdomen, as relaxation was not adequate, 50 mg. of succinylcholine was given and the patient's lungs inflated with oxygen. There was immediate apnœa, which lasted 5 minutes.

11.30 A.M.—Respirations recommenced, 6 per min., shallow, and jerky.

11.35 A.M.—Respirations ceased completely.

11.40 A.M.—Operation completed. Artificial respiration continued. Pulse-rate 80. Blood-pressure 140/85, as at commencement of operation.

12 NOON.—Neostigmine 1·5 mg., atropine gr. 1/100 given intravenously with no effect.

12.15 P.M.—Picrotoxin given intravenously.

Artificial respiration was carried on during the afternoon.

6 P.M. (6½ hr. after the administration of succinylcholine).—The patient started to breathe in a spasmodic jerky manner, 5 per min.

7 P.M.—Respirations were re-established at 16 per min. Pulse and blood-pressure unchanged. Patient remained unconscious. Endotracheal tube was removed.

7.30 P.M.—Blood-pressure 80/40. Pulse-rate now 110. Respirations 18 per min. 'Methedrine' 15 mg. given intravenously.

8 P.M.—Blood-pressure 120/85. Pulse-rate 90.

8.15 P.M.—Patient transferred to the ward. Respirations 18 per min.

9 P.M.—Pupils reacted to light, equal.

9.15 P.M.—Movement of arms and legs when stimulated.

9.45 P.M.—Patient able to talk and move without difficulty.

The patient's general condition was excellent until 7 days later when her abdominal wound burst. On this occasion the anæsthetic consisted of 0·25 g. thiopentone, nitrous oxide, oxygen, and ether, from which she made an uninterrupted recovery.

This patient may have had a low serum-esterase, and the duration of apnœa was doubtless prolonged by the neostigmine which was given, although this was only given 35 min. after the administration of the succinylcholine. It is, however, difficult to explain the fact that shallow, jerky respiration at a rate of 6 per min. did commence 5 minutes after the dose of succinylcholine only to stop completely at the end of a further 5 minutes and spontaneous respirations did not return until 6 hours later.

This case occurred 3 months ago, and since then succinylcholine has been used in this hospital for abdominal relaxation without further trouble.

South London Hospital for Women and
Children, S.W.4.
M. L. MACKAY
Anæsthetic Registrar.

CONTROLLED HYPOTENSION

SIR,—I do not think your leading article of July 5 exhibits that high standard of impartiality which I have come to expect from THE LANCET. Thus I was surprised to find the work of Dr. Mackinnon cited in support of an impaired renal circulation during hypotensive anæsthesia, for such work is obviously of doubtful significance when applied to the anæsthetised patient. At the same time no mention whatever is made of the work of Miles et al.[1] who presented irreproachable evidence that a controlled hypotension induced by pentamethonium did not reduce the renal blood-flow in the anæsthetised patient. The observations of Dr. Bromage on macroscopic liver changes only support the contention, so often stated, that a pressure of 55–65 mm. Hg should be considered a minimum for this technique. These two papers do not provide evidence on which to base a criticism of this technique. Their information will help to produce at some future date a balanced and critical evaluation.

On the other hand, many will agree with you in accusing anæsthetists of using this technique on unsuitable patients, often with no adequate supervision of the induced hypotension. Such errors of technique and judgment have been responsible for many of the ill effects observed. A *controlled* hypotension practised strictly within the limits outlined by various workers[2] is a safe procedure.

No responsible anæsthetist will deny the difficulties of a controlled hypotension in certain patients. They realise that the technique demands constant care and attention to maintain safety. The hard work which this entails is forthcoming not because controlled hypotension is regarded as "modern" or "progressive," but because the patient receives benefits which are unobtainable by any other means.

London, W.1.
G. E. HALE ENDERBY.

SIR,—I would like to reply to Dr. Saunders's letter (July 5).

He implies that cerebral blood-flow is not reduced because the cerebral vasodilatation very nearly compensates for the fall in arterial pressure. If it is taken for

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[1] Blainey, J. D. *Lancet*, 1952, i, 993.

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[1] Miles, B. E., de Wardener, H. E., Churchill-Davidson, H. C., Wylie, W. D. *Clin. Sci.* 1952, 11, 73.
[2] Griffiths, H. W. C., Gillies, J. *Anæsthesia*, 1948, 3, 134. Shackleton, R. P. W. *Brit. med. J.* 1951, i, 1054. Enderby, G. E. H. *Proc. R. Soc. Med.* 1951, 44, 829. Enderby, G. E. H., Pelmore, J. F. *Lancet*, 1951, i, 663.

granted that the same level of anæsthesia is maintained throughout, and therefore oxygen consumption by the brain is unchanged and the arterial oxygen saturation unchanged, then the above deduction is correct. However, the vascular supply of the brain has not been sufficiently explored to ensure that without doubt there is no alteration in vascular dynamics, such as, for example, an arterial shunt mechanism. If this were so the oxygen uptake by the brain could conceivably diminish with hypotension and mental deterioration take place without any change in cerebral venous oxygen content.

If we assume that there is no difference in cerebral oxygen metabolism (which cannot be measured unless total cerebral blood-flow is known) during hypotension, then, provided there is sufficient vasodilatation to compensate for the reduction in flow, cerebral functional activity will be unchanged; but once the limit of this type of compensation has been reached and the oxygen uptake by the brain falls, then cerebral anoxia will ensue. This critical level of hypotension will obviously vary with the amount of vasodilatation each individual is capable of, and is a factor difficult to assess before operation.

My experience is not entirely in agreement with Dr. Saunders's in that I have found a significant reduction in cerebral blood-oxygen under similar conditions. This work is not complete and certainly does not yet justify any firm conclusions.

Department of Anæsthesia,
University of Liverpool.

GOUGH HUGHES.

COOLEY'S ANÆMIA

SIR,—Dr. Choremis (July 5) states that he believes that "there is probably an ætiological relation between malaria and Cooley's anæmia."

One can accept this possibility in areas where malaria and Mediterranean anæmia coexist—for example, Italy. However, in New Haven, Connecticut, U.S.A., where there is a large population of Italian origin, Cooley's anæmia is not rare. The disease may be seen in second-generation Americans of Mediterranean origin, whilst malaria, on the other hand, is extremely uncommon. In these cases, it would be difficult to postulate any relationship between the two diseases. Incidentally, in these cases of Mediterranean anæmia in America the mongoloid facies were seen fairly often.

Cardiff.

B. H. BASS.

POSTS FOR TRAINEE PATHOLOGISTS IN THE U.S.A.

SIR,—An acquaintanceship with physicians in your country has made it possible for me to place several young British doctors as trainees in American hospital laboratories. Requests from both sides of the Atlantic have increased in number, and I am now attempting to enlarge the exchange service which, I must emphasise, is completely unofficial. The members of the Horse Shoe Club, which has graciously admitted me to its honorary membership, will assist by screening, by interview, the English applicants; the club, of course, can assume no financial or other responsibility.

Should any of your readers seek trainee positions in laboratory medicine, they may write to me giving full particulars about themselves, and stating any geographical preferences in the States. I shall then endeavour to suit American laboratory and English candidate. It should be understood that the Horse Shoe Club is not to be addressed by the applicant.

At a time when coöperation between our countries is of such great importance, medical exchanges can play an important rôle.

Department of Pathology,
Saint Joseph Hospital,
Fort Wayne, 2, Indiana, U.S.A.

S. M. RABSON.

SEVERE RUBELLA

SIR,—Rubella is normally such a mild complaint that the following case seems worthy of note.

On July 2 the mother of a boy, aged $3^1/_2$, brought him to me with a slight morbilliform rash on the face, chest, and occipital regions. His temperature was 99°F; there were no Koplik's spots; occipital glands were enlarged. I told her that it was german measles and that she should keep the boy at home for a few days.

On July 5 she telephoned to say that he was very feverish. I found that his temperature was 102°F; there was a little bronchitis; the rash on the face was fading, but was quite bright on both legs. I gave an expectorant.

On July 7 the mother said that the boy had passed no urine for 24 hours. His face was puffy; there were fine crepitations over both bases; and the right eardrum was injected. I gave 'Distaquaine' penicillin 300,000 units. That night he passed 3 oz. of urine, which contained albumin+.

The following day his temperature was 99°F. His general condition was improved, and he passed more urine with only a faint trace of albumin in it. Penicillin was repeated.

On July 9 his temperature was normal, rash gone, and lungs clear. Two days later it was difficult to believe that he had been ill.

London, E.11.

SIDNEY ABRAHAMS.

FUNGUS INFECTIONS OF THE FEET

SIR,—I have read with interest your annotation of June 7 and the subsequent correspondence.

Silver nitrate in 10% aqueous solution, containing 5% rectified spirit, can confidently be recommended for all cases. It will be found especially beneficial in those that have failed to respond to other remedies. One application, followed by exposure of the lesions for a few minutes to direct sunlight, is usually sufficient; but two or three applications at daily intervals are sometimes needed in the tropics.

London, W.6.

ADRIAN V. ADAMS.

PREVENTION OF SEASICKNESS

SIR,—It was hardly fair of Dr. Gay (July 12) to criticise Glaser and Hervey's paper on seasickness,[1] which is too weak to stand up even with the most partisan support.

The rest of us have known since 1949 that some anti-histamine drugs are approximately as effective as hyoscine.[2] [3] If, two years later, Glaser and Hervey were to contribute anything useful they had therefore to make some more exact comparison between what were likely to be active drugs. One of the drugs they decided to compare with hyoscine was 'Phenergan,' preferring the opinion from two uncontrolled investigations[4,5] to that expressed by Chinn et al.,[6] after a carefully controlled trial, that it was one of the less active drugs. As Bethel[7] has already pointed out, they then gave it with such a timing that it could not be effective during the experiment. Similarly, they gave 'Benadryl' in half the dose used by Chinn,[8] whose report they cite.

Dr. Gay has already given his reasons for condemning the timing of the benadryl dosage; and they will find it difficult to defend their trials in rubber boats since it was known to Strickland et al.[9] in 1950 that 'Dramamine' could be ineffective in swing-sickness while active in airsickness.

Christie Hospital,
Manchester.

M. B. MCEVEDY.

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1. Glaser, E. M., Hervey, G. R. *Lancet*, 1951, ii, 749.
2. Gay, L. N., Carliner, P. E. *Bull. Johns Hopk. Hosp.* 1949, 84, no. 5.
3. McEvedy, M. B. *Lancet*, 1949, i, 825.
4. Harper, J. *Ibid*, 1951, i, 1141.
5. Ambrus, J. L., Ambrus, C. M. *Ibid*, 1950, i, 326.
6. Chinn, H. I., Strickland, B. A., Oberst, F. W., Wilks, S. S., Tinkham, M. *J. Aviat. Med.* 1950, 21, 424.
7. Bethel, M. F. *Lancet*, 1951, ii, 888.
8. Chinn, H. I., Noell, W. K., Smith, P. K. *Arch. intern. Med.* 1950, 86, 810.
9. Strickland, B. A. jun., Hahn, G. L., Adler, H. *J. Aviat. Med.* 1950, 21, 90, 163.

ANATOMICAL NOMENCLATURE

SIR,—Professor Johnston's letter (July 5) indicates that British anatomists have at last decided to scrap the Birmingham revised (B.R.) terminology of 1933, which they have unsuccessfully endeavoured to impose on the medical profession in this country. As a student I had to learn two terminologies, known as the "Old and the New" (O.T. and B.N.A.). As a demonstrator I had to teach the B.R. terminology as well to the students, because the examinations were held in this terminology.

Professor Johnston is not proposing an innovation, but a welcome return to the B.N.A. which since 1895, and suitably modified with advance in knowledge, has enabled doctors of various countries to understand each other.

Barnstaple, Devon. MERVYN MOREL.

DIFFERENTIATION OF A.C.T.H. AND INTERMEDIN

SIR,—The observations of Sulman[1] on the colour change produced in *Hyla arborea*, the tree frog, following doses of preparations of A.C.T.H. have led to the contention that A.C.T.H. and intermedin are identical. Johnsson and Högberg[2], using *Rana temporaria*, support this contention. Recently, however, Geshwind et al.[3] have reported finding no correlation between the potency of A.C.T.H. preparations, measured by the ascorbic-acid depleting factor in rats, and the chromatophore response in *Rana pipiens*.

Morris[4] has drawn attention to the fact that A.C.T.H. is known to be rapidly destroyed by treatment with alkali, whereas the effect of intermedin is protected by such treatment; evidence also exists that intermedin and A.C.T.H. may be separated by electrophoretic and other procedures.[5]

Astwood[6] has postulated that different hormones may differently affect variously coloured chromatophores. *Xenopus laevis*, however, which possesses only melanophores, might be expected to give a less ambiguous response than species possessing other chromatophores. It was therefore thought that comparisons of the responses of hyla and xenopus might differentiate between A.C.T.H. and intermedin.

An A.C.T.H. fraction prepared from pig glands was treated by heating to 100°C for 10 minutes with N/10 NaOH, cooling, and neutralising. Treated and untreated material was given to the various test species as shown in the accompanying table.

EFFECT OF A.C.T.H. PREPARATIONS IN RAT, XENOPUS, AND HYLA

Species	Preparation*	Dose	No. of animals	Response	
Rat		*μg. per 100 g.:*		*Adrenal ascorbic acid (mg. per 100 g. tissue)*	
	A	15·0	4	475±15·4	
	B	1·5	4	357±35·0	
	Controls		4	490±28·0	
Xenopus		*μg. per 50 g.:*		*Melanophore index:*	
				1 hr.	*4 hr.*
	A	3·75	4	4·1	4·1
		1·87	4	3·0	2·8
	B	3·75	5	4·1	2·1
		1·87	5	2·7	1·9
	Controls		5	1·4	1·7
Hyla		*μg. per 5 g.:*		*Colour change 30 minutes †*	
	A	10·0	4	4/4	
		5·0	12	10/12	
		2·5	12	2·5/12	
		1·25	4	0·5/4	
	B	1·0	12	10/12	
		0·5	12	3·5/12	

* A = preparation treated with alkali. B = untreated preparation.
† A change to olive green was scored as 1·0, an intermediate change as 0·5.

These experiments show that when the adrenal ascorbic-acid depleting factor was almost completely destroyed by alkali, the potency to the chromatophore response in hyla was diminished about fivefold. On the other hand, the response of xenopus was quantitatively unchanged. The action was, however, prolonged (i.e., "protected") in both species. If the property of expanding the melanophores in xenopus is truly that of intermedin, these results indicate that: (1) hyla responds to both A.C.T.H. and intermedin; and (2) xenopus does not respond to A.C.T.H. and the response to intermedin is not influenced by the presence of A.C.T.H.

Further work is required to confirm whether these two species can reliably distinguish between the two factors in various hormone preparations and in body fluids.

Pharmacological Department,
Crookes Laboratories Ltd., London. J. A. LOCK.

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[1] Sulman, F. G. *Nature, Lond.* 1952, 169, 588; *Lancet*, i, 1161.
[2] Johnsson, S., Högberg, B. *Nature, Lond.* 1952, 169, 286.
[3] Geshwind, I. I., Reinhardt, W. O., Li, C. H. *Ibid*, p. 1061.
[4] Morris, C. J. O. R. *Lancet*, 1952, i, 1210.
[5] Kunkel, H. G., Tiselius, A. *J. gen. physiol.* 1951, 35, 118.
[6] Astwood, E. B. Cited by Stehle, R. L. *Ergebn. Vitamin Hormon-Forsch.* 1938, 1, 114.

PROVISION FOR THE MENTALLY DEFECTIVE

SIR,—Whilst it is possible to sympathise with Dr. Taylor in her difficulties with the parents of "educationally subnormal children," she has surely herself fallen into the very error against which she protests in her letter last week.

It has long been generally agreed that intelligence is distributed amongst the population in a continuous Gaussian curve, though with an actual ascertainment of numbers rather in excess of the theoretical expectation at the extreme lower end. Even so, the ascertainment of mental defectives of the feeble-minded class has been found to correspond very closely to the expected figure.

There is therefore no justification in making any distinction, other than an administrative one, between the "normal," the "educationally subnormal," and the "mentally defective." These three groups are all normal variations within the one human family. It is therefore scientifically incorrect—and, I might be allowed to add, morally shocking—to refer to the "stigma of mental defect." No such stigma exists, except in the minds of the ignorant or the prejudiced.

Those of us who spend our professional lives in the diagnosis, care, and treatment of mental defectiveness are surely entitled to expect that our colleagues should assist us in educating public opinion rather than in perpetuating ignorant prejudices by assuring the parents of "educationally subnormal children" that the "special schools" have nothing to do with "mental deficiency."

If Dr. Taylor doubts my facts, may I respectfully refer her to Prof. L. S. Penrose's *Biology of Mental Defect*?

Brockhall, Langho,
near Blackburn. D. J. ROSE.

BUTAZOLIDINE

SIR,—I am writing to confirm the findings of Dr. Currie and of Dr. Dudley Hart and Dr. Johnson (July 5) with regard to the use of butazolidine which I have administered in four cases.

The first was a woman, aged 45, with rheumatoid arthritis of long standing, without deformity but with swelling of the knees and wrists. She was in considerable pain, but she had had no previous treatment. She was given daily intramuscular injections of 5 ml. of a 20% solution of butazolidine, and the pain was very greatly eased and her general condition improved. A little residual pain was left in her knees but, as in the experience of the Westminster workers, the swelling remained the same.

The second case was a man, aged 52, who had had rheumatoid arthritis since 1933. He had considerable deformity of the elbows, fixation of the wrists, and limitation of movements of the knee. He had considerable pain and great difficulty in getting about. This patient had had much previous experience of therapy, having had many courses of gold, the usual anodynes, Spa treatment, and physiotherapy. He was started on butazolidine in May of this year and given a total of 50 injections (daily). After four days he reported that the pain was greatly eased; and though objectively the movement seemed to be the same, he stated that he had much more. The interest of this case is that the patient, with much previous experience of rheumatism therapy, volunteered that he had been helped by the butazolidine injections more than by earlier treatments.

The third case was a man, aged about 59, with rheumatoid arthritis; and he is still under treatment. He had had gold, physiotherapy, and anodynes, and volunteered that since he has had butazolidine movement has been much easier and that he feels better.

The fourth case has had only ten days' treatment, but the relief is so far the same as in the other three.

I am, of course, aware of the possible fallacies in estimating progress in rheumatoid arthritis; but this very small series includes three different types of case: (*a*) a case not previously treated, (*b*) a long-established case, and (*c*) two that may be termed "middle-grade." All these patients report improvement, and those with previous experience greater improvement than with any other form of treatment. At the moment I do not wish to do more than report these facts.

I am grateful to Pharmaceutical Laboratories Geigy Ltd., for a supply of butazolidine.

London, W.1. GERALD SLOT.

BREAD IN CŒLIAC DISEASE

IN his letter of May 3 (p. 928) Dr. Theodore James remarked that at the Duchess of York Hospital for Babies, Manchester, a diet for children with cœliac disease had been devised in accordance with the views of Dr. W. K. Dicke. This diet, which is free of wheat flour and gluten, includes bread with the following composition: 4 oz. cornflour, 4 oz. riceflour, 2 oz. glucose, 3 level teaspoons baking-powder, $^1/_2$ teaspoon salt, 1 egg, water to mix.

Put all dry ingredients together. Beat egg and add to remainder. Mix to a soft paste with water. Put into greased pie-dish. Bake in hot oven, reg. 7, until set (about 10 min.); then finish at reg. 2, until cooked. Total time about 25 min.

Medicine and the Law

The Prescription of Barbiturates

DURING a recent inquest at Doncaster, Dr. F. G. Tryhorn, director of the Forensic Science Laboratory at Wakefield, told the coroner that three-quarters of the deaths with which the laboratory dealt turned out to be due to phenobarbitone poisoning.

The inquest, reported in the *Manchester Daily Dispatch* (July 2), was upon the death of a widow, 79 years of age, who was said to have left a note stating that she had taken 150 tablets. There was evidence that she had taken at least 120 grains and that about 30 grains would be a fatal dose. A policeman said that he found in her house six boxes containing hundreds of tablets. The coroner expressed the view that there was too much laxity in prescribing the drug. It was prescribed, he thought, for "any sort of trouble" and doctors were often "not strong enough to resist when patients demanded more"; there should be more control. A verdict was returned of suicide while the balance of her mind was disturbed.

At another Doncaster inquest, on a woman of 35 found dead in her bath, Dr. Tryhorn said that there were 15 grains of an unidentified barbiturate in her blood-stream. Though this was a larger amount than would be prescribed, it would not be a suicidal dose. He agreed with the coroner that such drugs should not be taken before having a bath. There being no evidence of suicide, a verdict of death by misadventure was returned. In this case also the coroner commented on the need to control prescription of the drug.

Dr. R. W. L. Ward, secretary of the Doncaster branch of the British Medical Association, subsequently replied to these criticisms when interviewed by a correspondent of the *Yorkshire Post* (July 2). He thought the risk had been somewhat exaggerated. It had been stated at the first of these two inquests that barbiturate drugs were now prescribed as freely as were aspirins twenty or thirty years ago. He could not agree with the statement. These drugs were extensively used in treating high blood-pressure, which was increasingly diagnosed; they were used even more freely in the United States. He was unaware of the circumstances of the particular case, but some patients had to have barbiturate drugs over a very long period. A stock could easily be built up by a patient intent upon suicide.

Parliament

Prescription Charges

IN the House of Commons on July 11, replying to the motion for the adjournment, Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said the difficulties of collecting the shilling charge for prescriptions had been much exaggerated. In the experience of three large London hospitals—the London Hospital, Hammersmith Hospital, and the Royal Free Hospital—only one outpatient had been unable to pay the shilling. There had been a small increase in quantities prescribed, but as the charge had only been in operation for a month she would not like to say the figure was firm. On the limited survey they had been able to make the number of items per form had *risen from 1·57 to 1·7. From an assessment made in* a limited number of areas the falling off in the number of prescriptions seemed to be under 15%.

QUESTION TIME

Hospital Beds for Mental Defectives

Mr. B. R. BRAINE asked the Minister of Health the total number of beds set aside for mental defectives in each hospital region in England and Wales; the number of such beds occupied; and the number of persons awaiting admission, showing, separately, adults and children.—Mr. IAIN MACLEOD replied: The figures are given in the table. Column 2 shows how many beds ought to be provided, on standard, in space available; column 3 shows the number of beds which could be made available if staff could be found for them; this shortage of staff exacerbates the overcrowding; *column 4 shows the number of beds actually in use. The waiting-list figures are taken from returns from local health authorities, whose areas sometimes fall in more than one region; in the latter cases the lists have been apportioned to regions in ratio of the populations of the local authority areas:*

Region	Recognised bed space for mental defectives (2)	Beds in wards not in use (3)	Number of patients occupying beds (4)	Number awaiting admission	
				Adults (5)	Children (6)
Newcastle ..	1733	—	2428	483	425
Leeds.. ..	2892	144	3098	251	250
Sheffield ..	3530	52	3647	700	517
East Anglian	1020	—	1163	261	196
N.W. Met. ..	4648	366	4194	168	373
N.E. Met. ..	2199	—	2721	192	236
S.E. Met. ..	4377	546	3604	155	223
S.W. Met. ..	6318	208	7432	407	238
Oxford ..	1557	17	1523	82	150
South Western	5184	77	5803	98	146
Wales ..	1590	70	1517	699	312
Birmingham	4178	89	5016	134	375
Manchester ..	5923	498	6095	258	342
Liverpool ..	382	67	470	156	240
Total ..	46,431	2134	48,742	4017	4023

Fluorination of Water-supplies

MR. S. P. VIANT asked the Minister of Health which were the interested bodies represented on the mission which had visited the United States of America to examine American investigations into fluorine in water; whether the report of the mission would be made public; and whether the detailed evidence on which they formulated their report would also be published.—Mr. Macleod replied: The members of the mission were Miss Jean Forrest, L.D.S., dental officer, Ministry of Health; Mr. J. Longwell, D.SC., Government chemist's department; Prof. H. H. Stones, M.D., F.D.S. R.C.S., member of the Dental research committee, Medical Research Council; Dr. A. M. Thomson, nutrition research team, department of midwifery, University of Aberdeen. The question of publication will be considered when I have received the mission's report.

Obituary

JAMES OWEN DAVID WADE

O.B.E., M.S. Lond., F.R.C.S.

Mr. James Wade, who died on July 9 at the age of 66, had been senior surgeon at Cardiff Royal Infirmary for ten years, and it was only towards the end of last year that he retired from the active staff.

He began his medical studies in Cardiff and continued them at Charing Cross Hospital, graduating M.B. in 1909. After taking the F.R.C.S. in 1912 and the M.S. in 1913 he returned to Cardiff, where he was soon appointed to the staff of the infirmary. He began to demonstrate anatomy at the University College of South Wales as well as practise surgery. Throughout his life he retained his interest in anatomy, and after he retired he helped in the department of anatomy of the medical school. During the 1914–18 war he was consulting surgeon at the Prince of Wales Hospital for Limbless Soldiers and Sailors in Cardiff, and for this work he was appointed O.B.E.

L. R. writes: "Never in the best of health, 'Jimmy Wade' was none the less a great worker and he never spared himself; indeed many of his friends wondered that he was able to do so much and for so long. He was a good surgeon, in great demand both in Cardiff and the surrounding valleys and travelled much doing long lists of operations in many and various hospitals. A kindly man with a reassuring presence, a pleasant smile, and a cheerful countenance, he was a philosopher in his own way and he persuaded many a young man to give up chasing the *ignes fatui* and seek the substance rather than the shadow. He was a fighter, and would laughingly complain of a cold wind which made him short of breath; and above all he was a splendid family man devoting his life to his wife and sons, one of whom has succeeded him as a surgeon on the staff of the Royal Infirmary, while the three others are members of his and our profession. It was always good to see Jimmy Wade; one was the better for it; and at a time of controversy, which was sometimes heated, and when there was some ill feeling, his detachment and cheerful outlook and confidence in the things that matter, was an encouragement to many."

Births, Marriages, and Deaths

BIRTHS

Heron.—On July 10, at Little Place, Middleton, to Jean (née Bland), wife of Dr. Geoffrey Heron—a son.

Mackintosh.—On July 5, at Dunsfold, Bramhope, near Leeds, to Eileen (née Ormsby Johnson), wife of Dr. F. G. Mackintosh—a daughter.

Nelson.—On July 5, at Stourbridge, to Barbara, wife of Dr. Alastair Nelson—a daughter.

Reeks.—On July 2, at Windermere Nursing Home, Paignton, to Louise (née Atkinson), wife of Dr. J. J. Reeks—a daughter.

MARRIAGES

Hardy—Gosling.—On July 8, at Edgbaston, Hugh Nevill Hardy, B.M., to Mary Rose Gosling, of Edgbaston.

Woodmansey—Junor.—On June 30 at Benenden Church, Kent, Arnold Colin Woodmansey, M.D., B.SC., D.P.M., to Faith Junor M.A.O.T.

DEATHS

Atkins.—On July 7, John Francis Atkins, M.B. Birm., of Hove.

Benson.—On July 7, at Morchard-Bishop, Crediton, John Robinson Benson, F.R.C.S., aged 83.

Budden.—On July 4, at Greywell, Hants, Rev. Charles William Budden, M.A., M.D. Vict. Univ., aged 74.

Falkener.—On July 5, Lyon Falkener, M.A., M.D. Camb., D.P.H., of La Marette, Guernsey, aged 85.

Hulbert.—On July 4, in Ealing, Ernest Beddoe Hulbert, M.D. Durh.

Kirkpatrick-Picard.—On July 10, at Burgess Hill, Sussex, Arthur William Kirkpatrick-Picard, M.D. Lond., aged 83.

MacLaren.—On July 8, at Odstock Hospital, Salisbury, James Alexander MacLaren, M.D. Manc., aged 82.

Diary of the Week

JULY 20 TO 26

Tuesday, 22nd

Royal College of Surgeons, Lincoln's Inn Fields, W.C.2
4 P.M. Prof. R. R. Macintosh: Anæsthesia in Dental Surgery. (International Dental Congress lecture.)

Wednesday, 23rd

Institute of Psychiatry, Maudsley Hospital, Denmark Hill, S.E.5
8.15 P.M. Dr. Harold G. Wolff (New York): Headache Mechanisms.

Thursday, 24th

Royal College of Surgeons
4 P.M. Dr. W. S. McConnell: General Anæsthesia in the Dental Chair. (International Dental Congress lecture.)

Friday, 25th

Medical Society for the Study of Venereal Diseases, 11, Chandos Street, W.1
7.30 P.M. Dr. R. A. Nelson: Changing Concepts in the Serological Diagnosis of Syphilis—Wassermann Reagin Versus Specific Treponemal Antibody.

Saturday, 26th

Medical Society for the Study of Venereal Diseases
2.30 P.M. (St. Mary's Hospital, Paddington, W.2.) Dr. Herman Beerman (University of Pennsylvania): Cardiovascular Syphilis.

Appointments

Beech, John, M.B. Sheff., D.M.R.: asst. radiotherapist, radiotherapy centre, Derbyshire Royal Infirmary.

Blair, J. D., M.B., B.SC. Glasg., D.A.: asst. anæsthetist, Grimsby General Hospital, and Louth County Infirmary.

Durkin, Sheila, M.B. Aberd., D.P.H.: asst. M.O.H. and asst. school M.O., Smethwick.

Knowlson, Lydia, M.D. Leeds, D.P.H., D.C.H.: senior M.O. for maternity and child welfare for Monmouthshire.

Colonial Service:

Ahearne, Mary, M.B. N.U.I.: M.O., Nigeria.
Alvares, R. E., M.B. Hong-Kong: pathologist, Hong-Kong.
Barman, D., M.B.: M.O., Malaya.
Bryson, A. F., M.B. Camb., F.R.C.S.: senior orthopædic specialist, Nigeria.
Coghlan, C. T., M.B.: M.O. (anæsthetist), Kenya.
Gilchrist, K. J., M.B. Lond., F.R.C.S.: surgeon specialist, Fiji.
Griffiths, P. G., M.C., M.B. Manc., M.R.C.P., F.R.F.P.S.: physician specialist, Malaya.
Hing, E. W. Lou-, L.R.F.P.S.: M.O. (Grade C), Trinidad.
Hoar, C. E. W., M.B. Lond., D.C.P.: pathologist, Uganda.
Joly, J. S., M.B. Camb., F.R.C.S.: surgeon specialist, Trinidad.
Keeley, Russell, M.B.: M.O., Malaya.
Khaira, B. S., M.B.: M.O., Malaya.
Kraszewski, T. M., M.B., Polish School of Medicine, Edin.: M.O., Sarawak.
Mackie, J. B., M.B. Edin., D.P.H., D.T.M.: senior specialist, Hong-Kong.
Ndukwe, D. O., L.R.C.P.I., D.P.H.: M.O.H., Nigeria.
Richardson, R. K., M.R.C.P.: senior physician, British Guiana.
Slawinski, Karol, M.D. Beirut: M.O., Malaya.
Taylor, J. M., M.B.: M.O., Malaya.
Twomey, John, M.B. N.U.I.: M.O., Somaliland Protectorate.
Wilkinson, P. B., M.B. Lond., M.R.C.P.: senior specialist, Hong-Kong.

South-East Metropolitan Regional Hospital Board:

Cowie, T. N., M.D., B.SC. Glasg., D.M.R.D.: consultant radiologist, Woolwich, Greenwich, and Deptford group.
Ross, D. F., M.B. Aberd., D.M.R.D.: consultant radiologist, Hastings group.
Stamp, G. F., M.B. Birm.: asst. physician (geriatric services), Orpington and Sevenoaks, and Bromley group.

The Hospital for Sick Children, Great Ormond Street, London:

Batten, R. L., M.R.C.S.: house-surgeon.
Davies, H. E. F., M.B., B.SC. Lond.: house-physician.
Davies, O. W., M.B. Lond.: house-surgeon.
Dobson, J. R. E., M.B. N.Z., D.P.M.: part-time registrar to the department of psychological medicine.
McRobert, Catherine, M.B. Madras: asst. resident M.O., Tadworth Court.
Wells, Joan, M.D. Lond., M.R.C.P.: house-physician.

Welsh Regional Hospital Board:

Bevan, Beryl, M.B., B.SC. Wales: asst. M.O. (S.H.M.O.), Blood Transfusion Service, Cardiff.
Recht, W. C., M.D. Prague, F.R.C.S.E.: asst. orthopædic surgeon (S.H.M.O.), Newport and East Monmouthshire H.M.C.
Stephens, B. J., M.D. Lond.: consultant pathologist, St. David's Hospital, Cardiff.
Wowkonowicz, C., M.B., D.M.R.D.: asst. radiologist (S.H.M.O.), Caernarvon and Anglesey H.M.C.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

AN INTERNATIONAL SEMINAR ON MENTAL HEALTH

CLOUDY and speculative as much of our information must be, as yet, on the development of the mind and emotions, we have begun to master some of the key patterns in early behaviour and to find some practical rules for promoting mental well-being and avoiding gross emotional harm to the infant and young child. Some of this knowledge could be used at once if it were widely enough disseminated, and the World Federation for Mental Health have long been considering effective ways of spreading it.

As an experiment, this year, they are holding an international seminar on "Mental Health and Infant Development" at the Bishop Otter Training College, Chichester, from July 10 to Aug. 10. This will be a pilot run for future seminars, and is perhaps the forerunner of one, or even several, international institutes with continuous programmes of research and education.

Many national and international bodies have contributed generously to the expenses of this initial project, and the World Health Organisation, through its European regional office, has awarded fellowships to enable 38 Europeans to attend, and has offered technical services up to a value of over £3000. Through its other offices it is helping fellows to attend from other parts of the world. UNESCO, the National Advisory Mental Health Council of the U.S. Public Health Service, the International Children's Centre of Paris, and the Grant Foundation of New York have all given generous help.

Both the participants and the faculty will be learning from this new venture; but the faculty, a distinguished body of psychiatrists, psychologists, anthropologists, pædiatricians, and public-health and psychiatric social workers, will be there to share their experience with others and join in a group experiment in techniques of learning. The programme will cover child development patterns, comparative studies of case-material in North America, Great Britain, and France, and their relation to similar material in less developed countries, and the practical application of these studies.

CAR-DRIVERS WITH DEFECTIVE VISION

THE council of the Faculty of Ophthalmologists has issued a statement urging doctors to keep in mind the danger of visual disabilities in people driving motor vehicles. The statement continues: "Although the legal restrictions for driving refer only to defects in central vision there are potential dangers in other visual defects, such as night blindness and gross restriction of the visual fields. Patients suffering from such defects should either be warned about the need for care in driving, or (if the defect is serious) they should be emphatically advised not to drive at all."

RESEARCH IN DAIRYING

MUCH of the work at the National Institute for Research in Dairying is of interest to those concerned with health and disease in man. Much of it, too, is fundamental. A foreword to the report for 1951[1] observes: "This is the result of a deliberate policy, since it has been found, in practice, that if the whole of the time of a research department is given to the solution of urgent technological problems and no time is given to fundamental ones, that department tends to lose touch with new developments of scientific thought, and lags behind in the application of modern research methods and devices. As a result its ability to tackle even the *ad hoc* problems of the industry tends to diminish."

Nevertheless the report deals partly with work of immediate practical importance. Thus feeding experiments have confirmed that pigs reared indoors benefit from the addition to their diet of a small quantity of liver extract, and that, irrespective of treatment, animals reared out of doors grow better than those reared indoors. Evidence has been gathered, too, that for fattening pigs fed on a basal diet containing white fish meal, supplementary aureomycin mash, aureomycin itself, or penicillin promotes growth slightly; and when the basal diet is restricted to vegetable protein only, the addition of antibiotics and antibiotic residues enhances growth considerably—at least to the level obtained with a diet containing animal protein but no antibiotic. From studies of the œstrogen content of grassland herbage, undertaken in conjunction with the Courtauld Institute of Biochemistry, Middlesex Hospital, London, it now seems that plants contain more than one such active substance. The possibility that the œstrogen in leaf is associated with chloroplasts and that another œstrogen is associated with the more widespread cytoplasmic protein is being explored.

A NEW LEEDS JOURNAL

THE first issue of the *University of Leeds Medical Journal* contains an impressive group of articles on tuberculosis. In the first of them Dr. F. Ridehalgh ascribes the reduction of the tuberculosis death-rate during the past century mainly to social legislation and changes rather than medical care; but he believes that effective diagnosis, better case-finding, the development of antibiotics, and efficient units of thoracic medicine and surgery should accelerate the decline in mortality, and he lays stress on the need for proper support of the family in which the breadwinner falls ill. "Any measure," he says, "which maintains the standard of health and nutriment of a tuberculous family will ultimately be reflected in a fall in the total number of cases of tuberculosis." Other articles deal ably with the early diagnosis of phthisis, tuberculosis in childhood, radiological appearances, bone and joint tuberculosis, tuberculosis of the skin and glands, tuberculous meningitis, the surgery of pulmonary tuberculosis, sanatorium treatment, and the treatment of tuberculosis of the genito-urinary tract. Such an ambitious and capable first issue bodes well for the future, and we wish the new journal success. It is the lineal descendant of the *University of Leeds Medical Society Magazine*, by way of the *University of Leeds Medical Magazine*. From 1931 onwards these, like the tuberculous family, in turn strove with financial hardship and somehow managed to carry on. The stock is evidently tough.

BUCKSTON BROWNE DINNER

AT the Buckston Browne dinner, held at the Royal College of Surgeons of England on July 8, Miss Patricia Hornsby-Smith, in proposing the toast of The College, thanked her hosts for the help which the college had given the Ministry of Health in developing the National Health Service. The college, she continued, had been largely built by the faith of the medical profession, and many of the new consultants in the National Health Service owed their skill to facilities provided by endowments such as that provided by the patron of the evening, Buckston Browne. Through the generosity and foresight of past surgeons the college was today able to sustain new advances in its specialty. It had always shown itself ready to move with the times, and in particular it had constantly fostered imperial ties in surgery. Today Lincoln's Inn Fields was famous as a scientific and social centre of surgery throughout the whole world.

Sir Cecil Wakeley, F.R.C.S., began his reply by congratulating Buckston Browne's son-in-law, Sir Hugh Lett, on the jubilee of his fellowship. Turning to the customary annual presidential review he said that the most important event of the year had been the acceptance by Her Majesty the Queen (when Princess Elizabeth) of the honorary fellowship. The rebuilding of the college had started, and the erection of the first steel work was due to begin next month. The college was grateful to all subscribers to the restoration fund, not least to Sir Montague Burton, the most generous of its recent donors. But finance, Sir Cecil confessed, was an uneasy subject; for the college, like most institutions of its kind, suffered from a chronic difficulty in making ends meet. Indeed unless a substantial new source of income were found ends would be a long way apart when there was need to maintain buildings about twice the size of the present ones. With this difficulty in mind the council was seriously considering levying an annual subscription from all new fellows admitted in future. But the college, he ended, continued "mindful of tradition and the lessons of the past, lively in the affairs of the present, and poised alert on the springboard of further endeavour."

Mr. P. H. Mitchiner, the senior vice-president, welcomed The Guests to an occasion which he said their founder had insisted should be a family party. Mr. Justice Danckwerts, though he explained that as a Chancery Judge he was not supposed to know much about life, replied urbanely for his fellow guests and himself.

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[1] University of Reading. National Institute for Research in Dairying: Report, 1951. Published by the Institute, Shinfield, near Reading. Pp. 125. 3s.

University of London

At a recent examination for the academic postgraduate diploma in bacteriology the following were successful:

A. J. Beale, Aleck Bernstein, Svarna Lata Bhatia, Catherine M. P. Bradstreet, J. G. Brotherston, E. R. N. Cooke, Minnie K. Herring, Ma Hpay, M. H. Hughes, E. M. Mackay-Scollay, P. G. Mann, Kazi Abul Monsur, W. R. Parry, D. J. Ross, J. M. Talbot.

University of Liverpool

At recent examinations the following were successful:

M.D.—N. J. Gourdji, Helen T. Morgan, G. R. Wadsworth, D. C. Watson, A. S. Whitehead.

Final examination for M.B., Ch.B.—D. W. B. Woolven (first-class honours), R. J. Fallon, Irene M. Irving, W. G. Lamberd (second-class honours); Margaret M. Ashcroft, A. C. Beeby, F. Berry, A. S. Binnie, J. S. Birch, Elizabeth Bownass, N. H. Brodie, J. M. Brown, J. W. Brown, T. Bury, E. P. Carrigan, D. A. P. Cooke, W. E. Cooper, G. Corney, Enid C. Davies, J. C. Denmark, A. J. Entwistle, R. H. Fitzgerald, W. D. Fitzsimons, Mary I. Gibbons, A. E. Goetzee, L. V. Gould, K. Grainger, P. W. Green, S. J. Hargreaves, F. B. Hartley, Margaret H. Hellaby, N. St. J. Hennessy, Barbara M. Hitch, S. H. Hoddes, J. Hogan, R. P. Hoskinson, E. M. Hughes, G. Ingram, Brenda Jones, Winifred E. Jones, P. P. Keith, Jean Knowles, A. M. Laylee, D. G. G. McLeish, Maureen E. Murphy, A. Nixon, G. Park, F. P. Peach, G. C. S. Roberts, V. Rogers, H. G. Row, A. Sandieson, A. C. Saunders, S. J. Surtees, T. E. Tasker, P. G. Vivian, E. S. Watkins, W. A. Weston, A. H. Wilde, Mary P. K. Williams, P. H. Wright.

D.P.H.—M. S. Boparai, D. Brabott, J. L. Cotton, Angelika Haider, Hla Han, Na Ayudhia V. Israngura, N. N. Kanyarutoke, A. R. Kennedy, E. Lutfi, Lillie L. Munro, R. C. O'Gray, W. H. Parry, E. F. W. Richards, T. A. J. Thorpe, K. O. Torgersen, P. H. Waage.

D.M.R.-D.—F. G. Anderson, W. E. C. Astle, E. Walker, J. K. Walker.

University of Sheffield

Dr. E. H. Gillespie has been appointed honorary lecturer in bacteriology, and Dr. I. J. MacQueen and Dr. R. S. Sneath demonstrators in anatomy.

University of Glasgow

On July 5 the following degrees were conferred:

M.D.—T. D. V. Lawrie, Nanette H. Nisbet, and J. G. Stevenson (with high commendation); John Harkness and I. W. MacPhee (with commendation); John Simpson.

M.B., Ch.B.—J. H. Adams, T. G. Anderson, R. L. Andrews, T. W. Baillie, I. A. Bowie, K. D. Boyd, Marion S. Boyd, T. I. Boyd, R. T. Boyle, Janet C. Brash, P. I. Brown, W. M. Buchanan, A. I. Burleigh, Thomas Cairns, A. R. Cameron, Donald Campbell, E. C. Campbell, Roderick Campbell, W. M. Campbell, A. C. Cattanach, Denis Cavanagh, Thomas Chalmers, Thomas Christie, Henry Church, W. G. Clark, J. G. Clarkson, John Cleat, Anne M. Cormack, T. C. Coyle, John Diamond, Elspeth S. Dickie, J. D. Dickson, T. H. P. Dippie, J. R. Donald, J. M. Dubé, H. L. Duthie, Carl Edwards, J. R. Evans, J. S. Ferguson, J. A. L. Finch, G. S. Findlay, J. S. Findlay, D. H. Finlayson, D. J. B. Fletcher, N. C. Frame, W. T. Frame, G. A. Garrick, A. B. N. Gilfedder, David Glover, A. G. Graham, T. D. Grant, Sheila C. Gray, W. M. Gray, A. B. Gwan-Nulla, K. H. Haddow, T. G. Haddow, Isabel W. Haldane, William Hamilton, Sheila C. A. Stewart, D. Y. M. Hart, W. M. Hay, P. J. Hilley, Doreen L. Ireland, Arthur Jamieson, G. M. Johnstone, D. L. B. H. Jones, Herbert Kay, Denis Keown, W. G. Kilpatrick, D. M. Kirkwood, T. D. Lightbody, W. J. Lockie, Marjorie C. E. MacBeath, I. N. McCulloch, John McDonald, W. M. McFarlan, William McIntosh, Margaret Macintyre, J. R. McIver, Jean M. MacKay, G. B. McKelvie, A. M. MacKenzie, A. F. F. McLean, E. S. MacLean, J. W. McLellan, K. K. MacLeod, James McMichael, R. M. Macneill, G. P. McNicol, F. T. MacVicar, H. K. Mason, Sheila M. Y. Maxwell, P. E. Michaelides, J. B. Mitchell, J. H. Mitchell, W. C. Moffat, D. D. Moir, Donald Montgomery, Sasha R. Morris, M. S. Muir, I. P. C. Murray, George Neilson, D. H. Nimmo, Helen B. O'Hea, A. M. Orcharton, S. H. R. Palmer, Thomas Park, Ian Paterson, John Rankin, Ruth I. Rankin, Robert Rankine, M.A., I. O. Roxburgh, J. S. Roxburgh, James Ruffell, I. S. Scott, K. B. Scott, Ralph Shulman, J. A. Smith, R. A. Stark, Margaret P. D. Steen, W. A. Stevenson, I. G. Stewart, J. G. Stewart, R. C. Taylor, Ann R. Templeton, James Terendale, Anne C. E. Thompson, Mary F. Thomson, G. C. Timbury, A. P. Walker, F. C. Walker, W. H. R. Waters, J. R. Watson, W. A. K. Weir, J. W. Whitelaw, B. F. Whiteley, Christian F. Whyte, A. C. Wilson, Audrey M. S. Wilson, D. G. Wilson, William Wilson, H. L. C. Young, J. M. H. Young.

At a recent examination for the D.P.H. the following were successful:

Elspeth V. Beveridge, J. M. Boyd, D. H. Cawith, Mary E. Hamilton, J. H. Henderson, Ella Macdonald, Max Park, J. J. Prag, H. K. Rose, Hope B. T. Scott, A. G. Sked, W. D. Wilson.

National University of Ireland

On July 8 honorary degrees were conferred on medical men as follows:

LL.D.—Prof. E. P. McLoughlin, Dr. A. W. S. Sichel, Prof. Edward Keenan, Prof. Charles O'Malley.

D.Lit.—Mr. William Doolin, Senator Henry Barniville.

D.Sc.—Sir Henry Cohen (in absentia), Sir John Parkinson, Prof. Stephen Shea, Prof. James O'Donovan.

M.D.—Major P. J. Delaney, Sir Stewart Duke-Elder, Sir John McNie, Dr. Angus Macrae, Prof. Patrick Kiely, Dr. Francis Lavery, Prof. Henry Moore, Prof. John McGrath.

M.D.S.—Prof. James O'Connor.

University of Leeds

Dr. C. L. Oakley has been appointed to the Brotherton chair of bacteriology in succession to Prof. J. W. McLeod who is retiring.

Dr. Oakley, who was born in 1907, graduated in medicine from University College Hospital, London, and in science from Chelsea Polytechnic in 1930. During the next three years he was Graham scholar at University College Hospital Medical School where he studied liver pathology and the regulation of marrow activity. In 1933 he took his M.D., and the following year he was appointed experimental pathologist at the Wellcome Research Laboratories at Beckenham, where he did work on virus diseases. Later with Dr. G. H. Warrack and others he turned his attention to the soluble antigens of the pathogenic clostridia. During the late war he was in charge of a subsidiary unit of the Beckenham Laboratories which produced antitoxins for the Army. In 1947 Dr. Oakley became head of the immunology and experimental pathology department at Beckenham. He was elected a fellow of University College in 1950. In his most recent work on the sites of origin of antibodies he has demonstrated that, in rabbits, injection of alum-precipitated diphtheria or tetanus toxoid into skin, fat, or muscle leads to local production of specific antitoxin.

Royal College of Surgeons of England

At a meeting of the council held on July 10, Sir Cecil Wakeley was re-elected president for the ensuing year. Sir James Paterson Ross and Sir Reginald Watson-Jones were elected vice-presidents. Sir Clement Price Thomas, Mr. C. Naunton Morgan, Mr. Hedley Atkins, and Mr. Myles Formby were admitted as members of the council, and Dr. O. C. Carter (representing general practice) and Dr. Bernard Johnson (representing anæsthetics) were coöpted to the council for 1952–53.

Mr. F. McGuckin (Newcastle) was admitted to the fellowship ad eundem, and Mr. A. J. Boase (Uganda) as a member of 20 years' standing.

Prof. Gilbert Causey was admitted as the Sir William Collins professor of human and comparative anatomy. Dr. D. R. Lucas was appointed research pathologist to the ophthalmological research unit. A Macloghlin scholarship was awarded to Brian Greenwood of Halifax.

The following lecturers were appointed:

Hunterian professorships.—Prof. Naguib Makar Bey, Pathogenesis of Cancer in the Bilharzial Bladder; Mr. Terence Cawthorne, Surgery of the Temporal Bone; Mr. Wilfred Hynes, Pharyngoplasty by Muscle Transplantation in Failed Cleft Palate Cases; Mr. R. F. Phillips, Neuroblastoma; Mr. K. W. Starr, Acute Postoperative Dilatation of the Stomach; Mr. Rodney Smith, Pancreatic Neoplasms; Mr. J. E. Richardson, Early Renal Symptoms of Parathyroid Tumour; Mr. James Moroney, Colonic Replacement and Restoration of the Human Stomach; Mr. J. B. Wyman, Use of Pentamethonium and Hexamethonium Salts in Major Surgery; Mr. Douglas Jackson, Burns; Mr. G. K. Tutton, Cerebral Abscess; Mr. H. H. G. Eastcott, Arterial Grafting for the Ischæmic Lower Limb; Mr. S. S. Rose, Cases of Recurrent Swellings of the Salivary Glands; Mr. F. A. Henley, Gastrectomy with Replacement; Surgeon Commander Frank Ellis; Mr. Paul Brand.

Arris and Gale lecturers.—Mr. Cedric J. Longland, Collateral Arterial Circulation in the Limb; Mr. A. A. G. Lewis, Control of the Excretion of Water by the Human Kidney; Mr. H. F. Lunn, High Ligation of the Neck of the Sac in Inguinal Hernia; Mr. L. P. Le Quesne, Water and Electrolyte Administration during the Postoperative Period.

Erasmus Wilson demonstrators.—Mr. Philip H. Mitchiner; Dr. L. W. Proger, Dr. Magnus Haines.

Arnott demonstrators.—Mr. Mitchiner; Prof. Lambert C. Rogers Mr. Frank Stansfield; Prof. R. J. Last.

The following diplomas were granted, jointly with the Royal College of Physicians:

D.L.O.—A. G. Ackerley, E. C. Atkinson, Sushil Chandra Banerji, J. S. Brown, B. W. M. Bushell, P. P. Clifford, Frank Fleming, A. W. Halfhide, Savitri Itchhaporia, H. B. Juby, Kershaw Burjor Khambatta, E. H. Ross, G. E. Rousseaux, P. R. McH. Scales, Rama Heramb Prasad Sinha, T. C. Taylor, P. H. Wood.

D.P.M.—J. S. Dawson, Aleck Folkson, David Glendinning, Nest Kahan, G. A. Levinson, G. S. Mansell, Hyman Rosenberg.

D.A.—R. J. H. Hodges.

D.T.M. & H.—H. P. M. Perera, R. T. Scholes.

Royal Australasian College of Physicians

At the annual meeting of the college held in Adelaide in May, 1952, with Dr. Alex Murphy, the president, in the chair, the following were elected to the fellowship:

C. G. Bayliss, J. H. Colebatch, K. J. Grice, W. E. King.

The following, having satisfied the boards of censors in Australia and New Zealand, were admitted to the membership:

J. L. Allsop, A. L. Anderson, G. E. Bauer, D. A. Ballantyne, B. P. Billington, J. V. Cable, R. G. Dreadon, A. A. Ferris, J. J. Fitzwater, A. J. Goble, C. Gresson, P. F. Hall, D. A. Henderson, K. H. Holdgate, C. W. Howden, J. D. Hunter, I. R. Mackay, T. G. Maddison, J. W. Perry, D. W. Piper, V. E. Sampson, G. Selby, B. C. Sinclair-Smith, I. D. Thomas, A. R. Tink, D. Tomlinson, A. S. Turner, R. H. Vines, C. E. Watson.

The diplomas of F.R.A.C.P. and M.R.A.C.P. have lately been given recognition by the General Medical Council.

Society of Physicians in Wales

This society, which was founded a year ago, held its third meeting at Swansea on June 27 and 28, under the chairmanship of Dr. Esmond Rees. Papers were read by Prof. Harold Scarborough, Dr. J. M. Swithinbank, Dr. Leonard Howells, Dr. Philip Evans, Dr. J. D. Spillane, and Dr. F. L. Dyson. In future, meetings will be held annually, and it is proposed to hold the next in North Wales on June 26 and 27, 1953. The hon. secretary of the society is Dr. Leonard Howells, 71, Cathedral Road, Cardiff.

Congress of Therapeutics

The third International Congress of Therapeutics is to be held in Madrid from Oct. 16 to 18. The main subjects chosen for discussion are Potassium, Massive Hormone Therapy, and Radio-isotopes. The speakers will include Dr. A. S. Macfarlan and Dr. Eric Pochin. Further particulars may be had from the secretariat of the congress, Instituto de Farmacologia, Ciudad Universitaria, Madrid, Spain.

Infantile Paralysis Fellowship

The first welfare conference of the fellowship, which was held in London last month, was attended by delegates from nearly all of the fellowship's 40 branches in the British Isles. The conference was addressed by Mr. Greaves, a local officer of the National Assistance Board, and by Mr. Dalby, a group disablement resettlement officer of the Ministry of Labour. The address of the fellowship is Rugby Chambers, Great James Street, London, W.C.1.

A Conference on Loyalties

At a meeting to be held in Oxford from Aug. 2 to 9 the Present Question Conference, founded in 1945, will discuss Conflicts of Loyalties. The programme may be had from the secretariat at 37, Middleway, London, N.W.11.

A New Antibiotic

The discovery of a new antibiotic, named 'Ilotycin,' has been announced by Messrs. Eli Lilly and Company. This drug, which is still in the experimental stage and is not yet generally released, has a broad spectrum and has proved effective against certain organisms which have developed resistance to penicillin or other antibiotics. It can be given by mouth.

West London Medico-Chirurgical Society

This society held its 61st annual dinner on July 8 in the Drapers Hall. Alderman C. L. Ackroyd, proposing the first toast, said that Mr. B. Sangster Simmonds was not only president of the society but also master of the Drapers' Company, and had been elected to the latter office for a second year—almost a miracle in City circles. Mr. Sangster Simmonds pointed out that the society consisted mainly of practitioners and consultants in the West of London, and on this evening the matron and other members of the nursing staff of the West London Hospital were joining them. The years 1911 and 1948 had certainly not brought Utopia to general practitioners; indeed, the increasing demands of the population had almost overwhelmed them. But he hoped the time was not far off when practitioners would work as part of the organisation of a hospital, with the help of everyone else in that organisation. Mr. G. B. Woodd-Walker, proposing The Guests and Kindred Societies, managed to put all of them in a favourable light. Sir Ernest Pooley, responding, said that the medical profession has passed through difficult times, but he hoped that the working of the National Health Service Act will improve as years go by—given continuous effort by the profession. For the ordinary labouring man the provision of medical care was better than before—though there was still room for improvement. And it was a comfort not to have to pay for it directly. As "one of the oldest Drapers in existence," Sir Ernest recalled that the company had lived on the same site since the days of Henry VIII, and that its remaining garden contained a mulberry tree planted in James I's time and still bearing fruit. Dr. B. T. Parsons-Smith, president of the Hunterian Society, spoke of the features common to the West London and its fellow societies—all of them with their lectures, debates, and discussions (held without formality and with a minimum of ceremony), and their published transactions. Working independently of the National Health Service, these societies maintain, he said, the mastery of their traditions and their destinies.

Royal Institute of Philosophy

Six lectures are to be given at the institute, 14, Gordon Square, London, W.C.1, during the Michaelmas term on Fridays at 5.15 P.M., on Mind and its Place in Nature. Prof. J. Z. Young, F.R.S., is to give the first lecture on Oct. 17, and the other speakers will include Dr. C. G. Phillips and Dr. Macdonald Critchley.

Symposium on Brain Biochemistry

In a symposium on Brain B[illegible]s relation to Mental Disease, held at th[illegible] Bristol, on July 8 and 9, the following took part:

G. B. Ansell and D. Richter (Cardiff); S. P. Bessman, E. C. Layne, and S. Udenfriend (Washington); P. B. Bradley, J. Elkes, and J. B. Finean (Birmingham); J. J. Gordon and M. Reiss (Bristol); C. C. Kratzing, H. McIlwain, R. Rodnight (London); M. Schou (Denmark); H. Waelsch (New York).

Emergency Bed Service

The south western branch of the service at Wimbledon will be closed from 9 P.M. on July 20. The work of this office is being reallocated to the head office at Old Jewry, and the other three branch offices as follows:

The Boroughs of Wandsworth and Battersea will be covered by the head office at Old Jewry (Monarch 3000).

The county borough of Croydon will be covered by the south-eastern branch office at Woolwich (Woolwich 3471).

The remainder of the area will be covered by the western office at Ealing (Ealing 6671).

Recovering Silver from X-ray Films

The means by which something like 500,000 oz. of silver, worth over £150,000, can be recovered from used X-ray film each year, have been indicated to hospital authorities in England and Wales by the Ministry of Health. The silver recovered in this way will be returned to the X-ray film manufacturers to help overcome the shortage of this metal—a dollar import—which is essential in the making of X-ray films.

London County Council

Dr. A. B. Stewart, who is at present a divisional medical officer of health, has been promoted to the post of deputy medical officer of health.

Dr. Stewart, who is 44 years of age, graduated M.B. at the University of St. Andrews in 1931. After holding house-appointments at the Dundee Royal Infirmary he became lecturer and assistant in bacteriology in the medical school. In 1934 he took the D.P.H., and two years later he obtained his M.D. with commendation and was awarded the Rutherford silver medal for his thesis. He held the post of assistant M.O.H. at Tynemouth before he was appointed M.O.H. for Finsbury, and he is now acting M.O.H. for Paddington. His earlier published papers dealt with the identification and activity of streptococci. His later papers have discussed problems of public-health administration such as health centres and local-authority health services.

Prescriptions for Cod-liver Oil and for Glucose

In a circular to executive councils (E.C.L. 51/52) the Ministry of Health says that a number of [illegible] told by executive councils that [illegible] cases where cod-liver oil and malt extract has been prescribed. The Ministry recalls that in its first report (H.M. Stationery Office, 1950) the Joint Subcommittee on the Definition of Drugs recommended that, as a general principle, preparations intended primarily to provide nourishment in established disease should be classed as drugs; and it suggested that cod-liver oil, cod-liver oil and malt, and other vitamin preparations might be regarded as drugs when used, for example, in the treatment of tuberculosis or vitamin deficiency. The circular says that there also seems to have been some confusion over surcharging prescriptions for glucose. The joint subcommittee suggested that glucose, though primarily a food, might be a drug when given, for example, by intravenous injection or as compressed tablets for use by diabetics.

Dr. E. R. A. Merewether, senior medical inspector of factories in the Ministry of Labour, has been appointed medical advisor to the Ministry of Agriculture on medical questions arising out of the use of poisonous substances in agriculture.

The first number of the medical section of the *Bulletin Scientifique Roumain* was published in Paris this year. The bulletin is the organ of the former Rumanian Royal University Foundation of King Carol which has now been reconstituted in Paris. The following are members of the editorial committee: Dr. P. Atanasiu, Dr. J. [illegible]ovici, Prof. C. Levaditi, Prof. N. Metta, [illegible], Prof. P. Sergescu, Dr. T. Stoicoiu. The [illegible] Atanasiu, 6 rue de Val-de-Grâce, Paris, V, [illegible] Broussais, 96 rue Didot, Paris XIV.

AN OUTBREAK OF FEBRILE ILLNESS ASSOCIATED WITH A COXSACKIE VIRUS

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ISOLATION of a Coxsackie virus from the fæces of children with paralysis was first reported by Dalldorf and his co-workers (1948, 1949), and Curnen et al. (1949) isolated a Coxsackie virus from patients with a disease resembling non-paralytic poliomyelitis. Other reports associated these viruses with epidemic pleurodynia and Bornholm disease (Weller et al. 1950, Findlay and Howard 1950) and with a mild febrile illness of three to five days' duration, mainly among children (Huebner et al. 1950, Howitt 1950). Since then strains of Coxsackie virus have been isolated from patients with herpangina, a condition characterised by fever, sore throat, and a vesicular or ulcerative pharyngitis (Huebner et al. 1951, Parrott et al. 1951).

On the basis of the lesions in newborn mice, two groups of virus have been described: group A causes diffuse myositis only, and group B causes cerebral and visceral lesions, with changes in the fat pads and less obvious myositis. In addition immunologically distinct strains of virus occur within the groups.

In human serum both neutralising and complement-fixing antibodies develop in response to invasion by these viruses, and it is thus likely that they can cause illness in man.

We describe here an outbreak, in a semi-closed community, of an illness associated with a group-B strain of Coxsackie virus.

Epidemiological Background

In May, 1951, illness broke out in a residential children's home, established in a mansion in the country a few miles from the outskirts of Coventry, where the children attend either an ordinary school or a nursery school, according to age. All the children in the home and most of the resident staff receive medical attention from one of us (H. K.), who is also the family doctor for many of the local children going to the same schools. No illness appearing clinically identical with that in the children's home was noted in these other children or their families, although, during the same period as the outbreak in the children's home, two types of brief febrile illness, lasting less than a week, were encountered in the district, the one undistinguished by any particular clinical feature and the other accompanied by transient neck rigidity. The illness in more than half the cases in the children's home lasted longer than a week and no neck rigidity was found. At this time another of us (J. F. G.) noted, in another part of the Coventry area, a family outbreak of a similar febrile illness, involving three children: a girl aged 3 years, and boys aged 8 and 10. The girl and the younger boy had febrile illnesses with a maximum temperature of 103°F and lasting for about two days; the elder boy had a febrile illness with a maximum temperature of 105°F, malaise, and headache, and lasting for about ten days.

The children in the residential home, in number just over 60, vary in age from 3 years to 15 and are in three groups—namely, "infants" aged 3–6 years, and separate groups of boys and girls aged 7–15. Each group has separate accommodation for sleeping and dining. Of the staff 11 are resident and 12 non-resident. On May 15, 1951, the foster-mother of the infants and one of her charges, a boy aged 6, sickened. From then until June 1, the main period of the outbreak, no day passed without at least one new case, the greatest number of new cases on any one day being 6. During the first eight days of this period (up to and including May 22) cases arose exclusively in the infant group or in adults associated with that group; on May 23 and thereafter the older children were involved (see figure).

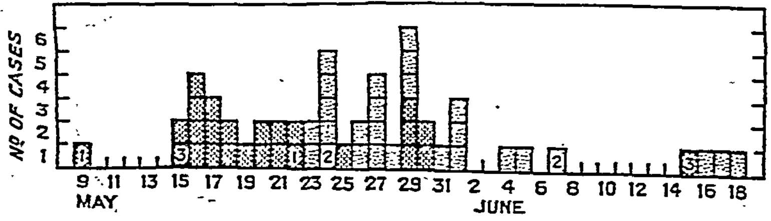
It may be noted that a child aged 4 had become feverish and vomited on May 9; she recovered quickly, however, and no particular significance was attached to this at the time. The child again sickened on May 22, and it is interesting to conjecture whether this second illness was her first attack of the epidemic disease or a relapse. If it was a relapse her illness of May 9 and 10 was the first case in the outbreak, preceding all the others by six days.

TABLE I—AGE AND SEX INCIDENCE

Age-group (yr.)	No. of males in group	No. of males affected	No. of females in group	No. of females affected
3–6	12	12	11	9
7–15	18	9 (1)	22	14
Resident adult staff..	3	0 (1)	9	6
Total	33	21 (2)	42	29

The numerals in parentheses represent cases not mentioned in the clinical notes or in the figure, because detailed records were unavailable.

Two patients who fell sick in the main period of the outbreak relapsed 31 and 14 days after the initial onset (see figure), and other patients had short intermissions of symptoms and signs lasting a day or two. In all, 52 out of 75 residents in the home and possibly 3 of the non-resident staff were affected. The following notes are based on a study of 50 of these cases (including 44 children) for whom detailed records are available.



Time-incidence of cases: *hatched*, Infants aged 3–6 years and 3 adults associated with them; *stippled*, children aged 7–15 years and 2 adults associated with them and 1 kitchen worker. Paired numerals relate to relapses.

Clinical Features

The illness showed a fairly uniform pattern with pyrexia, headache, nuchal pain, repeated vomiting, and vague abdominal pain as the commoner features. The rapid spread involved many children at the same time, and the bedrooms in the home were quickly filled with sick children, who, however, recovered as soon as their temperatures finally settled. No difference in sex-incidence was apparent, but the "infants" appeared to be somewhat more susceptible than the older children and adults, although a high degree of susceptibility was general (table I).

Pyrexia

Pyrexia was present in all cases and started abruptly with a rapid rise of temperature to 101°–102°F with a maximum of about 104°F. There was great variation in the duration of the pyrexia, which could be as brief as two or three days or as long as six weeks. Thus, whereas in 18 cases the temperature settled within seven days, in 12 cases it finally settled between seven and fourteen days and in the remaining 20 cases lasted for more than fourteen days. In the 12 cases of medium duration the temperature after the first days of illness either fell to a lower level, at which it remained until finally settling (5 cases), or else, after a return to normal for about forty-eight hours, recrudesced before final resolution (7 cases). In the longer cases an irregular pyrexia with several sharp peaks was the general finding.

Toxæmia

No patient was so ill as to cause serious anxiety, but in the early stages prostration was noticeable, especially where vomiting was pronounced; after lasting for a few hours or a day it often ended suddenly.

Headache and Nuchal Pain

A *frontal headache*, often unilateral, occurred in all cases, lasted one to three days, and was always a presenting symptom. It was complained of at onset and recurred (as a rule less severely) with any recrudescence of pyrexia.

A fairly severe *nuchal ache* was noted in 34 cases; this too was an early symptom. It did not usually return with a recrudescence. Neck rigidity was carefully sought by three of us but never found. In 2 cases in which lumbar puncture was done the cerebrospinal fluid (C.S.F.) was normal.

Backache was complained of in only 1 case, and limb pains were not of a severity to be especially noted.

Nausea and Vomiting, Diarrhœa, Abdominal Pain

Repeated vomiting, during the first one to three days occurred in 34 cases and was troublesome; in 2 others there was nausea alone. The number of vomits varied from 1 to 8 in twenty-four hours, usually recurring with a recrudescence or relapse.

Diarrhœa occurred in 8 cases—all towards the end of the outbreak. The stools did not contain macroscopic blood or mucus. In 7 of these cases there was vomiting also.

Abdominal pain occurred in 41 cases but was vague, diffuse, and never sharp or severe or a cause of anxiety.

Chest Pain

Pain in the chest was described in 18 cases either at onset or with a recrudescence. It lasted for a day or two and took the form of a "tight" aching sensation in the sternal area. Cough was not complained of, nor were physical signs found in the chest. Of the more prolonged cases, 7 had chest radiographs in the later stages, but the only notable finding was a temporary enlargement of hilar glands in one child. This child and one other had a suggestion of diffuse and light inflammatory change in the right lower zone; both these children had had pain in the chest.

Herpes Simplex

Herpes occurred in 24 cases in the common circumoral position, and ulcerative stomatitis in 2 others. The most pronounced herpes was seen in a case in the short-duration group, which, however, had the smallest proportion—3 herpes in 18 cases, compared with 11 of 12 in the medium-duration group and 12 of 20 in the longer-duration group. Age did not seem to influence the incidence of herpes.

Sore Throat

Definite sore throat occurred in 6 cases; 4 of these had soft white tonsillar exudate, and 3 of them were swabbed for culture. A few other patients had congested fauces—in 1 case unilateral.

Other Symptoms

In 2 cases there was an urticarial rash. A girl, aged 18, who was ill for thirty-nine days, had temporary mistiness of vision, and a woman, aged 42, with a twelve-day attack, complained of fainting and vertigo.

Treatment

At the beginning of the outbreak patients were placed on a five-day course of sulphamerazine, but this was soon abandoned because it seemed to exert no influence, and treatment thereafter was symptomatic only. It was decided to try aureomycin in 2 prolonged cases, but the temperatures became normal just before the drug could be given and so may have saved a *post hoc propter hoc* dilemma.

Case-records

The following are summaries of 5 cases which provided specimens for virus investigations.

Case 1.—An epileptic girl, aged 15, had pyrexia reaching 102°F, headache, nuchal ache, pain in the chest, and abdominal pain, but no vomiting. On the fourth day her pyrexia subsided, but ten days later it recurred, reaching 101·8°F, and remained at a lower level until it finally subsided in the third week of the second attack.

Case 2.—A girl, aged 7, had a temperature reaching 102°F which became normal on the third day. She complained of headache, nuchal ache, and chest pains; she did not vomit or have abdominal pain. She had herpes simplex and injected fauces.

Case 3.—A boy, aged 9, had a normal temperature on the third day, but had further small rises between the fourth and seventh days, followed by two pronounced spikes (from normal level up to about 103°F) on the eleventh and fifteenth days. His pyrexia finally settled on the nineteenth day. He complained of headache and severe nuchal pain and vomited, and he had herpes simplex. His C.S.F. gave normal findings: cells less than 1 per c.mm.; chlorides 760 mg., protein 40 mg., and sugar 54 mg. per 100 ml.

Case 4.—A boy, aged 5, had pyrexia which finally settled about the sixth day. He complained of headache, nuchal pain, and abdominal pain. He also vomited repeatedly and copiously during his first two days' illness. His C.S.F. was normal: leucocytes less than 1 per c.mm.; chlorides 780 mg., proteins 30 mg., and sugar 72 mg. per 100 ml.

Case 5.—A boy, aged 8, had pyrexia reaching 101°F which did not finally settle until the eighth day, though the temperature had been normal on the fourth and sixth days. He complained of headache and abdominal pain and vomited.

Laboratory Investigations

Specimens of fæces from cases 1–5 were negative when cultured for the salmonella and dysentery groups of organisms.

In 2 cases (case 4 and another) agglutination tests were negative for the enteric group and non-specific for salmonella and *Brucella abortus*.

In 3 cases with prolonged pyrexia—2 girls (A.B. and C.D., aged 8 and 13 respectively) and a boy (E.F., aged 9)—the cold agglutinin reactions and Paul-Bunnell tests were negative. A.B. and E.F. had white-cell counts of 8000 and 7000 per c.mm. respectively, with normal differential counts, but C.D. had a white-cell count of 9500 per c.mm. (polymorphs 31%, lymphocytes 65%, large mononuclears 4%).

Chest radiographs were taken of A.B. and C.D. in a search for the cause of the continued pyrexia. C.D. had some enlargement of the hilar glands visible on the lateral film, and in the lung fields of both A.B. and C.D. there were slight basal changes. The hilar enlargement and the basal changes had disappeared when radio-

ABLE II—SPECIMENS USED FOR VIRUS INVESTIGATIONS

e	Specimens A, B, C	Duration of illness (days)		
		A	B	C
	Throat washings and fæces A; serum A, B, C	1	22	192
	Throat washings and fæces A; serum A, B, C	1	22	192
	Throat washings and fæces A; serum A, B, C	1	22	206
	Throat washings A; serum A, C	3	—	203
	Throat washings A; serum A	5	—	—

aphy was repeated a fortnight later. Both A.B. d C.D. were Mantoux-negative 1/1000. Five other ildren with prolonged pyrexia had normal chest diographs.

In 3 cases with tonsillar exudate faucial cultures were egative for β-hæmolytic streptococci and *Coryne-* *cterium diphtheriæ*. Stained smears showed no Vincent's ganisms.

VIRUS INVESTIGATIONS

From the specimens shown in table II virus-isolation nd serological investigations were undertaken.

Iethods used in Virus Isolation

From the original specimens pools of material were repared as follows:

Pool 1 consisted of equal volumes of throat washings from ases 1, 2, and 5.

Pool 2 consisted of equal volumes of throat washings from ases 3 and 4. Each pool contained 1000 units of penicillin nd streptomycin per ml. The separate throat washings were subsequently investigated also.

Pool 3.—A 20% suspension in saline solution was prepared rom each specimen of fæces. After standing overnight in the efrigerator the suspensions were centrifuged on a horizontal entrifuge at 5000 r.p.m. for one hour. The supernatant fluids were retained, deposits being discarded. Portions of each suspension containing 200 units penicillin and 2000 units of streptomycin per ml. were set aside. Equal volumes of these were mixed to form a pool. The separate suspensions and the pool were left for one hour at room-temperature and next stored in the refrigerator until aerobic and anaerobic cultures were made on blood-agar plates.

Inoculation of Mice

Litters of newborn mice were inoculated when available. Single litters averaging 5–9 mice were used unless 3 or more litters born on the same day were available, when these were pooled and distributed evenly. A standard inoculum of 0·02 ml. of suspension was injected subcutaneously over the scapular region of mice aged twenty-four to forty-eight hours. Deaths occurring within forty-eight hours after inoculation were regarded as non-specific. From forty-eight hours to twelve to fourteen days, deaths involving most of the inoculated animals were accepted as specific if preceded by retardation of growth, weakness, ataxia, coarse tremors, and paralysis. For passage, mice were killed with ether when they showed signs of illness. They were decapitated, skinned, and eviscerated, and 20% suspensions in saline solution were prepared. After overnight storage in the refrigerator these were centrifuged at 3000 r.p.m. for thirty minutes, and the supernatant fluids were used. Titrations were made with tenfold dilutions in saline solution.

Neutralisation Tests

These were made with the available specimens of serum and the newly isolated strains of Coxsackie virus. After inactivation at 56°–58°C for thirty minutes ndiluted or diluted sera were mixed with equal volumes of saline suspensions containing about 100 LD$_{50}$ of virus. The mixtures were shaken and left at room-temperature for one hour before inoculation into mice.

Preparation of Immune Mouse Serum

Adult mice were given six intraperitoneal injections of 0·2 ml. of a 33% suspension of pool-3 infected newborn mouse tissue within a period of three weeks. They were bled out ten days after the last inoculation. Repeated intraperitoneal inoculation of adult mice and guineapigs with concentrated virus suspension did not cause illness in either species of animal.

Isolation of Coxsackie Virus

Strains of Coxsackie virus were isolated from pools 1, 2, and 3, from all the individual throat washings, and from individual fæcal suspensions from cases 1 and 2, but not from case 5. Signs of illness were noted five to eleven days after inoculation and progressed to complete paralysis and death usually within two or three days. Despite the development of weakness and tremors, recovery sometimes took place, especially during initial passages. Repeated passage brought the incubation period to five or six days after inoculation, and titres of about 10^{-6} dilution of suspension were usually obtained. No lesions were caused by this virus on the chorio-allantoic membranes of fertile eggs. This fact, together with the isolation of virus from fæces, excluded the possibility of its being a strain of herpes-simplex virus.

Histological examination of mice infected with the strain of virus isolated from pool 3 was undertaken by Dr. A. Beck, of the North West Group Laboratory, London, who reported as follows:

Heart.—Small areas of necrosis and disintegration of muscle-fibres and infiltration of the ventricular wall with polymorphs and histiocytes.

Fat pads.—Small areas of degeneration and necrosis in the lobules of embryonal fat and infiltration with polymorphs and histiocytes.

Brain.—A few small foci of lymphocytic infiltration in the grey matter.

Influenza Virus

An unsuccessful attempt was made by Dr. B. P. Marmion to isolate influenza virus from the pools of throat washings.

Herpes-simplex Virus

No attempts were made to isolate this virus from the circumoral vesicles which appeared in many of the affected children.

SEROLOGICAL INVESTIGATIONS

Complement-fixation Tests

The A and B specimens of serum from the 5 patients were negative when tested against influenza A and B, psittacosis group, and *Rickettsia burneti* antigens. The *Streptococcus M.G.* agglutinations were also negative.

TABLE III—RESULTS OF NEUTRALISATION TESTS WITH POOL-3 VIRUS SUSPENSION AND HUMAN SERA

Case no.	Serum	Serum dilution				Saline control
		1/1	1/5	1/10	1/50	
1	A (1)†	..	4/4*	..	..	3/3*
,,	B (22)	..	0/4	..	2/4	3/3
,,	C (192)	..	2/5	..	..	4/4
2	A (1)	4/4	4/4	..	..	4/4
,,	B (22)	..	..	2/4	4/4	3/3
,,	C (206)	0/6	..	..	..	4/4
3	A (3)	8/8	..	..	..	3/3
,,	C (203)	1/5	..	..	..	2/2
4	A (5)	2/3	..	..	..	3/3
5	C (192)	2/4	..	..	..	4/4

* This indicates the number of mice which died as a result of the inoculation over the number of mice inoculated. Surviving mice were those alive at the time of weaning, when they were four weeks old. Deaths from specific infection took place up to fourteen days after inoculation, and mice which survived until then rarely succumbed afterwards.

† The figures in parentheses represent the day of illness on which the serum was obtained.

The A specimens of serum from cases 3 and 4 and the B specimens from cases 1 and 2 were negative when tested against Dalldorf's types I and II and Melnick's High Point strains of Coxsackie virus antigens.

Neutralisation Tests

The A and B specimens of serum from case 5 had all been used; so neutralisation tests could not be attempted. Only small volumes of some of the other samples were available, and the tests had to be made with these, starting with the lowest dilution of serum possible. The results are given in table III.

Only limited conclusions may be drawn from these tests, because only a few mice were used and only small amounts of some of the sera were available. It does appear, however, that the strain of virus used was not neutralised by sera obtained before the fifth day of illness, and that some neutralising antibody was present on the fifth day of illness, being still there about six or seven months after the infection.

It was necessary to decide whether the strains of virus isolated from the different suspensions were identical. A neutralisation test was first made with the newly prepared immune mouse serum and the homologous virus suspension as follows:

Virus	Immune mouse serum dilutions			Control saline
	1/5	1/50	1/500	
Pool-3 suspension	0/4*	2/5	2/5	1/3

* See table III.

Although only 1 of the 3 control mice died, the control mice and those inoculated with the 1/500 dilution of serum developed weakness and coarse tremors of the head and limbs after inoculation, whereas those given the 1/5 and 1/50 dilutions of serum did not. It was therefore decided to use a 1/50 or lower dilution of serum in the subsequent tests. The results are given in table IV.

The results indicate that all the strains of virus were neutralised by the immune mouse serum and were antigenically related if not identical.

As histological examination of infected mice had shown that the newly isolated virus belong to the Coxsackie-B group of viruses, an investigation to see whether there was an antigenic relationship to the Connecticut-5 strain of virus was carried out. In this a strain of Connecticut-5 virus received from Dr. Melnick and some group-B1 mouse antiserum from Dr. Dalldorf were used. The results are given in table V. No antigenic relationship between the newly isolated virus and the Connecticut-5 strain of Coxsackie virus is apparent.

Discussion

The epidemic was a troublesome episode. The work of the residential home was temporarily dislocated, and the difficulties of nursing so many children at once were great, especially as some of the staff were also ill. Certainly none of the children were dangerously ill, but many o them were quite poorly in the early stages, and ofte the illness was rather prolonged.

Of the 75 residents in the children's home 52 becam ill, and 45 of these cases arose during a period of eightee days. The condition was thus highly infectious withi the semi-closed community of the children's home that there was also a general susceptibility was mos obvious in the infants (21 cases out of 23) but als evident in the adults, 6 of 9 female staff being affecte (*table* I).

Although there was great variability in duration of the illness from several days up to about a month, there was a uniformity of clinical picture easiest to appreciate in the early stages. The longer cases showed remissions or intermissions. In 3 cases there were intermissions, of thirteen, fourteen, and thirty-one days, and they are indicated in the accompanying figure as relapses. In view of the long period of intermission in these cases the recurrence of illness possibly followed infection by a different strain of virus. This point was not investigated.

The commonest features were headache, nausea and vomiting, vague abdominal pain, and a nuchal ache without rigidity. Less constantly there was an aching pain in the sternal area. Backache was not a feature. A few patients had sore throats, and a few diarrhœa. Toxæmia was never severe, but some patients were somewhat prostrated at the onset.

The influenza epidemic of 1951 died out in this area about the end of February, and the comparatively long course of many of the present cases and the general lack of respiratory symptoms were inconsistent with a diagnosis of influenza. The absence of any sharp pain in chest or abdomen was against Bornholm disease. The lack of meningeal signs or paralysis virtually excluded poliomyelitis, and the C.S.F. was normal in 2 cases tested; though cases of a non-paralytic syndrome were at this time appearing with increasing frequency in Coventry. 7 patients had their chest radiographed, and the slender findings in 2 of these, though insufficient for forming any conclusions, generated a suspicion that radiography at an earlier stage might have revealed something more definite. In 3 cases Paul-Bunnell and cold-agglutinin tests were made; they gave negative results. None of the clinical features were characteristic of enteric fever, and fæcal specimens from 5 patients were negative for salmonella organisms. Sera from the same patients were negative for the psittacosis group, *R. burneti*, *Strep. M.G.*, and influenza A and B.

Finally, from the same 5 cases throat-washings and fæces were examined for Coxsackie virus because of the unusual clinical characteristics of the outbreak, and an apparently identical strain of group-B Coxsackie virus was recovered. Neutralising antibody was not found in serum taken in the first three days of illness but was found in serum taken on the fifth day or later. The evidence suggests that this strain of Coxsackie virus was the cause of the outbreak.

The immediate origin of this strain is conjectural. It has been stated that, in the area served by the school used by the residential home, there was some minor

TABLE IV—RESULTS OF NEUTRALISATION TESTS WITH 1/50 DILUTION OF IMMUNE MOUSE SERUM

Virus suspension	Serum and virus	Control saline and virus
Pool 1, 4th-passage suspension	1/7*	1/1†
Pool 2, 2nd-passage suspension..	0/6	1/1†
Case 1, 1st-passage stool suspension	0/5	3/3
Case 2, 3rd-passage stool suspension	1/5	2/2
Case 5, 2nd-passage throat washings suspension	1/6	4/4

* See table III.

† Although only one control mouse has been included in these tests it was known from previous results that the dilution of suspension used would invariably cause the death of inoculated mice.

TABLE V—RESULTS OF NEUTRALISATION TESTS

Virus	Serum dilutions		Control
	Pool-3 mouse antiserum		
	1/10	1/50	
Conn.-5 suspension	5/5*	5/5	4/4
	Coxsackie-B1 mouse antiserum		
Pool-3 suspension	4/4		3/3

* See table III.

febrile illness whose constant brevity and very mild nature did not suggest identity with the illness at the children's home. It is, however, easiest to believe that the virus was of local origin and imported into the children's home through school or other contact, especially as present knowledge suggests that man is the main reservoir and conveyor of Coxsackie virus. Further, a pathogenic virus present in throat washings and probably capable of droplet spread would have optimum conditions for direct aerial transmission within a susceptible population living under one roof. The rapid involvement of the infant group, followed by the equally rapid spread through the associated but separate groups of older children, seemed consistent with this mode of spread, as also did the infection of 2 adult staff who were friendly and who fell sick consecutively, with illnesses separated by a few days. Indirect transmission through food and drink or other contaminated articles was another possibility, which may have become more likely as fæcal convalescent carriers accumulated. Infection from an animal reservoir, such as rodent pests might provide, appears to be on the whole unsupported by present knowledge of Coxsackie epidemiology. Much the same problems regarding mode of spread arise in poliomyelitis as arose in this outbreak of febrile illness.

If the spread was direct from case to case, the incubation period was about a week. This view is based on the period between the start of the main outbreak in the "infants" and that in the older children (eight days); the period between the first two peak days on May 16 and May 24 (also eight days); the interval between the illnesses of the 2 adult friends mentioned earlier (six days); and between the illness of the child on May 9 and the first cases of the main batch on May 15 (six days), if the sick child on May 9 (whose illness achieved importance mainly in view of subsequent events) can be accepted as the actual first case—a point on which we are not unanimous.

In conclusion it may be said that the problem of "pyrexia of unknown origin" is one which, even in these days of rapidly expanding knowledge and wide range of laboratory tests, still baffles. Experience in this outbreak, however, suggests that the problem may be further reduced when facilities for Coxsackie virus investigations become increasingly available.

Summary

An outbreak of febrile illness involving 52 out of 75 persons in a residential children's home is described.

A group-B strain of Coxsackie virus was isolated from mouth washings and fæcal specimens from patients; neutralising antibody was absent in early sera but appeared in sera from the fifth day onwards.

The differential diagnosis and the possible immediate origin of the outbreak are discussed briefly.

Our thanks are due to Dr. R. Ewart Jones for bacteriological and other assistance; to Dr. A. Beck for the pathological report; to Dr. B. P. Marmion; to Dr. J. L. Melnick for the strain of Connecticut-5 virus; and to Dr. G. Dalldorf for the group-B antiserum. We are also much indebted to Mr. and Mrs. D. Parsley, then superintendent and matron of the residential children's home, for their coöperation and help.

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INTRA-ARTERIAL TRANSFUSION

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TRAUMATIC shock, a clinical syndrome in which the outstanding feature is acute collapse of the peripheral circulation, is an ever-present emergency both in peace and war. It requires immediate and effective treatment, if life and limb are to be saved, and deliberate curative surgery made possible.

SHOCK

Fundamentally, shock may be defined as that state which results when disparity arises between the volume of the vascular bed and the circulating blood volume. This may occur:

(1) When the circulating blood volume is rapidly reduced by hæmorrhage, loss of plasma, or excessive loss of body-fluids. (Any combination of these three causes of blood-volume depletion may occur.)

(2) When the volume of the vascular bed is rapidly increased without comparable increase in circulating blood volume. This may take place with great rapidity as the result of widespread and rapid decrease in tone of small arteries, veins, and capillaries, either reflexly or from some other cause.

In both main groups of causes the all-important sequel is inadequate filling of the vascular bed. As a result blood-pressure rapidly falls until an unstable equilibrium between blood volume, vascular-bed volume, and the now reduced blood-pressure is established. Later, owing to the urgent necessity for maintaining the rate of blood-flow through vital organs—e.g., brain, heart, liver, and kidneys—the circulating blood volume is increased by extraction of fluid from the tissue spaces, and the vascular-bed volume is reduced by an increase of tone in small blood-vessels and widespread contraction of capillaries. Equality or near equality may thus be re-established between blood volume and vascular-bed volume, and blood-pressure will accordingly rise, perhaps even to normal, and shock may apparently be overcome. This apparent recovery from shock is dangerously misleading and is often spoken of as the compensatory phase of shock, or "masked shock," and a patient who is operated on while in this phase, without preliminary blood-transfusion to restore his blood volume to its former level, is in great danger of developing an overwhelming degree of shock from the additional trauma of the operation.

Another and highly lethal set of circumstances may arise in the patient who has lost a substantial fraction of his blood volume but has, for the time being, wholly or partly overcome the initial depression of blood-pressure by compensatory mechanisms. Much of his apparent recovery is due to widespread constriction of small blood-vessels in relatively less important organs such as the skin and subcutaneous tissues. This state of enhanced vascular tone cannot be indefinitely sustained, because tissues deprived of their normal blood-supply are also deprived of their normal nutrition and means of getting rid of the waste products of their metabolism. Injurious metabolites consequently accumulate in such relatively ischæmic tissues until they reach a concentration at which they cause local vasodilatation, and probably also a generalised decrease in vascular tone. As a result the vascular-bed volume begins to enlarge, and an increasing degree of disparity between it and the circulating blood volume arises, with a resulting drop in blood-pressure and a decreased rate of blood-flow through all the body tissues. A vicious circle then develops which leads rapidly on to irreversibility, a state in which peripheral vascular failure is so profound that pooling and laking of the remaining circulating blood in the relaxed vascular bed take place, and transfusion, even in apparently adequate amounts, is then unable to prevent the death of the patient.

From this brief discussion, which could be elaborated almost indefinitely, one outstanding concept emerges—namely, that, to sustain the well-being and nutrition of each one of us, not only must the heart deliver at a normal pressure an adequate quantity of blood but also (so that normal blood-flow through all the tissues shall be maintained) the blood volume, the volume of the vascular bed, and blood-pressure (peripheral resistance) must be normal. Thus, assuming that the heart can work properly, circulatory efficiency depends on the presence of a normal blood volume, a normal vascular-bed volume, and normal tone or peripheral resistance in the vascular channels. Perhaps this concept can conveniently be expressed in the following equations:

(1) Circulatory efficiency = normal blood volume + normal vascular-bed volume + normal blood-pressure.

(2) Circulatory inefficiency or shock = reduced blood volume + abnormal vascular-bed volume + reduced blood-pressure.

These concepts (represented diagrammatically in fig. 1) will, I believe, be generally acceptable. Until recently, however, efforts to resuscitate patients in a state of shock or circulatory inefficiency have largely been directed towards restoring blood volume to normal by intravenous blood-transfusion.

This method has justly been acclaimed as an immensely valuable means of overcoming shock and has saved countless lives. But it depends for its success on a substantial and increasing degree of tone in the smaller peripheral vascular channels, so that blood added to the blood volume intravenously will be returned to the heart and thus to the general circulation. If a reasonable degree of vascular tone is not present—e.g., in late and severe shock—blood which is given intravenously will largely accumulate in venous channels and capillaries, and may indeed never pass through the heart and lungs to the arterial side of the circulation. Tissue anoxia and malnutrition thus persist, and the patient's condition becomes progressively more perilous.

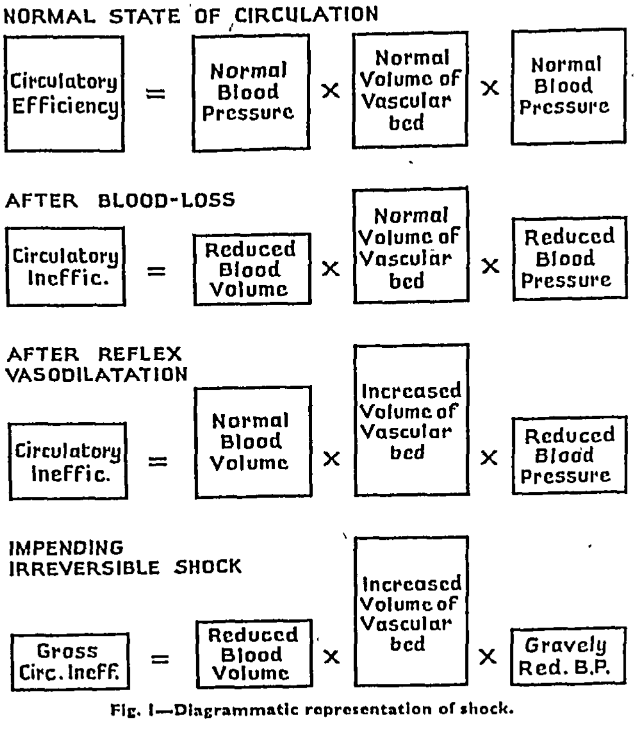

Fig. 1—Diagrammatic representation of shock.

Attempts to reduce the volume of the vascular bed with vasopressor drugs have been disappointing and even deleterious in severe shock. In the early phases they add to the already severe vasoconstriction and thus further deplete capillary blood-flow and increase tissue anoxia. In the later stages of shock their vasoconstrictor effort is fleeting, the anoxic, relaxed, and malnourished capillaries being incapable of sustained contraction even when adequate intravenous blood-volume replacement has provided at least one of the primary requisites for recovery.

A third alternative is, however, available—that of increasing blood-pressure rapidly to normal by intra-arterial transfusion at or above physiological pressures.

INTRA-ARTERIAL BLOOD-TRANSFUSION

The introduction of blood into the arterial tree under pressure at about 120 mm. Hg, or slightly above this figure, causes the blood-pressure within the whole arterial system to rise rapidly to normal (Robertson et al. 1948). Intra-arteriolar and intracapillary pressure is restored, and perhaps pooled and laked blood, lurking in flaccid capillaries and venules, is pushed onwards into the great veins and so back to the heart, which is thus once again provided with blood to pump onwards.

A dangerous state of circulatory collapse may thus be reversed almost immediately. Indeed, circulatory puissance replaces circulatory prostration, and the nutrition of the whole body is improved. Almost inevitable death may thus be avoided and probable recovery substituted.

In broad outline the valuable results of intra-arterial transfusion in shock are:

(1) Normal systolic blood-pressure is restored throughout the whole arterial system almost at once.

(2) The rate of blood-flow through all body tissues—notably the brain, the coronary vessels, the liver, and the kidneys—rises rapidly.

(3) Adequate tissue oxidation replaces gross and increasing tissue anoxia.

(4) Accumulating tissue metabolites are washed away to their sites of detoxication or excretion.

(5) Lost blood is replaced as easily and quickly as by the intravenous route.

It is curious that intra-arterial transfusion has not yet been universally adopted for the treatment and prevention of shock. Indeed it does not seem to have been seriously used at all until 1939 when Birillo employed it with success. Kohlstaedt and Page, acting on a suggestion of Colonel Sam F. Seeley, Medical Corps, U.S. Army, first used the method in the United States in 1943. Since that time Glasser and Page (1946), Shaffer (1947), Kay and Hacker (1947), and Robertson et al. (1948) have reported on it. It was this last report that enlisted my own interest, and since 1949, at the Queen's University, we have investigated its possibilities both clinically and experimentally. The experimental studies are being reported elsewhere by L. S. deS. Carey and his associates. In summary, these workers have found that intra-arterial transfusion is much more effective than intravenous transfusion in the treatment of hæmorrhagic shock, and that its advantages include immediate restoration of coronary, cerebral, and renal circulation to normal and rapid return of blood-pressure to normal (Carey and Harrison).

Clinically we now use intra-arterial transfusion both in the treatment of established shock and as a prophylactic measure in all major surgical operations—e.g., pneumonectomy, thoracolumbar sympathectomy, and major abdominal operations—which may be complicated by severe shock.

METHOD

The apparatus is simple (fig. 2). An ordinary Baxter transfusion bottle containing 500 ml. of blood is used.

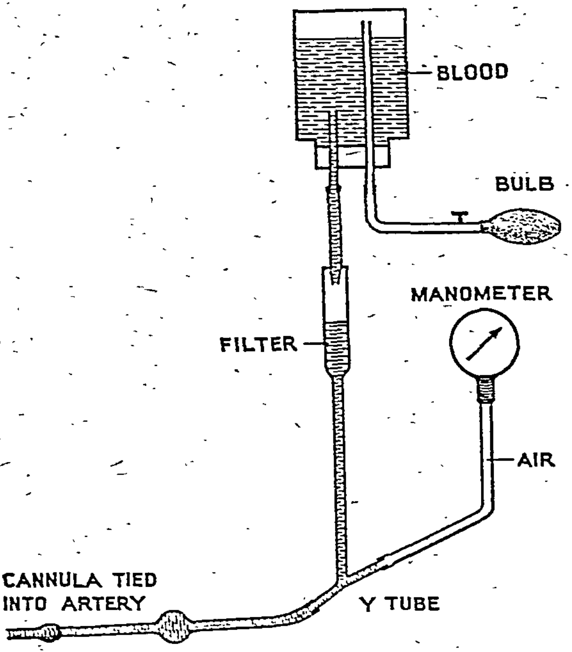

Fig. 2—Apparatus for intra-arterial blood-transfusion.

Heparin (1000 units) is added to the blood as an additional safeguard against clotting. To the longer glass tube, which reaches nearly to the bottom of the bottle, is attached a sphygmomanometer bulb by which controlled air-pressure can be applied to any desired level above the blood in the reservoir. To the shorter glass tube is attached the usual sterile rubber or latex tubing containing a filter. Beyond the blood filter there is a sterile glass Y-tube, from one arm of which is led a sterile rubber tube containing air. This tube is connected to an ordinary aneroid gauge attached to a stand slightly above heart level. The final rubber tube for the administration of blood to the patient is then attached to a cannula inserted into either the radial or the dorsalis pedis artery. This apparatus is the simplest and most foolproof that we have been able to devise with materials available in almost any hospital. Pressure within the system is continuously recorded by the manometer, which depicts the pressure at which blood is being delivered into the arterial system. It also is a valuable means of estimating intra-arterial pressure.

The following are among the minor difficulties we have encountered. Connections between tubing and cannula, bottle, blood filter, and aneroid manometer must be secure, or leakage may occur. The cannula must be directed towards the heart and must be tied into the artery, or leakage round it may take place. It is desirable to support the arm with a lightly applied crêpe bandage to present suffusion of the limb. In two cases ischæmia of the radial half of the hand developed: in one case this was immediately overcome by injection of the stellate ganglion with 0·5% procaine, and in the second case the terminal phalanx of the index finger was lost. Apart from these difficulties we have encountered no important complications. On the contrary, we have experienced nothing but satisfaction from intra-arterial transfusion. It has saved at least six lives and greatly facilitated and accelerated the recovery of many other patients.

One other possible danger exists—air embolism. We have not yet encountered this complication, because all the intra-arterial transfusions are continuously supervised. In addition a check valve is being incorporated into the apparatus to prevent its occurrence.

Intra-arterial transfusion has recently been used in the treatment of the phase of hypotension which succeeds coronary infarction from coronary thrombosis. Frequently these patients are admitted to hospital moribund with a systolic blood-pressure of 60 mm. Hg or less. Although it may seem unwise to add blood to the circulation, the immediate increase in intra-arterial pressure which results from intra-arterial transfusion may reverse the state of shock and save the patient. My colleague, Prof. Malcolm Brown, has lately had experience of such a case, and when more experience has accumulated he will no doubt be reporting his impressions.

ILLUSTRATIVE CASES

Case 1.—Mr. A had carcinoma of the left lung, and was undergoing pneumonectomy. Five minutes after the left pulmonary artery was ligated the atheromatous vessel ruptured at the proximal ligature. There was an immediate and profound fall of blood-pressure, with considerable loss of blood. Fortunately an intra-arterial transfusion was running. The bleeding pulmonary artery was secured, and within fifteen minutes of accelerating the rate and increasing the pressure of the intra-arterial transfusion the patient's systolic blood-pressure returned to its former level of 120 mm. Hg. He left hospital fifteen days later.

Case 2.—Mrs. B, aged 72, had carcinoma of the rectum, and was undergoing abdomino-perineal resection. All went normally until the rectum was removed; but then numerous small veins on the side walls of the pelvis and on the posterior aspect of the vagina bled profusely and were very difficult to control either by ligature or by pressure. In spite of intravenous transfusion, which kept pace with the rate of blood-loss, the systolic blood-pressure fell to 65 mm. Hg. An intra-arterial transfusion was then started, and within ten minutes her blood-pressure had risen again to 130 mm. Hg, after which her progress was uneventful.

In these and many other operations, which would either not have been attempted or have occasioned great anxiety after operation, the patients have either been saved or their immediate postoperative period has been much simplified. I can think of no measure more reassuring to the surgeon, and more capable of averting catastrophe, and I only wish that I had had it at my command during my service with field surgical units in the late war.

CONCLUSIONS AND SUMMARY

The treatment of peripheral circulatory collapse or shock is described, with special reference to intra-arterial transfusion.

Experience of more than 100 cases suggests that intra-arterial transfusion is far superior to intravenous transfusion both in the treatment of established shock and as a preventive measure in operations where serious shock is expected.

Apparatus for intra-arterial transfusion should be immediately available in the operating-rooms and casualty departments of all hospitals, in advanced hospitals and field ambulances on active service, and in blood-banks and treatment centres of civil defence organisations.

I should like to record my gratitude to Dr. Lewis S. Carey and his associates for their careful experimental and clinical work on this problem, and to Dr. James H. S. Mahood, my anæsthetist, for his unfailing interest in the care of my patients, and his constant supervision of intra-arterial transfusions during and after operation.

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ISONICOTINIC ACID HYDRAZIDE IN THE TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN

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THERE is little doubt that the hydrazine derivatives of isonicotinic acid represent a further advance in the treatment of tuberculosis. The clinical results published so far appear to be confined to the treatment of chronic respiratory tuberculosis. This paper reports the provisional results of the treatment of four children with tuberculous meningitis with isonicotinic acid hydrazide (I.N.H.). All four patients have been followed up for 10 weeks. In one case treatment was stopped at 8 weeks, and in another at 9 weeks; treatment in the other two cases is continuing.

The following investigations were carried out before treatment and then at regular intervals:

Daily analysis of the urine and hæmoglobin estimation; twice-weekly full blood-counts, cerebrospinal-fluid (C.S.F.) analysis, and liver-function tests (alkaline phosphatase, thymol turbidity, and icteric index); and weekly blood-urea estimations. An electrocardiogram (E.C.G.) and a bone-marrow biopsy were made at 10 weeks in three of the cases.

CASE-REPORTS

Case 1.—A girl, aged 5½, was admitted in a stupor. 2½ years before, she had been given intrathecal and intramuscular streptomycin, together with *p*-aminosalicylic acid (P.A.S.) by mouth, intermittently for 3 months. She was reported to be physically and mentally normal on discharge; her C.S.F. still showed 10 cells, but was otherwise within normal limits. Follow-up was incomplete. She remained well until 10 days before readmission when she became listless, irritable, and increasingly drowsy.

On admission she could not recognise her parents, and lay curled up, actively resisting interference. Her C.S.F. contained 60 lymphocytes, 80 mg. of protein, and 38 mg. of glucose per 100 ml. Treatment was started with 0·05 g. of streptomycin intrathecally daily, 0·25 g. intramuscularly twice daily, and P.A.S. by mouth. The response was good, and after a month's treatment she appeared physically well. Mentally, however, she had regressed to the level of a child of 2–3 years. Early deafness was suspected which, in association with her mental state, made the further use of streptomycin undesirable, and treatment was stopped.

When I.N.H. became available a month later, treatment was restarted with 4 mg. per kg. body-weight daily by mouth in 6-hourly doses, increasing after 2 days to 8 mg. per kg. 8 weeks later, the C.S.F. still contained 36 cells, 100 mg. of protein, and 30 mg. of glucose per 100 ml. The dosage of I.N.H. was increased to 16 mg. per kg. A week later the C.S.F. had improved to 10 cells, 40 mg. of protein, and 42 mg. of glucose per 100 ml. She had been very active with an excellent appetite, but now she began to tire easily, her appetite failed, and vomiting and diarrhœa developed. Treatment was stopped and within a few days her symptoms had ceased. A week after stopping treatment her C.S.F. glucose had risen to 68 mg. per 100 ml.

Apart from slight deafness, the child remains physically well. There has been no obvious change in her mental state, which remains that of a child of 2–3 years. Laboratory tests revealed no abnormality other than a fall of hæmoglobin from over 100 to 85% a few days after the dosage of I.N.H. had been increased. The hæmoglobin quickly returned to over 100% when treatment was stopped.

Case 2.—A boy, aged 15 months, was admitted after 3 weeks' listlessness, anorexia, and loss of weight. He was extremely irritable with marked meningeal signs. The Mantoux reaction (1 : 1000) was positive. The C.S.F. findings were: 33 cells (80% lymphocytes), protein 250 mg., and glucose 18 mg. per 100 ml. X-ray examination of the chest was negative. Treatment was started with streptomycin 0·025 g. intrathecally daily and 0·25 g. intramuscularly twice daily with P.A.S. by mouth. Bacteriological proof of tuberculosis was obtained by guineapig inoculation. There was no response to treatment; the child's condition slowly deteriorated and the stiffness of the back and neck increased.

After a fortnight he was given I.N.H. (4 mg. per kg. daily in 6-hourly doses) in addition to the streptomycin and P.A.S. This was increased to 8 mg. per kg. after 2 days. 48 hours later a marked improvement became apparent; he took his food eagerly, and within a week he was sitting up in his cot playing with his toys. His appetite became voracious, and his weight increased at the rate of nearly 1 lb. per week. After 10 weeks the child appeared physically and mentally normal, save for some weakness of one arm. The glucose content of the C.S.F. became normal after 6 weeks, but the cells and protein remained raised (150 cells and 200 mg. of protein per 100 ml.) at 10 weeks. No other abnormality in the laboratory investigations has been found. The E.C.G. and bone-marrow examination were within normal limits at 10 weeks.

Case 3.—A girl, aged 2, was admitted with 3 weeks' history of anorexia, constipation, and fretfulness. The child was irritable, pale, and flabby. No other abnormal physical signs could be found. The C.S.F. contained 20 cells (all lymphocytes), 70 mg. of protein, and 47 mg. of glucose per 100 ml. The Mantoux (1 : 1000) was positive. X-ray examination of the chest showed nothing abnormal. Guineapig inoculation was finally positive.

Treatment was started with streptomycin and P.A.S., and there was some initial response, but during the 4th week the child's condition deteriorated. Intrathecal treatment became increasingly difficult. Streptomycin and P.A.S. were stopped, and I.N.H. (8 mg. per kg. daily) was given by mouth. A week later a slight but definite improvement was noted; the previously swinging temperature settled and the child began to take food by mouth. But this improvement was not maintained and at the end of a further 3 weeks streptomycin and P.A.S. were given in addition to I.N.H.

The child's condition continued to deteriorate, and she now presents the picture of decerebrate rigidity. The appearance was one of toxic rigidity; the legs were extended and plantar flexed, and the upper limbs were extended with the hands flexed at the wrists, the forearms pronated, and the fingers curved into the palms. All attempts at passive movements meet with great resistance. It is very doubtful whether therapy should be continued. Again laboratory tests showed no evidence of I.N.H. toxicity other than a temporary fall in hæmoglobin.

Case 4.—A girl, aged 6, was admitted after 6 days of constipation, anorexia, headache, and photophobia. On examination she was irritable but coöperative, and had marked meningeal signs. The C.S.F. contained 110 cells (90% lymphocytes), 80 mg. of protein, and 39 mg. of glucose per 100 ml. Tubercle bacilli were seen in a direct smear of the C.S.F. The mother was found to have open pulmonary tuberculosis.

Treatment was started with I.N.H. (8 mg. per kg. daily in 6-hourly doses by mouth). 3 days later she was symptom-free, her appetite being almost insatiable, and after a week she was running happily around the ward. Her weight increased at the rate of over 1 lb. per week for 5 weeks, after which it remained stationary. Her C.S.F. was within normal limits 8 weeks after the start of treatment (5 cells, 20 mg. of protein, and 60 mg. of glucose per 100 ml.). C.S.F. examination at 10 weeks showed 4 cells, 20 mg. of protein, and 50 mg. of glucose per 100 ml. A radiograph of the chest taken on admission showed no abnormality, and another taken 3 weeks later showed a hilar adenitis with no visible infiltration in the lung parenchyma.

After 8 weeks she complained of nausea and began to vomit after meals. The same day her liver-function tests became abnormal (thymol turbidity 7 units, alkaline phosphatase 24 King-Armstrong units, icteric index 11 units) and bile was present in her urine for the first time. Treatment was stopped. 2 days later she had a slight icteric tinge, and her liver became palpable for two fingers below the costal margin. Alkaline phosphatase had risen to 35 units, and thymol turbidity to 30 units. The vomiting stopped after 48 hours. A week later the jaundice had disappeared, the liver was no longer palpable, and the urine was free from bile. The liver-function tests improved quickly (thymol turbidity 15 units, alkaline phosphatase 15 units, icteric index 6 units). With the onset of nausea the child lost ¾ lb. in 2 days, but she regained it during the following week.

A month before, two children in the same ward had had infective hepatitis; two nurses in the ward also contracted it some time later. It seems that this child also had infective hepatitis—fortunately of a very mild degree.

Throughout treatment she remained fully coöperative. She never showed any signs or symptoms other than those associated with tuberculous meningitis or infective hepatitis. We observed none of the reactions such as headache, dryness of the mouth, hyperflexia, leg twitching, vertigo, constipation, reflex disturbances of micturition, or dyspnœa, which have been described during treatment with I.N.H. in adults (Selikoff and Robitzek 1952, Robitzek and Selikoff 1952). A gradual fall of 20% in hæmoglobin occurred during the first few weeks of treatment, but corrected itself without treatment during the following weeks. Except for the abnormal liver-function tests associated with an intercurrent attack of infective hepatitis, the other laboratory tests remained within normal limits. An E.C.G. and marrow biopsy at 10 weeks were also normal.

DISCUSSION

Four patients are too few and 10 weeks too short for any firm deductions to be made, but some points are worth noting.

Case 1 responded well to streptomycin clinically, but there was no improvement in the C.S.F. Streptomycin was stopped and I.N.H. substituted because of her deafness and mental condition. Only after the dosage of I.N.H. had been increased to 16 mg. per kg. did improvement in the C.S.F. occur. Treatment with the increased dose had to be stopped after a week because of intolerance.

Case 2 only responded to I.N.H. and streptomycin combined. Progressive clinical improvement was not, however, accompanied by improvement in the C.S.F., which remained very abnormal.

Case 3 showed only an initial response to streptomycin, and later to I.N.H. Later deterioration was uninfluenced by the two drugs in combination.

Case 4, the only child treated with I.N.H. alone, showed a dramatic response, and she was clinically well within a week. Treatment was stopped at 8 weeks because of intercurrent infection. This success is encouraging, and, though the possibility of relapse cannot be excluded, it seems unlikely. It is doubtful whether streptomycin could have produced such a rapid improvement, either clinically or in the C.S.F.

The contrast between the two forms of therapy could hardly be greater. Streptomycin requires a long course of intrathecal and intramuscular injections, distressing alike to patient, parents, and staff. I.N.H. on the other hand can be given by mouth as a pleasantly flavoured syrup and is eagerly taken.

The scheme of dosage of I.N.H. was devised more or less arbitrarily from the preliminary reports on its use in chronic pulmonary tuberculosis in adults and in animal experiments. No acute toxic effects were observed after 10 weeks on 8 mg. per kg. daily. One child showed signs of intolerance when the dose was increased to 16 mg. per kg., but these signs quickly disappeared when treatment was stopped. Chronic toxicity cannot be assessed in such a short time; it would be expected to affect mainly parenchymatous organs, notably the liver, kidney, and bone-marrow.

Rubin et al. (1952) showed that prolonged administration of I.N.H. in dogs resulted in fatty degeneration of the liver and in jaundice. In case 4 evidence of liver damage occurred after 8 weeks. This was almost certainly the result of an intercurrent attack of infective hepatitis from which the child made a good recovery. In retrospect, this attack of infective hepatitis could be regarded as fortuitous, for it showed that I.N.H. in the dosage used is unlikely to cause liver damage. If such damage was present it is improbable that the child would have had such a mild attack of infective hepatitis or made such a rapid recovery.

Analysis of the urine and weekly blood-urea estimations showed no evidence of renal damage. Urine concentration and dilution tests remained within normal limits. In each case a fall in the hæmoglobin occurred, varying from 10 to 25%, but this fall was seen to be reversible without stopping treatment. There were no significant changes in the white cells. Bone-marrow biopsies at 10 weeks showed a normal cellular tissue with the usual proportion of red and white blood-forming elements. Periodic pulse and blood-pressure readings and an E.C.G. at 10 weeks showed no deviation from normal.

SUMMARY

Four children with tuberculous meningitis were treated with isonicotinic acid hydrazide, either alone or combined with streptomycin, for a period of 8–10 weeks.

A child who had I.N.H. alone showed dramatic improvement, and became clinically well within a week. Her C.S.F. became normal in 8 weeks, and remained so for at least 2 weeks after stopping treatment.

The three other cases were treated initially with streptomycin and later with I.N.H., or with the two together. The results were equivocal.

There were no signs of drug toxicity, other than a temporary fall in hæmoglobin level, but signs of intolerance appeared when the dosage was increased to 16 mg. per kg. body-weight.

Our thanks are due to the resident medical and nursing staff, and also to the laboratory staffs in both Hospital Groups for their technical assistance.

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ALKYLAMINES IN THE TREATMENT OF LEUKÆMIA

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Since the war-time investigations of Wilkinson, who as early as 1942 obtained remissions in chronic leukæmia by the intravenous administration of nitrogen mustards, many reports have been published about these compounds in leukæmia, Hodgkin's disease, and allied disorders. Owing to war-time restrictions, the original observations made here were not published until after the war (Wilkinson and Fletcher 1947), but earlier reports came from American workers (Goodman et al. 1946, Rhoads 1946, Jacobson et al. 1946). Since then the many reports on the therapeutic effects of nitrogen mustards have been conveniently summarised by Karnofsky (1948), Gellhorn and Jones (1949), Burchenal (1950), and Reinhard et al. (1950).

We have treated various diseases with the nitrogen mustard group of drugs in a large number of patients in this department of the Manchester Royal Infirmary; but we report here only our results obtained in 102 patients with leukæmia. In this relatively large series the long period of observation has enabled us to observe both the early and the late results of treatment, thus facilitating a better assessment of the therapeutic value of these alkylamines. In most of the cases published hitherto only the early results have been reported.

MATERIAL AND METHODS

The chemistry and pharmacology of the alkylamines have been extensively studied experimentally by British workers, many of the results remaining unpublished, and some post-war reviews have appeared (Gilman and Philips 1946, Anslow et al. 1947, Columbic et al. 1947a and b, Karnofsky 1948); and the investigations on the

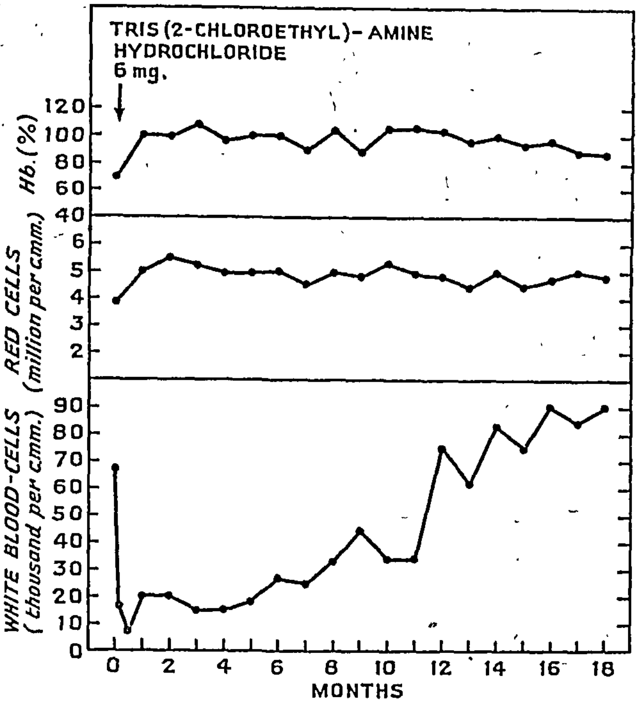
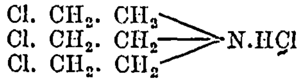


Fig. 1—Reduction in number of leucocytes after single injection of tris (2-chloroethyl)-amine hydrochloride 6 mg. in chronic lymphatic leukæmia.

effects of mitotic poisons in general have been reviewed by Ahlström (1951).

In this series the "tris" compound, tris (2-chloroethyl)-amine hydrochloride



$$\begin{matrix}\mathrm{Cl.\,CH_2.\,CH_2} \\ \mathrm{Cl.\,CH_2.\,CH_2} \\ \mathrm{Cl.\,CH_2.\,CH_2}\end{matrix}\Big> \mathrm{N.HCl}$$

was used almost exclusively, for Wilkinson and Fletcher (1947) had previously found that this compound in their hands did not give any serious complications and was more convenient to handle than the "bis" derivative; other workers have preferred the latter.

We have already reported our results obtained in another series of cases treated with β-naphthyl-di-2-chloroethylamine ('R48;') orally and shown, that as a whole they were inferior to those obtained with the intravenous 2-chloroethylamines (Gardikas and Wilkinson 1951). In this paper we shall not consider further this oral therapy with R48.

Dosage

The standard single dose was 6 mg. of the tris (2-chloroethyl)-amine hydrochloride, but in a few cases we gave 6–12 mg. in a later course of treatment without any unusual or untoward effect. The treatment was given in courses, each course usually comprising 3–6 injections. The remissions did not always last the same time, and we awaited a relapse before giving the patient another course of treatment.

Our routine technique differs slightly from that of other workers, who give the injections on consecutive or alternate days. According to the initial blood-count and clinical state of the patient, we usually give the first two injections on the first and third days, although occasionally only the first one may be needed. With daily leucocyte-counts, and twice-weekly full blood-counts, no further treatment is given until the decrease in the number of leucocytes has ceased (from several days to two weeks in different patients). During this time the reaction can be watched, and then further treatment is given, if required, until the leucocyte-count is at the desired level. This type of control is, we feel, an essential precaution if the best results are to be obtained, since sensitivity to alkylamines varies greatly, and occasionally we have seen the leucocytes returning to normal after only one 6-mg. injection, as shown in fig. 1, while the patient experiences the minimal disturbance.

TABLE I—PARTIAL HÆMATOLOGICAL REMISSION OBTAINED IN FOUR CASES OF ACUTE LEUKÆMIA

Case no.	Type of acute leukæmia	No. of white cells per c.mm.		Amount of "tris" compound used (mg.)
		Before treatment	After treatment	
1	Myeloblastic	120,000	3700	6
2	Myeloblastic	140,000	6800	6
3	Lymphatic	64,000	13,000	16
4	Monocytic	55,000	1200	6

Clinical Cases

This series includes 20 patients with acute leukæmia, 50 patients with chronic myeloid leukæmia, and 32 patients with chronic lymphatic leukæmia.

RESULTS IN ACUTE LEUKÆMIA

The 20 patients with acute leukæmia were classified according to the morphological differentiation of the immature cells in the bone-marrow and the peripheral blood; there were 12 with acute myeloblastic, 4 with acute lymphatic, and 4 with acute monocytic leukæmia.

The results have been *disappointing*; a slight clinical improvement was obtained in 2 patients, but the remission lasted a very short time, and then the patient went rapidly downhill, as with all other forms of treatment. A partial hæmatological remission, in the sense that the white-cell count fell from a high level to normal or subnormal, was obtained in 4 cases (see table I).

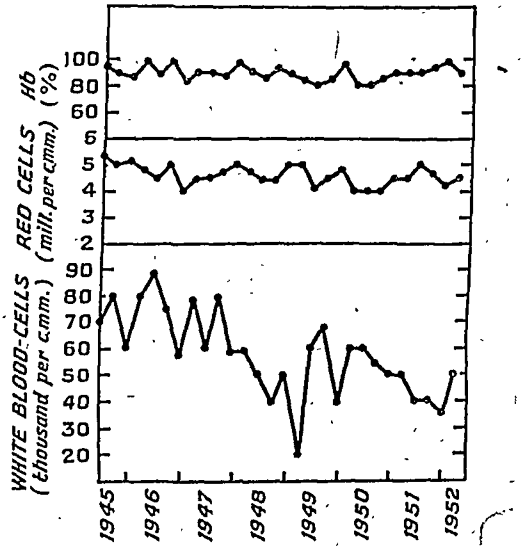


Fig. 2—A case of slowly progressive chronic lymphatic leukæmia in which the patient has remained well for years without specific treatment.

In spite of the considerable reduction in the number of leucocytes the *relative* numbers of blasts and other immature cells remained unchanged. In contrast to experience with folic-acid antagonists (Wilkinson and Gardikas 1951), A.C.T.H. and cortisone (Wilkinson and Gardikas, to be published), and urethane (Heilmeyer 1948), no case treated with the nitrogen mustard drugs showed complete hæmatological remission with the production of normal bone-marrow and blood picture.

RESULTS IN CHRONIC LEUKÆMIA

In this series 82 patients had chronic leukæmia; 50 having chronic myeloid leukæmia (25 men and 25 women.

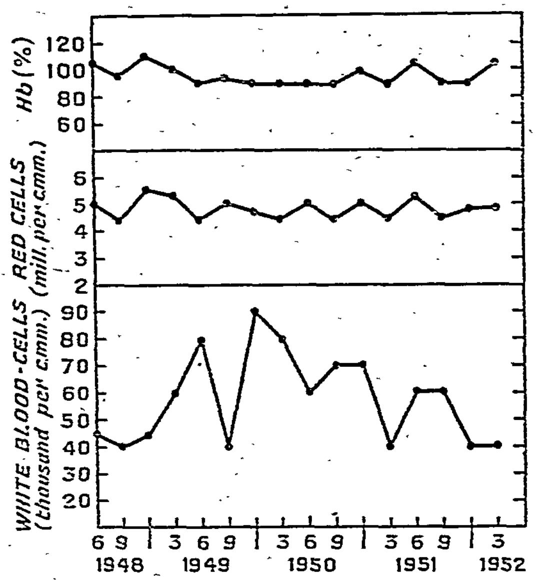


Fig. 3—Another case of slowly progressive chronic lymphatic leukæmia in which the patient has remained well for years without specific treatment.

aged 17–69), and 32 having chronic lymphatic leukæmia (23 men and 9 women aged 32–78).

Only progressive and severe forms of chronic leukæmia reaching a rather advanced stage were submitted to treatment, for we are of the opinion that treatment—and this applies to any form of treatment—should not be given until clinical symptoms and signs require it. Many patients, particularly with chronic lymphatic leukæmia, can and do get along for many years in fair or even good health with normal working capacity, the disorder remaining stationary or only progressing very slowly. This type should be referred to as the slowly progressive form of chronic leukæmia; the term "benign" type of leukæmia, which many workers use, seems to us inappropriate, since the ultimate issue is always fatal. Illustrative examples of this type of the disease are given in figs. 2–4. Most workers share our view, but Osgood (1951) has advocated treatment as soon as the diagnosis of leukæmia is established.

The main indication for the application of treatment is a poor or deteriorating general condition with constitutional symptoms—weakness, fatigue, loss of weight, pyrexia, and sweating. Severe anæmia—i.e., with Hb 60–70% (8·8–10·3 g. per 100 ml.)—constitutes per se an indication for treatment. Severe splenomegaly, even when other indications are not present, should also be considered as an indication, not only because of the "mechanical" disability it causes to the patient but also because the leukæmic process tends to take, sooner or later, a "malignant" course in patients with big spleens if no therapy is given. The same applies to severe lymph-node enlargement. The leucocyte-count, on the other hand, is not per se an indication for treatment. Patients with high leucocyte-counts—e.g., 60,000–100,000 per c.mm.—may be left without treatment, provided that other indications are absent. Conversely, a low leucocyte-count is not a contra-indication for treatment, since "subleukæmic" or "aleukæmic" forms are not synonymous with mild forms, and the peripheral picture does not reflect the activity of the leukæmic process.

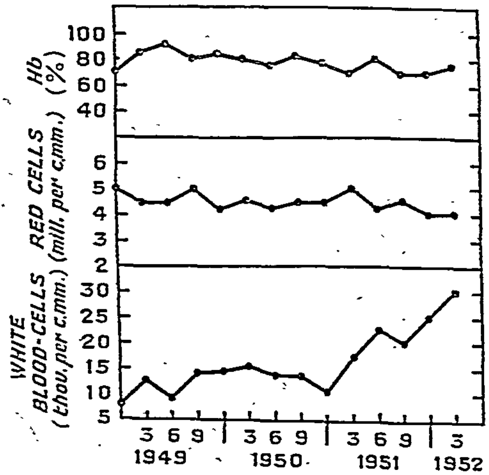


Fig. 4—A case of slowly progressive chronic myeloid leukæmia in which the patient has remained well for years without specific treatment.

No further treatment is given to the patients until they show clinical or hæmatological relapses, and for this reason we keep all our patients under regular and frequent supervision, seeing them at least monthly.

42 of the 50 patients with chronic myeloid leukæmia and 26 of the 32 with chronic lymphatic leukæmia showed a satisfactory remission after the first course of treatment.

Blood-count

A considerable fall took place in the total leucocyte-count after the treatment, the leucocyte-count returning to within the normal range or to a predetermined level by appropriate adjustment of the dose.

TABLE II—RESPONSE OF SIGNS AND SYMPTOMS FOLLOWING NITROGEN MUSTARD THERAPY IN 82 CASES OF CHRONIC LEUKÆMIA

Sign or symptom	No. of patients in whom symptom or sign was present before treatment	After treatment		
		Relieved		Unrelieved
		Completely	Partially	
Splenomegaly ..	M 45	20	22	3
	L 15	5	8	2
Lymphadenopathy	L 32	10	19	3
Fatigability ..	M 50	26	19	5
	L 31	12	14	5
Anorexia	M 40	20	16	4
	L 20	10	6	4
Fever	M 8	3	2	3
	L 4	2	2	..
Sweating	M 20	16	..	4
	L 21	19	..	2
		Gain	No change	Loss
Loss of weight ..	M 48	34	6	8
	L 30	20	6	4

M, chronic myeloid leukæmia.
L, chronic lymphatic leukæmia.

The immature cells in the peripheral blood were much reduced in number or completely disappeared.

There was often a correction of the anæmia, even without blood-transfusions in some cases; thus the hæmoglobin levels, which were low before the start of treatment in 62 patients, showed a definite rise in 44, remained unaltered in 8, and fell in 10 of these patients. This improvement of the anæmia was less often observed in chronic lymphatic leukæmia; thus only 6 of 18 patients who had severe anæmia before treatment showed significant increase in the hæmoglobin levels after treatment, whereas of 44 similar patients with chronic myeloid leukæmia the hæmoglobin levels improved considerably in 38.

Spleen and Lymph-node Enlargement

In 45 of 50 patients with chronic myeloid leukæmia a considerable splenomegaly was present before the start of treatment; after treatment splenomegaly regressed completely, the spleen becoming impalpable in 20 patients, partially palpable in 22, and practically unchanged in 3.

Of 15 patients with chronic lymphatic leukæmia and considerable splenomegaly the splenic enlargement disappeared completely in 5 and partially in 8, and remained unchanged in 2.

Severe lymph-node enlargement, which was present before the start of treatment in all 32 patients with chronic lymphatic leukæmia, disappeared completely in 10, diminished in 19, and remained unchanged in 3 (see table II).

Constitutional Changes

Most of the patients showed much improvement in appetite, increase in weight, and return of energy and vitality. Nocturnal sweats and pyrexia, if present, often disappeared, and in many cases the patient regained normal or almost normal working capacity (see table II).

The response is independent of the duration and, to a great extent, of the severity of the disease. Dramatic responses have been obtained even in apparently moribund patients.

Length of Remissions

The length of remissions—i.e., the length of period between two successive courses of treatment—varied widely, as table III shows.

The remissions were followed by hæmatological and clinical relapses with reappearance of one or more of the initial symptoms. The subsequent courses were equally effective, but in the prolonged treatment the response appeared to become less pronounced, and finally a more or less refractory stage was reached and the patient went rapidly downhill.

TABLE III—DURATION OF REMISSIONS

Duration (mos.)	No. of cases	Duration (mos.)	No. of cases
> 24	1	4–6	20
13–24	6	1–3	40
7–12	9	<–1	6

TOXIC EFFECTS

Toxic effects may be local or general; the latter can be subdivided into immediate and late.

Local toxic effects are usually due to errors in technique. If the solution infiltrates the tissue round the veins, a severe and possibly necrosing inflammation may result locally. No accident of this kind was encountered in our series. Local thrombophlebitis may develop, but a good dilution of the solution will minimise its incidence. In spite of the very large number of nitrogen mustard injections that we have administered, we have had only a very few cases of phlebosclerosis, and these have been of quite moderate degree without constitutional symptoms, and have subsided with rest within a few days (table IV).

Immediate general toxic effects are usually nausea, anorexia, and vomiting, which were noted after about 30% of the injections; in most cases they were mild, and only in 2% of these cases was the reaction severe, with some vomiting for 24–48 hours accompanied by prostration; in no case were the gastro-intestinal disturbances so severe as to necessitate discontinuance of treatment. Anti-histamine drugs of the 'Dramamine' or 'Avomine' type were tried because of evidence of their good effect in controlling motion sickness; one tablet (25 mg.) was given immediately after the end of the injection, and another tablet four hours later. Our impression was that these were helpful, but their real value was difficult to assess accurately.

TABLE IV—COMPLICATIONS OF NITROGEN MUSTARD TREATMENT OBSERVED IN 408 COURSES OF TREATMENT (EACH COURSE COMPRISING 2–7 INJECTIONS OF THE "TRIS" COMPOUND)

Complication	Frequency (%)
Moderate nausea	20
Moderate nausea and vomiting	12
Severe vomiting	2
Phlebosclerosis	2
Fever and rigor	0·4
Agranulocytosis (temporary and symptomless)	0·5

Late general toxic effects belong almost exclusively to the hæmopoietic system and could be described as a mere extension of the therapeutic effect of these substances. Severe leucopenia, with leucocyte-counts as low as 700–800 per c.mm., has only very occasionally been encountered after a course of treatment; with such leucopenia the patient has not felt disturbed or presented any constitutional symptom due thereto, and the leucocytes have rapidly returned to normal spontaneously. Severe complications or fatalities attributable to the treatment were not observed in this series. In table IV there is a brief summary of the observed complications and their frequency.

DISCUSSION

The present study shows that the tris (2-chloroethyl)-amine hydrochloride, though of no value in the treatment of acute leukæmias, can induce a satisfactory remission of clinical and hæmatological manifestations in many cases of chronic myeloid and chronic lymphatic leukæmias; and that, when it is given in the recommended dosage of 0·1 mg. per kg. of body-weight per single injection and under sufficient hæmatological control, the side-effects are not to be feared.

Naturally, at this stage, there arises the question of the relative value of nitrogen mustard treatment compared with other forms of therapy, especially irradiation. That the nitrogen mustard treatment presents certain advantages is obvious; it is inexpensive and easily administered, and it can be, and has usually been, given in an outpatient clinic, except for the first course, which is best initiated under hospital conditions and laboratory control. Further, since the therapeutic effect appears rapidly, the toxicity of the drug can be controlled more precisely than irradiation; and finally, while on treatment, the patient continues under his physician's care.

When, however, the question of the comparative value of the nitrogen mustard treatment is discussed, in most of the reports so far published the opinion is expressed that irradiation is by far superior in the management of chronic leukæmias, and the view is put forward that nitrogen mustards should only be given either in cases which, after a long period of irradiation, are refractory to it, or in cases which from the beginning do not seem to respond to irradiation.

Our impression with the nitrogen mustards has been quite to the contrary; and, since we have obtained impressive, often dramatic, results with persistent frequency, a comparison of our data with those available in published reports dealing with other forms of treatment may give us some more information.

The value, however, of such a comparative study is very limited; the published data are inadequate, since they deal mostly with average survival-rates since the onset of the disease, and very few statistical studies mention average survival-rates since treatment began. The number of patients in each series is relatively small, and for a disease with a protean clinical course like leukæmia this is a serious drawback. Pitfalls are numerous, and an example of the need for caution in drawing conclusions may be opportune at this place. If we compare the average survival-rate since the onset of the disease in the two groups of our cases of chronic myeloid leukæmia—the group of those treated with nitrogen mustard and the group who received no treatment—it will be seen that the corresponding figures for these two groups are 44·8 and 13·4 months. This finding, however,

TABLE V—AVERAGE SURVIVAL-RATE SINCE ONSET IN CHRONIC LEUKÆMIA TREATED BY VARIOUS METHODS

Reference	No. of cases	Treatment	Average survival (yr.)
Myeloid leukæmia :			
Arendt and Gloor (1932)	39	Irradiation	3·0
Krebs and Bichel (1947)	44	Irradiation	3·4
Lawrence et al. (1948)	110	P^{32}	3·7
Leavell (1938)	87	Irradiation	3·2
McAlpin et al. (1931)	18	Irradiation	3·0
Minot et al. (1924)	78	Irradiation	3·5
Müller (1950)	35	Irradiation	2·5
Osgood (1951)	58	P^{32}	3·6
Shimkin et al. (1951)	121	Irradiation	3·3
Vogt (1949)	86	Irradiation	2·5
Gardikas and Wilkinson (1952)	42	Nitrogen mustard	3·7
Lymphatic leukæmia :			
Leavell (1938)	49	Irradiation	3·6
Minot and Isaacs (1924)	80	Irradiation	3·4
Müller (1950)	34	Irradiation	2·5
Vogt (1949)	65	Irradiation	2·7
Gardikas and Wilkinson (1952)	24	Nitrogen mustard	3·6

loses much of its importance since one could reasonably argue that the second group—the untreated patients—includes some who were, when seen, desperately ill and who, because of this, did not receive treatment. So far as we know, no study has been published in which alternate cases without selection were treated by one form of therapy or another; and it is, of course, clear that this method alone, applied to large numbers, would provide accurate information for the comparative value of various forms of treatment.

Though a comparative study of the therapeutic effect of various forms of treatment is of limited value if not computed on the above-mentioned basis, we have attempted in the following section to compare our results, obtained with the alkylamines, with those obtained by various workers using other forms of treatment.

In the group of patients with chronic leukæmia who received alkylamine treatment and who have been followed up until death there are 42 patients with chronic myeloid leukæmia and 24 with chronic lymphatic leukæmia. In table V the average survival-rate since symptoms began in these patients is given, together with the average survival-rate given by other workers in similar series receiving other forms of treatment. In table VI the average survival-rate since the start of treatment is given. It will be noted that the results of treatment with the nitrogen mustard (2-alkylamine) are at least equal to those of treatment with P^{32} and with irradiation.

Statistical studies dealing with the degree of improvement following application of a form of treatment have not been published except one by Bethell (1943) who treated by irradiation 104 patients with chronic myeloid leukæmia. He classified his results as follows:

Excellent, if remission lasted more than 12 months.

Very good, if clinical and hæmatological improvement lasted 6–12 months.

Good, if clinical and hæmatological improvement lasted 3–6 months.

Fair, if there was transient clinical improvement but no real remission.

TABLE VI—AVERAGE SURVIVAL-RATE SINCE START OF TREATMENT IN CHRONIC LEUKÆMIA

Reference	No. of cases	Treatment	Average survival (yr.)
Myeloid leukæmia :			
Hoffman and Craver (1931)	71	Irradiation	2·6
Vogt (1949)	86	Irradiation	1·6
Wintrobe and Hasenbush (1939)	23	Irradiation	1·68*
Gardikas and Wilkinson (1952)	42	Nitrogen mustard	2·25
Lymphatic leukæmia :			
Vogt (1949)	65	Irradiation	1·6
Gardikas and Wilkinson (1952)	24	Nitrogen mustard	2·1

* Since diagnosis was established.

In table VII our results with 50 cases of chronic myeloid leukæmia treated with nitrogen mustard are compared with Bethell's treated by irradiation, his criteria of classification being used.

In conclusion, it is clear that the alkylamines are powerful therapeutic agents in the treatment of chronic leukæmia; the simplicity of their administration and their numerous advantages have been emphasised. In our material the remissions were impressive in most of the patients, and in some of them the results were even dramatic. Most of the patients were enabled to lead a normal, or almost normal, life for a long time without much discomfort or disability. Further, a review of the published cases and a comparison of our results obtained with alkylamines and those obtained by other workers using other forms of treatment, such as deep irradiation and radioactive phosphorus, casts doubts on the view held by some that the latter kinds of treatment are superior to the alkylamines.

SUMMARY

102 patients with leukæmia were treated with intravenous chloralkylamines (nitrogen mustard). There were 20 cases with acute leukæmia, 50 with chronic myeloid leukæmia, and 32 with chronic lymphatic leukæmia.

TABLE VII—RESULTS OBTAINED IN 50 CASES OF CHRONIC MYELOID LEUKÆMIA TREATED WITH NITROGEN MUSTARD COMPARED WITH BETHELL'S 104 CASES TREATED BY IRRADIATION. BETHELL'S CRITERIA ARE USED

Results	In Bethell's (1943) series (%)	In present series (%)
Excellent	12·5	24·0
Very good	41·3	22·0
Good	36·5	36·0
Fair	7·7	12·0
No effect	1·9	6·0

The therapeutic results in the acute leukæmias were completely disappointing.

Of the 82 patients with chronic leukæmia, good clinical and hæmatological remissions were effected in 61.

The length of remissions—i.e., the interval between two successive courses of treatment—varied: in 1 patient it was more than 24 months; in 6 patients 13–24 months; in 9 patients 7–12 months; in 20 patients 4–6 months; in 40 patients 1–3 months; and in 6 patients either less than 1 month or absent. With careful dosage the toxic effects were infrequent and, as a rule, of little severity.

In 42 patients with chronic myeloid leukæmia treated with 2-chloralkylamine (nitrogen mustard) and followed up to death, the average survival from the onset of the disease was 3·7 years, and the average survival from the start of treatment 2·25 years; in 24 patients with chronic lymphatic leukæmia the corresponding figures were 3·6 and 2·1 years respectively.

From a comparison of our results obtained with 2-chloralkylamines with those already reported by several workers using X-ray irradiation and radioactive phosphorus, these chemotherapeutic methods seem to offer equally effective scope in the treatment of chronic leukæmias.

Part of this work was done during the tenure of the Sybil Mary Pilkington Fellowship by one of us (C. G.); and our thanks are due to the Trustees of that Fund for support, and to the Crookes Laboratories Ltd. for kindly supplying tris(2-chloroethyl)-amine.

References overleaf

CHLORAMPHENICOL IN ACUTE SHIGELLA DYSENTERY

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ALTHOUGH sulphonamide derivatives are well established as the drugs of choice in the treatment of shigella dysentery, general agreement has not been reached about which is the most effective sulphonamide. We subscribe to the opinion that the soluble and easily absorbed sulphadiazine is more effective and consequently preferable to sulphaguanidine and succinylsulphathiazole. There are, however, drawbacks and limitations to sulphonamide therapy, especially treatment with sulphadiazine: (1) there is the risk of drug toxicity; (2) there is the danger of initiating therapy in cases with dehydration, with consequent delay in starting treatment; and (3) sulphonamide-resistant strains develop, leading to relapse, chronic dysentery, or increase in the carrier state.

In view of the demonstration of the sensitivity of shigella organisms to chloramphenicol in vitro and the report of Ross et al. (1950), among others, of the efficacy of chloramphenicol in the treatment of shigella dysentery in children, it was thought desirable to determine its value in shigella dysentery in adults.

MATERIAL AND METHODS

96 cases of shigella dysentery occurring in Hong-Kong from January to December, 1951, were treated with chloramphenicol. The control series consisted of 92 cases occurring within the same period and treated with sulphadiazine. In our opinion it is important that the controls should be cases occurring in the same period, for different factors may cause the severity of the dysentery to vary from year to year.

The age and sex distribution are set out in table I. In both groups the average duration of symptoms before admission was forty-eight hours.

On admission the stool was examined microscopically, and those patients whose stools showed "typical bacillary exudate" were selected for treatment. Treatment was started pending bacteriological report, and only the cases proved bacteriologically are included in this report. The bacteriological findings in both groups are set out in table I, from which it will be seen that *Shigella flexneri* was the most common organism.

Cases were classified as mild to moderate, severe, and severe with dehydration, according to clinical assessment based on the degree of toxæmia, the severity of the dysenteric symptoms, and clinical and laboratory evidence of salt and water deficiency. The distribution of cases in both groups is set out in table I. The routine management of all the cases was the same. Where salt and water deficiency existed, physiological saline solution and 5% glucose were given intravenously until the urinary chlorides were within normal limits and the eight-hour output of urine was at least 500 ml. During the later phase of restoration of extracellular volume a solution of potassium salts was added to the infusion. In cases which initially showed dehydration in the group treated with sulphadiazine, treatment was not started until the urinary volume was restored. This delay was not necessary with chloramphenicol.

The patients treated with chloramphenicol were given an initial loading dose of 30 mg. per kg. of body-weight, and thereafter 30 mg. per kg. of body-weight daily in divided doses four-hourly. This was continued for three days after the first negative stool culture. The patients in the control group were given 2 g. of sulphadiazine and thereafter 1 g. four-hourly for three days after the first negative stool culture or until a total of 38 g. had been administered.

Stool cultures were made daily until three consecutive negative findings were obtained. When no stool was passed, specimens were obtained by rectal swab through a short proctoscope. Thereafter all stools passed were examined bacteriologically until discharge from hospital. The initial medium used was desoxycholate citrate agar. In all cases the medium was inoculated immediately the stool was passed or the swab taken.

Sigmoidoscopy was done in all cases after cessation of the acute diarrhœa.

The conditions of employment of 20 patients in the chloramphenicol-treated group and of 10 in the sulphadiazine-treated group were such as would lead to any relapse being brought to our notice. 74 of the remaining 76 in the chloramphenicol group and 75 of the remaining 82 in the sulphadiazine group reported for follow-up examination eight weeks after discharge from hospital.

RESULTS

Bacteriological Findings

The time which elapsed in both groups between the start of treatment and the first negative bacteriological report, with daily specimens, is set out in table II. In no case in either group was the organism isolated subsequent to the first negative report. In 22 of the 72 cases in the chloramphenicol-treated group with negative stools within twenty-four hours, each stool passed in that period was examined bacteriologically. The average time required for disappearance of the organism was sixteen hours.

It should be noted that in the sulphadiazine-treated group in 9 of the 11 cases showing evidence of salt and water loss there was a delay of twelve to twenty-four hours before treatment with sulphadiazine.

Table II shows that the stools of all the patients treated with chloramphenicol were bacteriologically negative four days after the start of treatment. In the sulphadiazine-treated group 9 patients had positive stool cultures at the end of the course of 38 g. six days after the start of treatment. Only 1 of these patients had a previous history of "diarrhœa," which had been treated with sulphaguanidine some two years previously. In 8 of the

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DR. GARDIKAS, DR. WILKINSON: REFERENCES

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TABLE I—DISTRIBUTION, SEVERITY, AND BACTERIOLOGICAL FINDINGS

Treatment	No. of cases	Age (yr.)			Sex		Severity			*Shigella*			
		15–25	25–35	35–50	M	F	Mild to moderate	Severe	Severe with dehydration	*flexneri*	*sonnei*	*Schmitzii*	Untyped*
Chloramphenicol ..	96	36	42	18	72	24	49	22	25 (5 critically ill)	70	14	1	11
Sulphadiazine ..	92	41	40	11	69	23	65	16	11	71	5	2	14

*In the earlier part of the investigation an adequate supply of typing sera was not available.

9 cases in-vitro sensitivity tests showed the organism to be highly resistant to sulphadiazine. Chloramphenicol was given, and this led to negative stool cultures in twenty-four hours in 4 cases, in forty-eight hours in 3 cases, and in ninety-six hours in 1 case. An in-vitro sensitivity test was not made in the 9th case, but a second course of sulphadiazine led to negative stool cultures after forty-eight hours.

Clinical Findings

In all the cases treated with chloramphenicol the fever resolved within twenty-four hours, and coincidentally there was much improvement in subjective symptoms. In the group treated with sulphadiazine fever resolved on average in 2·2 days, and resolution of subjective symptoms was less dramatic. Diarrhœa was considered to have ceased when three or less semi-formed or formed normal stools were passed. This occurred in the chloramphenicol group on average in 3·5 days, and in the sulphadiazine group in 5·6 days. The average time required for macroscopic blood to disappear from the stools was 1·5 days in the chloramphenicol-treated group and 3·6 days in the sulphadiazine-treated group. Sigmoidoscopy, done on average six days after the start of treatment, showed no significant difference between the two groups.

Dosage

The average total dose of chloramphenicol was 9·5 g., the individual doses ranged from 7·75 to 16 g. Treatment with sulphadiazine was discontinued because of toxic complications in 2 cases on the fourth and fifth days. Both patients had bacteriologically negative stools, and neither case relapsed.

Relapses

No relapses were encountered in either group.

Toxic Complications and Side-effects

In the chloramphenicol-treated group 5 patients developed mild glossitis and 4 pruritus ani. The symptoms and signs rapidly resolved when chloramphenicol was withheld. In the sulphadiazine-treated group indications requiring prompt cessation of treatment were encountered in 2 cases: 1 patient had severe hæmaturia on the 4th day, which in our opinion was occasioned by inadequate supervision of urinary output; and the other patient developed acute intravascular hæmolysis with hæmoglobinuria.

TABLE II—COMPARISON OF CHLORAMPHENICOL THERAPY WITH SULPHADIAZINE THERAPY

Treatment	24 hours		2 days		3 days		4 days		5 days		6 days	
	No. negative	No. remaining positive	No. negative	No. remaining positive	No. negative	No. remaining positive	No. negative	No. remaining positive	No. negative	No. remaining positive	No. negative	No. remaining positive
Chloramphenicol (96 cases)	72	24	17 72 89	7	4 89 93	3	3 93 96	Nil				
Sulphadiazine (92 cases)	19	73	42 19 61	31	19 61 80	12	2 80 82	10	1 82 83	9	..	9

DISCUSSION

Table II shows that the pathogens disappeared from the stools more rapidly in the chloramphenicol-treated group than in the sulphadiazine-treated group. This confirms the observation of Ross et al. (1950), reporting on chloramphenicol in the treatment of 35 cases of shigella dysentery (33 *Shigella sonnei*, 2 *Shigella flexneri*) in children aged from 3 months to 7 years, that the stools became bacteriologically negative on average in 0·76 day. These workers had previously treated 20 cases with sulphadiazine and found that the stools became negative on average in 2 days. Using the rapidity of disappearance of pathogens as the therapeutic index they considered that there was no statistically significant difference between the two groups. In our series a significant difference does emerge. Within four days all of the chloramphenicol-treated group had negative stool cultures, whereas in the control group 9 cases remained positive six days after the start of sulphadiazine therapy, when a total dosage of 38 g. had been given.

Further, not only was bacteriological improvement more rapid in the chloramphenicol-treated group but also the patients' clinical progress. Fever resolved more rapidly, as did the dysenteric symptoms. Abnormal constituents in the stools disappeared earlier than in the controls.

The persistent pathogens in 8 of the 9 cases treated with sulphadiazine were shown in vitro to be highly resistant to sulphadiazine. Treatment with chloramphenicol led to their rapid removal. This confirms the observations of Cooper and Keller (1950), who reported rapid resolution with chloramphenicol of 4 cases of dysentery in children due to sulphadiazine-resistant *Shigella sonnei*. These workers also reported the disappearance of sulphadiazine-resistant *Shigella sonnei* from the stools of an adult carrier after treatment with chloramphenicol.

Perhaps the happiest aspect of the use of chloramphenicol in acute bacillary dysentery is the relaxation of the rigid supervision of urinary output so essential in patients receiving sulphadiazine. Further, the use of chloramphenicol allows treatment to be started at the earliest moment, even in cases of salt and water deficiency, whereas the administration of sulphadiazine may require to be delayed until the urinary output is satisfactory.

SUMMARY AND CONCLUSIONS

Chloramphenicol is a very efficient agent in the treatment of acute shigella dysentery. It is also effective in the treatment of sulphadiazine-resistant pathogens.

It is more efficient than sulphadiazine, which is regarded by many as the sulphonamide of choice, for the following reasons: (1) resolution, bacteriological and clinical, is more rapid; (2) resistance to chloramphenicol has not been encountered, whereas sulphadiazine resistance has a significant incidence; and (3) treatment can be started in the presence of salt and water deficiency.

We have pleasure in expressing our appreciation of the able assistance of Lieut.-Colonel A. C. S. Hobson, R.A.M.C., and Captain D. Fraser, R.A.M.C., who supervised clinically some of the present cases.

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ACUTE COLONIC OBSTRUCTION DUE TO PANCREATITIS

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THE colon may be obstructed by pressure from pathological neighbouring structures, and this usually happens at those sites where the large bowel is fixed—i.e., at the flexures—and in the pelvis, where the recto-sigmoid loop may be occluded by a large inflammatory mass or by adhesions due to previous inflammation.

Two patients were recently admitted to this hospital with acute obstruction of the colon due to pressure from an inflammatory mass at the splenic flexure. The masses proved to be due to pancreatitis.

CASE-RECORDS

Case 1.—A man, aged 73, was admitted to hospital on Aug. 11, 1951, with four days' history of colicky central abdominal pain with nausea but no vomiting, several years' history of constipation, and eight days' history of stoppage of the bowels. He had lost about 35 lb. in weight in a year.

Examination.—He was very thin, weighing just under 98 lb., and dehydrated. His respirations were shallow and mucosæ pale. His pulse-rate was 92 and pulse bounding and regular. His blood-pressure was 180/80 mm. Hg. His heart sounds were of moderate quality, with a systolic murmur at the apex. His abdomen exhibited gross central and right peripheral distension, with much tympanicity to percussion centrally but shifting dullness in the flanks. The abdominal wall over the subumbilical region was œdematous. There were generalised guarding and tenderness over the abdomen, with no apparent localisation. The rectum was ballooned.

Treatment.—Two gentle soap-and-water enemata were given on admission, without producing either fæces or flatus. As the urinary chlorides were deficient, treatment with intravenous glucose-saline solution was begun.

Operation.—About five hours after admission laparotomy through a left lower paramedian incision showed that the peritoneal cavity contained purulent fluid. The small bowel, cæcum, and colon were distended as far distally as the splenic flexure, but beyond this the large intestine was collapsed and empty. At the splenic flexure a mass was palpable, but it was difficult to determine whether this was malignant or not, because it was enclosed in omentum. In view of the patient's poor general condition and peritonitis, proximal drainage through a cæcostomy was instituted, and the abdomen was closed round a drainage tube to the pelvis.

Postoperatively the patient's condition remained poor for seven days, but with restoration of his electrolyte balance and with antibiotic therapy it slowly improved. A high-protein diet was prescribed, and within five weeks his weight had increased to 120 lb.

Further Operation.—On Oct. 11 laparotomy through a left subcostal incision showed that the palpable mass found at the previous operation was still present and incorporated the spleen, the splenic flexure, omentum, and the tail of the pancreas. Mobilisation of the mass, with splenectomy and removal of the omentum and the tail and part of the body of the pancreas, revealed the splenic flexure to be free from obstruction. The continuity of the colon was not disturbed. During the dissection the pancreas was found to be necrotic over a wide area. The abdomen was closed.

Operation Specimen.—The tissue removed at operation consisted of spleen, omentum, and a portion of pancreas. The pancreas presented numerous areas of fat-necrosis and hæmorrhage. The spleen showed a moderate degree of perisplenitis. The portion of omentum examined showed severe fat-necrosis.

Postoperatively the patient's condition immediately after the operation was satisfactory, but after forty-eight hours he became collapsed and cyanosed, and showed evidence of peripheral circulatory failure. His pulse-rate rose to 130 and his blood-pressure fell to 100/68 mm. Hg. His pupils became unequal, the left becoming dilated. No other abnormality of the central nervous system was detected. He became comatose and died.

Necropsy Findings.—The heart was enlarged and showed left ventricular hypertrophy. There was no valvular disease, but the myocardium was of poor quality. The aorta and coronary vessels exhibited patchy atheroma. The lungs showed terminal hypostatic pneumonia. No obstruction was found in the intestine. The remnant of the pancreas showed fat-necrosis. There was a massive hæmorrhage into the left suprarenal gland. The right adrenal showed no macroscopic abnormality. The brain showed only œdema, with no focal lesion to explain the ante-mortem inequality of the pupils.

Case 2.—A carter, aged 71, was admitted to hospital on Sept. 22, 1951, complaining of progressive weakness over the last few days, with severe recurrent generalised abdominal colic and vomiting for thirty-six hours. There had been no bowel movement for twenty-four hours.

Examination.—He appeared toxic and dehydrated, with a dry furred tongue, pulse-rate 94, volume of pulse moderate, heart sounds fairly good, abdomen distended and tympanitic, with generalised tenderness, maximal over the epigastrium, which showed muscle guarding. Very active bowel sounds were heard on auscultation. Digital examination revealed an empty and slightly ballooned rectum.

Operation.—After intravenous therapy to combat dehydration and electrolyte imbalance, the abdomen was opened, under general anæsthesia, through a right rectus-splitting incision. The cæcum and ascending and transverse colon were much distended, but the ileum showed only minimal dilatation. Obstruction was due to a fixed mass close to the splenic flexure. Cæcostomy was done.

Postoperative recovery was good, with continuation of intravenous fluid therapy. On Oct. 8, the bowel moved per rectum, and a barium enema revealed normal passage of contrast medium to the cæcum without any evidence of blockage or neoplasm. On Oct. 12, the patient developed retrosternal pain and appeared ill. He said he had had several similar attacks before his present illness, and electrocardiography showed coronary insufficiency. Convalescence was satisfactory, and on Nov. 6 laparotomy was done. A fibrotic omentum was found wrapped round the transverse colon, and areas of fat-necrosis were numerous. The pancreas was nodular and indurated and showed areas of fat-necrosis. The tail of the pancreas and the omentum were adherent, and were separated from the colon, which then showed no obstruction. A specimen of omentum showed fat-necrosis. There was no evidence of biliary disease. The cæcostomy and abdomen were closed, and recovery has been uneventful. He remains well to date.

COMMENTS

The secondary involvement of contiguous viscera from inflammation of the pancreas has often been described, but it is uncommon for the presenting secondary condition to be so severe that the primary cause is completely masked. The two cases reported here exhibited an almost identical clinical picture, no feature of which, even at the first operation, suggested that the pancreas was at fault. The patients were both old men. There was no history of dyspepsia or of biliary upset, and both patients appeared to have acute intestinal obstruction.

The complications of pancreatitis are many and varied, but implication of the colon is uncommon, though an abscess may rupture into the lumen (Aird 1949). Obstruction of the lumen of the colon is, however, very rare, and we can only trace three published cases; all concerned the splenic flexure:

Forlini (1927) reported a man, aged 38, who died of acute colonic obstruction after a 15-month history. Necropsy revealed that the cause of the occlusion was fibrosis following pancreatitis.

Remington et al. (1947) added two further very similar cases, one in a man aged 45, and the other in a woman aged 44, which presented with chronic colonic block and a history of proved pancreatitis of many years' duration. Both patients were successfully treated by excision of the tail of the pancreas and the occluded segment of colon.

Of our patients, the first had acute obstruction following a long chronic disease, and the second had a primary acute attack which must have been due to œdema and matting of pancreas and omentum to colon, this subsiding spontaneously on relief of the intestinal obstruction.

Thanks are due to Mr. G. T. Mowat, in whose wards these cases were, for permission to publish, and to Prof. G. L. Montgomery for pathological reports.

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THE ASSESSMENT OF MOBILITY IN JOINTS

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In patients undergoing treatment for rheumatoid arthritis the methods of assessing improvement are unsatisfactory.

One of the most useful objective measurements of improvement is the change in range of movement of a joint. In the past this has usually been measured with a protractor to which two arms are attached and laid along the parts of the limb comprising the joint. This way of measuring the angle of movement has in practice the following disadvantages:

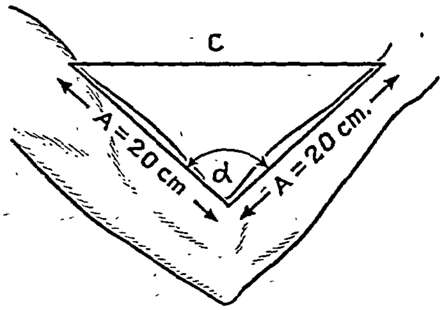

Fig. 1—Hypotenuse used at elbow-joint.

(1) With movement of the joint, muscle masses tend to interfere with correct measurement of the angle.

(2) Swelling of the joint or periarticular tissues—e.g., an olecranon bursa—may interfere with the position of the protractors.

(3) In joints where it is impossible to lay the protractor arms along straight edges the correct position of the protractor arms can only be determined by eye and is hence open to considerable inaccuracies. This is true of the knee, shoulder, and hip.

In this paper I give an account of a simple method of determining the angle of movement of a joint which avoids all the above difficulties. In the following description it is applied to the elbow.

Two points 20 cm. from the crease at the bend of the elbow are marked on the upper arm and on the forearm (fig. 1). The distances (C) between these points in full extension and flexion are measured and compared. This distance C varies with the angle of movement of the joint, according to the formula

$$\cos\alpha = 1 - \frac{C^2}{2A^2}$$

As C and A are known, a graph can be plotted (fig. 2) showing the relation of the angle α to the length C. From this graph the angle of movement of the joint can be read off directly when the distance C is known.

TABLE I—APPLICATION OF METHOD

Joint	Movement	Position of axis	Distance from and position of skin crease
Elbow	Flexion in full supination	Arm and forearm	In cubital fossa 20 cm.
Shoulder	Abduction with palm facing side of body	Arm and side of body	In axilla 30 cm.
Knee	Flexion	Thigh and leg	In popliteal fossa 30 cm.

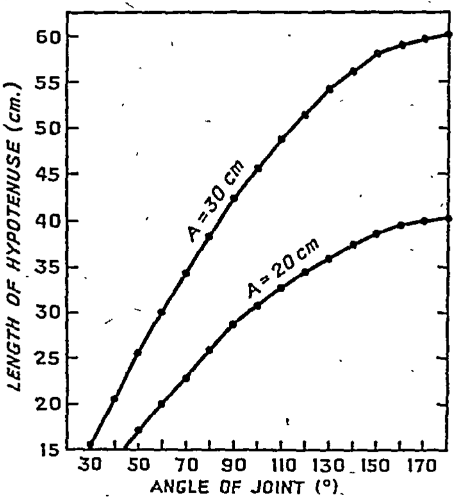

Fig. 2—Relation between hypotenuse and angle of movement of a joint.

This method of measurement can be applied to the joints and movements shown in table I.

For the purpose of comparison of one patient with another it is necessary to measure equal distances from the joint along both the arms of the angle they contain. If bony points were taken, a separate graph would have to be constructed for each patient.

In assessing the progress of a patient it is unnecessary to convert the hypotenuse to the angle, because the distances will show how much improvement has taken place.

An attempt has been made to compare this method with the method of angle measurement. It is almost impossible to do this accurately, because the difficulties of measuring the included angle are insuperable. If, however, ink lines are drawn along arm and forearm from the axis of the elbow-joint and the angle contained by these lines is measured, very close correspondence is found between this angle and that obtained from fig. 2 by measuring the hypotenuse.

TABLE II—COMPARISON OF METHODS

Observer	Case 1			Case 2		
	Angle by protractor	Hypotenuse	Angle from hypot.	Angle by protractor	Hypotenuse	Angle from hypot.
A	118	32·5	108	125	37·5	140
B	104	32·5	108	136	38	145
C	123	32·8	110	136	38	145
D	115	32·5	108	140	38	145
E	115	32·4	107	127	37	135

Comparison of the error of the two methods has been made as follows: Five observers were independently asked to measure the angle and the hypotenuse opposite the angle of two fixed joints. An elbow was chosen in each case, and the results were as follows: a variation range of (1) 104–123°, (2) 125–140° by the protractor method and of (1) 107–110°, (2) 135–145° by the method described above. The variations between the observers are shown in table II.

It is clear from fig. 2 that by the method described small angles are measured much more accurately than angles greater than 140°. Accordingly, improvement in flexion is more accurately measured than improvement in extension.

I have to thank Dr. Ernest Fletcher, physician in charge of the department, for advice and encouragement and for access to patients.

Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Daraprim in Malaria

At a meeting of this society held on July 17 with Sir Neil Hamilton Fairley, F.R.S., the president, in the chair, papers were presented on the new antimalarial drug, 'Daraprim.'

Dr. G. H. Hitchings (New York) opened with a discussion of the biochemical properties of the diaminopyrimidines. These drugs are competitive antagonists of the folic-folinic acid system in the growth of *Lactobacillus casei.* A formal structural analogy between members of the series and proguanil, and certain similarities of microbiological behaviour, led to the trial of the compounds as antimalarials. A comprehensive series of some 300 diaminopyrimidines, having different substituents in the 5- and 6- positions, were studied, and from among these daraprim (2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) was selected for clinical trial because of its high activity against several species of malaria parasites in laboratory animals.

Experiments were described which suggested that the antimalarial action of daraprim is probably associated with its activity as an anti-metabolite of the folic-acid series of vitamins and that the drug may be regarded as a structural analogue of folinic acid of a rather remote sort, particularly well adapted to displacement of the metabolite from its apoenzyme in the malaria parasite.

Mr. I. M. Rollo described the methods used for testing the antimalarial activity of these compounds against *Plasmodium gallinaceum* in chicks and *P. berghei* in mice, and traced the steps by which daraprim was selected. He mentioned resistance as a potential limiting factor of the usefulness of the drug and said that, by a specially adjusted system of dosage, he had produced daraprim-resistant strains of *P. gallinaceum* and *P. berghei.* He had found that a strain of *P. gallinaceum* resistant to proguanil was only slightly resistant to daraprim, but the position of cross-resistance in general was still somewhat confused.

Dr. L. G. Goodwin gave a review of clinical trials and pharmacology. The first results came from Lagos, where it was found that single doses of as little as 5 mg. of daraprim cleared the asexual parasites of *P. falciparum* from the peripheral circulation of symptom-free "carriers" (school-children) for about a month. From Gambia, Tunisia, India, and Indo-China results in the treatment of overt attacks of malignant, benign tertian, and quartan malaria were favourable. A single dose, usually of 50 mg., served to bring about clinical cure in most premunised subjects, though the rate of disappearance of parasites and fever was occasionally slow. Gametocytes of *P. falciparum* appeared to be unaffected, but in fact failed to develop when ingested by the mosquito. In Malaya results were less satisfactory and a number of failures had been recorded. In the Belgian Congo, an experiment in mass suppression gave very favourable results.

Daraprim, when given in large doses, produces symptoms which are probably associated with a deficiency of the folic-folinic acid series of vitamins. As the recommended therapeutic and suppressive dose is less than a hundredth of the amount required to produce such symptoms in the monkey, the question of toxicity in man does not arise. Relatively high doses have been taken by volunteers over varying periods without ill effect.

A report from Dr. G. Robert Coatney of the National Institutes of Health, Bethesda, Maryland, was read. He found that a weekly dose of 25 mg. of daraprim, given to volunteers infected on one occasion only by mosquito-bite with the Chesson strain of *P. vivax,* completely suppressed the infection; no relapses occurred up to 251 days after cessation of treatment. With repeated infections, two out of the three volunteers relapsed some time after withdrawal of the drug. With weekly doses of 12·5 mg. or less, relapses occurred when medication ceased, but even 0·78 mg. once weekly caused complete suppression while the drug was being taken. A weekly dose of 0·39 mg. did not give complete suppression; transient fever and parasitæmia were observed but there were no frank attacks. Once-weekly doses of 300 mg. of proguanil or of chloroquine in parallel experiments suppressed the infection, but relapses occurred on withdrawal. Dr. Coatney also had some evidence of true causal prophylactic action. Treatment of early malarial attacks with a single dose of 25 mg. of daraprim reduced the fever almost as quickly as 600 mg. of chloroquine, although parasitæmia persisted longer after daraprim. A tolerance test in twelve volunteers showed that, during treatment with 25 mg. daily for seven weeks, a fall in red blood-cells occurred in one of them, and Dr. Coatney thinks that this dosage may exceed the limit of tolerance for some individuals.

Dr. C. L. Oakley showed slides of the lesions in bone-marrow, spleen, adrenal, and kidney, produced in monkeys by repeated high doses of daraprim, and expressed the opinion that they arose from arrested maturation of the cells and could be attributed to folic-folinic acid deficiency. He was satisfied that, with the possible exception of metaplasia of the epithelium of the kidney and bladder, the changes were reversible. He emphasised that these toxic results occurred irregularly and with doses vastly in excess of those used for therapy or suppression. Other speakers in the discussion which followed recorded observations in general agreement with these conclusions.

Dr. Dean Smith described successful trials in Gambia, where daraprim had been used both therapeutically and for mass suppression. It had also been given in weekly doses to infants from birth onwards with good results. For this particular purpose, and indeed for all mass suppression, the fact that the drug was tasteless was of considerable importance.

Dr. Thomas Wilson (Kuala Lumpur) discussed the findings in Malaya, where in several cases daraprim had failed to effect cure. Similar results were being obtained with proguanil, but this did not appear to be due to cross-resistance. He did not regard daraprim as a suitable drug for use against the Malayan strain of *P. falciparum.*

Sir George McRobert told of six cases of relapsing *vivax* infection from Korea which had been treated in the Tropical Diseases Hospital. In these the parasitæmia had persisted for a number of days. On the other hand, Mr. P. G. Shute (Epsom) had found that a single dose of 25 mg. produced apparent cure in a patient infected with *P. vivax* for therapeutic purposes. The patient had subsequently to be reinfected.

The President, referring to these discrepancies, drew attention to the well-known but oft-forgotten fact that different races of the malaria parasite vary greatly in their response to different drugs. He saw a strong similarity between the action of daraprim and proguanil and expressed the opinion that in the cases of *vivax* infection he had seen in the Tropical Diseases Hospital subinoculations after perhaps the third day would have failed to produce infection despite the presence of parasites in the blood. Though he was unable to explain the failures in Dr. Coatney's multiple-infection experiment he considered his results of great interest, and thought it possible that daraprim might have specific activity against the late tissue forms of *P. vivax.*

He thought that neither daraprim nor proguanil were altogether suitable for the treatment of overt malaria, and that their most important rôle was as suppressants.

New Inventions

A ONE-WAY VALVE FOR MULTIPLE INJECTIONS FROM ONE SYRINGE

THE danger of using one syringe to give multiple injections is well known. Hughes[1] and Evans and Spooner[2] have shown that contamination of the syringe may be due to the negative pressure induced in the syringe when the needle is detached. The presence of this negative pressure is easily shown by the fact that a drop of fluid hanging from the point of the needle is sucked in at the moment of removal. Reflux of fluid to the syringe at some stage of the injection—e.g., during the withdrawal of the needle from the skin—is another cause of contamination, which can be shown by injections into fluids under a known pressure (" artificial mouse ").

Up to now the only safe method of preventing such contamination has been the sterilisation of needle and syringe after each inoculation. Changing the needle after each inoculation, according to the recommendations of the Medical Research Council seven years ago,[3] appears to be a sure method of transferring infection. The advice of Fleming and Ogilvie[4] to dip the needle, without detaching it from the syringe, in a hot oil bath (liquid paraffin at 130°C) for 10 seconds, applies only to contamination of the needle and not to that of the syringe.

But, as is shown in the following experiment, even the needle cannot be sterilised in this way, if it has been contaminated with a virus beforehand.

A sterile syringe was filled with sterile broth. The needle (size 12) was infected by dipping half the shaft in a 5% emulsion of a vaccinia egg-culture. The infected part or more of the needle was dipped in a hot oil bath (130°C) for 10 seconds. Then one drop of the broth was pressed through the needle and inoculated on to the chorio-allantoic membrane of each of four duck's eggs. All of them showed vaccinia infection after 3 days. The experiment was repeated on three occasions; on each occasion vaccinia infection of the membrane resulted.

The only way to avoid the necessity of sterilising both needle and syringe after each injection is to prevent reflux of fluid on to the nozzle of the syringe *in all circumstances*, so that the nozzle and the syringe contents are protected from contamination. A simple device which achieves this object is described here.*

THE APPARATUS

A one-way valve between the needle and the syringe allows the fluid to pass only from syringe to needle.

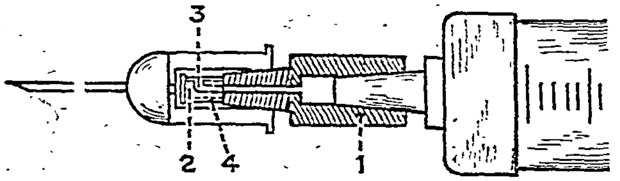

Fig. 1—Construction of one-way valve: 1, brass tube; 2, tapered end; 3, aperture; 4, rubber collar.

The valve (see figs. 1 and 2) is a tapering nickel-plated brass tube, with two lateral apertures closed by a rubber collar. The fluid forced by the piston from the syringe through the tube passes through the lateral openings, displacing the rubber collar, into the needle. Back pressure from the needle to the syringe merely closes the valve, preventing reflux of fluid and protecting the syringe against contamination. After every inoculation the needle and valve must be changed, but there is no need to sterilise the syringe.

EXPERIMENTS ON ANIMALS

The efficacy of the valve is easily demonstrated in the laboratory by the mouse-inoculation method.

Mice were infected intraperitoneally with a highly virulent strain of streptococcus (Aronson), which in very small doses kills mice within twenty-four hours. After eighteen hours an infected dead mouse was injected intraperitoneally with 0·5 ml. of sterile broth from a 'Record' syringe containing 2 ml. The needle was left in the abdominal cavity for ten seconds; it was then withdrawn, care being taken not to move the plunger. Another sterile needle was then substituted for the first, and 0·25 ml. of broth from the same syringe was injected intraperitoneally into a normal mouse. Three separate series of such experiments were made, using 5, 6, and 10 normal mice. All the mice died within twenty-four hours (see table).

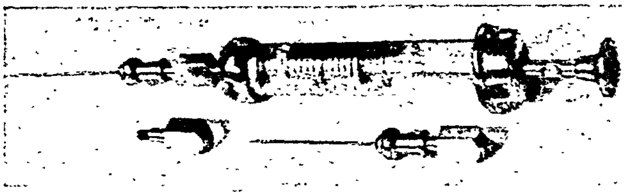

Fig. 2—The valve, the valve fitted to the needle, and the valve and needle fitted to the syringe.

Simultaneously, three similar series of experiments were made with the needle and one-way valve described above, no care being taken to avoid movement of the plunger during withdrawal of the needle from the abdominal cavity of the infected mice; the set was changed after each injection into an infected mouse; and series of 9, 8, and 8 normal mice were treated. *None of these 25 mice showed symptoms* of infection during the observation period of two weeks (see table).

NORMAL MICE INJECTED INTRAPERITONEALLY WITH 0·25 ML. BROTH FROM A SYRINGE PREVIOUSLY USED FOR THE INJECTION OF 0·5 ML. BROTH INTO THE PERITONEAL CAVITY OF A MOUSE THAT HAD DIED FROM STREPTOCOCCAL INFECTION

Test	Without valve. Changing the needle between the inoculations into the infected and normal mouse		With valve. Changing the valve-needle set between the inoculations into the infected and normal mouse	
	No. of mice inoculated	No. of deaths within 24 hours	No. of mice inoculated	No. of deaths or diseased mice
I	5	5	9	0
II	6	6	8	0
III	10	10	8	0
Total	21	21	25	0

These experiments show that the valve affords full protection against transmission of streptococci. Since this effect does not depend on the properties of the infecting agent, similar protection can be expected against transmission of any virus. The valve is now being used at our institute for the purpose of preventing serum-hepatitis arising from mass inoculations.

DIRECTIONS FOR USE

The one-way valve should be used when a single sterile syringe has to serve for multiple injections without being sterilised between injections. The valve cannot be used for withdrawing fluids. The working of the valve is tested by feeling resistance when the plunger is pulled. (It has to be remembered, however, that old syringes may be leaky, leading to underestimation of the tightness of the valve.) The injection is given in the usual way. The rubber collar offers some resistance to the fluid, but this can easily be overcome. It is essential that the valve-needle set should fit the nozzle of the syringe firmly so that it is not blown off. In giving intravenous injections, to check the position of the needle in the vein, the syringe and valve together can be disconnected from the needle to allow the blood to

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1. Hughes, R. R. *Brit. med. J.* 1946, ii, 685.
2. Evans, R. J., Spooner, E. T. C. *Ibid*, 1950, ii, 185.
3. Medical Research Council War Memorandum no. 15. H.M. Stationery Office, 1945.
4. Fleming, A., Ogilvie, A. C. *Brit. med. J.* 1951, i, 543.

* Those interested in the manufacture may apply to Rijks Instituut voor de Volksgezondheid (general director: Dr. J. Spaander), Sterrenbos 1, Utrecht, for further particulars. Patents applied for.

flow out for a moment. After each injection the valve and needle must be exchanged for a fresh sterile set.

Cleaning and Sterilisation

A little water is syringed through the valve to remove remnants of injection fluid. The valves can be sterilised by boiling or by autoclaving. In the latter instance it is convenient to assemble the needles and valves before sterilisation. Disinfection in alcohol is unreliable and damages the rubber collar.

Testing Valves

The valve is fitted to a needle and syringe. The needle is dipped in water, and the plunger is pulled for ten seconds; no water should enter the syringe. The test is best done with a tuberculin syringe (1 ml.) immediately before sterilising valves and needles.

Repair

The rubber collar withstands numerous injections and sterilisations. Condemned valves can be repaired by renewing the rubber collar.

R. GISPEN
M.D. Amsterdam
From the National Institute of Public Health, Utrecht

Reviews of Books

Commentary on Age

KENNETH WALKER, F.R.C.S. London: Jonathan Cape. 1952. Pp. 192. 12*s*. 6*d*.

Mr. Walker has found "old age to be far less disconcerting at close quarters than it appeared at a distance"; and that is, in brief, the lesson he tries to teach. (He admits, however, that he is really only now approaching the fringes of old age.) It is slowly being realised that many unpleasant things once thought to be the necessary concomitants of old age can be prevented—not by a regimen, in youth, of deadening austerity, but by an awareness that changes will become necessary, and that the transition from middle to old age can be painless.

Mr. Walker gives a clear account of the ageing process, both anatomically and physiologically, and follows this by a sensible summing up of the various controversies on rejuvenation. He emphasises how important is the psychological aspect of any rejuvenation operation, but warns that "ageing is a highly complex process and if it is ever to be arrested or reversed it will be by means of remedies so difficult to apply that our patients may well prefer to keep to the customary road and to grow old in accordance with the dictates of Nature." But the prospect is not all pleasing: the waning of the influence of the Church has left a void in many a person's emotional life, and unless that can be filled "the last stages of the journey through life become a journey of weariness and despair." On the whole, however, this is a useful and encouraging book by one who has developed a realistic and helpful philosophy.

Understanding Natural Childbirth

HERBERT J. THOMS, M.D., in collaboration with LAURENCE G. ROTH, M.D.; Picture Story by DAVID LINTON. New York and London: Staples Press. 1952. Pp. 112. 17*s*. 6*d*.

THIS book is designed to prepare the pregnant mother for the bodily changes of pregnancy and to help her to coöperate fully during her labour and delivery. There have been books similar in aim, of the "natural childbirth" school, but they have lacked the dramatic serial photographs of the process by David Linton, some of which were published in *Time* and *Life* and *Picture Post* while others are seen here for the first time. These are very well done, presenting beautifully the familiar emotional landmarks of labour. Some previous books in this category have been either over-emotional or over-technical. This one presents complex facts in a simple and detached manner, the message of each section being summed up in chapter headings quoted from such English authorities as Prof. W. C. W. Nixon, Dr. Grantly Dick Read, Dr. Janet Vaughan, and the late Mrs. Helen Heardman, as well as from American sources. The text shows well how a maternity hospital can be run on a basis of mutual understanding between all its participants, and reminds readers that if the father is allowed to help, a woman need never be left alone during labour; that the baby who is put to the breast immediately after birth acquires the sucking habit easily, giving the mother confidence in suckling, and aiding involution; and finally that group discussion is a good way to allay fear.

Urine and the Urinary Sediment

A practical manual and atlas. RICHARD W. LIPPMAN, M.D., research associate, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 124. 55*s*.

A COLLEAGUE of the late Dr. Thomas Addis, Dr. Lippman has long been a keen and careful observer of the urinary sediment in disease; and the main feature of his book is a series of beautiful colour photographs of casts, cells, and crystals, as they occur in the urine in various diseases. These pictures are splendid and the methods and findings well described. Here, perhaps, is the last word on the urinary sediment. The price is high, but many hospital laboratories will want to possess this book, both as a work of reference and for the instruction of medical students and technicians.

Biological Antioxidants

Transactions of the Fifth Conference Nov. 30–Dec. 1, 1950. Editor: COSMO G. MACKENZIE, department of biochemistry, University of Colorado. New York: Josiah Macy, Jr., Foundation. 1952. Pp. 229. $3.75.

THE discussions at this conference were primarily about the chemical effects, particularly the oxidative effects, of radiation on biological systems—from that of the whole mouse (A. M. Brues) to that of the humblest bacterium (O. Wyss).

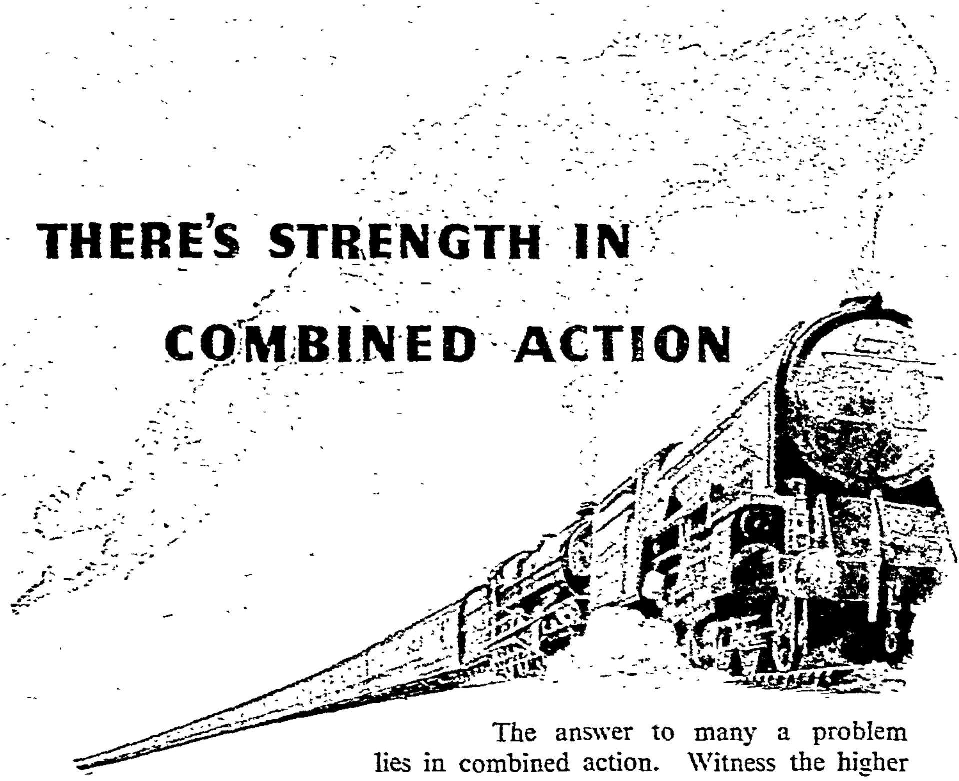
Discussions on the physicochemical effects of radiation on solutions in vitro (R. S. Livingston), and the effects of sulphydral systems, chiefly enzymes, also in vitro (E. S. Guzman Barron) are reported fully. These communications deal primarily with oxidation and to a much smaller and more variable extent with antioxidants; however, Free Radicals, Peroxides, and Antioxidants in Some Biological Processes, by E. V. Jensen, is packed with good meat on antioxidants.

While the report will be of interest to radiobiologists and others with previous experience in the field, it is doubtful if it will be intelligible to the newcomer or the general reader. The proceedings have been reported verbatim and interjections seem to have been encouraged. Many of these result in remote deviations from the theme, so that continuity of argument is lost. If the tea-table conversation of a rather large and progressive laboratory were reported it would perhaps read like this report.

Essentials of Anæsthesia (5th ed. Oxford: Blackwell Scientific Publications. 1952. Pp. 378. 40*s*.).—The fifth edition of this useful general work by Prof. R. R. Macintosh and Dr. Freda Bannister includes a chapter on curare and other muscle relaxants introduced during the last few years. The impact of these drugs on anæsthesia has, indeed, made additions and modifications necessary throughout the book, but otherwise it is much the same. Dr. Bannister has been entirely responsible for the latest revision.

Clark's Applied Pharmacology (8th ed. London: J. & A. Churchill. 1952. Pp. 691. 37*s*. 6*d*.).—For a long time to come the doctor's knowledge of pharmacology is likely to be composite—derived in part from experimental work in the pharmacological and physiological laboratories, in part from the mass of empirical therapeutics which he learned as a student in the wards, and in part from the announcements of the manufacturing pharmacists. The textbook which deals adequately with both experimental and empirical pharmacology has still to be written, but "Clark" has always been deservedly popular with senior students and practitioners because it shows some awareness of the pharmacological problems of medical practice. In their revision Prof. Andrew Wilson and Dr. H. O. Schild have maintained this tradition, but their wish to be comprehensive has involved compensatory sacrifices, and some sections of the book seem unnecessarily meagre—to physiologist and clinician alike. They are to be congratulated on bringing the text up to date without impairing the structure of the original, but there are perhaps more misprints and minor errors than there should be. Some of the lighter touches are of a kind which will not be well received by all readers, and the need for plain words is apparent here and there.

THERE'S STRENGTH IN COMBINED ACTION



The answer to many a problem lies in combined action. Witness the higher blood levels and the greater clinical efficacy that have been reported from the oral administration of penicillin and the sulphonamides simultaneously in cases when the oral administration of the antibiotic or chemotherapeutic agent alone has been ineffective. A convenient means of applying this combined antibacterial therapy is Sulpenin. Containing penicillin, sulphadiazine and sulphamerazine in balanced dosage, it provides a valuable treatment for many infections due to susceptible micro-organisms. By utilising the synergistic action between penicillin and the sulphonamides the antibacterial range is increased, the likelihood of kidney damage is lessened and the tendency for the bacteria to develop mutant strains resistant to one or other of the component drugs is reduced.

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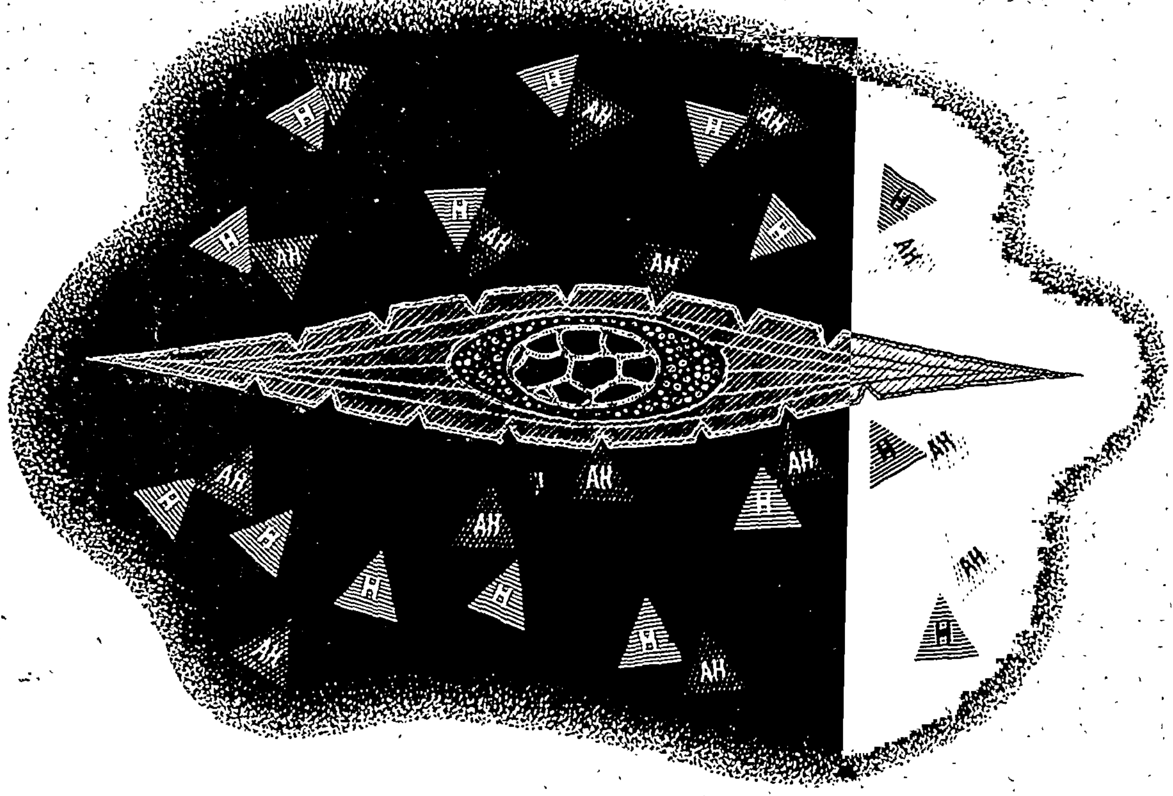

Diagram symbolizing competition for "shock-tissue" receptor sites by histamine (H) and an antihistaminic (AH).

Modus operandi....

The clinical use of antihistaminics such as mepyramine maleate and promethazine hydrochloride for the symptomatic relief of allergic and anaphylactic conditions is based on the theory of histamine-release.

According to this concept, allergy is the result of a reaction between the sensitizing substance, the allergen or antigen, and specific antibodies produced by the body. Once the hypersensitive individual has become sensitized, further exposure to the offending substance results in excess release of histamine or a histamine-like compound, which in turn provokes the allergic manifestation. The nature of this response in a particular individual depends on the part or parts of the body acting as "shock-tissues".

The antihistaminics are not believed to prevent the antigen-antibody reaction in the "shock-tissue", nor to destroy the histamine thereby released, but it is thought that in some unknown manner, perhaps by competing for and occupying or blocking the receptor-sites in the "shock-tissues", they prevent tissue damage by histamine.

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THE LANCET

LONDON: SATURDAY, JULY 26, 1952

Rational Use of Antibiotics

THE need is great, though the time is not ripe, for a simple guide to the intelligent use of antimicrobial drugs. The ordinary doctor is bewildered by the complexities of chemotherapy. On the one hand the number of drugs steadily increases, while on the other the sensitivity of bacteria to these drugs seems steadily to decrease, and there are dangers of sensitisation and of "superinfection" with endogenous drug-resistant bacteria and fungi.

There is probably much sense in the old adage "use the new drug while it still acts"; for the microbial reaction to attack by the new antibiotics is to develop variants which resist one or more of these agents. Because of this and the evidence that a combination of two drugs may be more effective than each separately, and may inhibit the emergence of resistant bacterial strains, combined chemotherapy is becoming more usual. The outstanding example is the combination of streptomycin and P.A.S., which in pulmonary tuberculosis is therapeutically better than either drug alone and is most effective in preventing the development of streptomycin-resistant tubercle bacilli.[1] However, one swallow does not make a summer; and "shot-gun" therapy has its risks. The recent studies of JAWETZ and his colleagues[2] illustrate the possible dangers of certain combinations of antibiotics. JAWETZ[3] has suggested certain rules for the rational use of existing antimicrobial agents. These he divides into two broad groups: (*a*) group 1, which contains the bactericidal drugs such as penicillin, streptomycin, and bacitracin; and (*b*) group 2, which consists of drugs that are mainly bacteriostatic (e.g., aureomycin, chloramphenicol, terramycin, and possibly the sulphonamides). Pairs of drugs from either group or from both groups may have an increased activity, either additive or synergistic; or they may have a decreased or antagonistic activity; or they may simply have the activity of one or other of the drugs alone. With an additive action a half dose of each of two drugs has the same effect as a full dose of one or the other; this has little to recommend it unless it is indicated on pharmacological grounds to reduce toxicity or promote absorption. A synergistic effect implies an increased bactericidal action and a rate of cure beyond that obtained additively; while antagonism has the opposite implication. The agents in JAWETZ's group 1 when used in combination, either in the test-tube or in experimental infections, are commonly synergistic, occasionally indifferent, but never antagonistic. The synergistic action is corroborated by clinical experience, as when penicillin plus streptomycin cures subacute bacterial endocarditis which has resisted penicillin or streptomycin alone. Members of group 2 are neither synergistic nor antagonistic when used together, but simple additive effects are usual. Thus, there is little to be gained by combining small doses of aureomycin and chloramphenicol when an adequate dose of one or other would be effective. Incidentally, the optimum dose of these new drugs may be less than was originally suggested; for example, in the U.S.A. aureomycin is now being given in doses of 0·25 g., instead of 0·5 g., three or four times daily.

Difficulties arise when a bactericidal drug is used in combination with a bacteriostatic drug. If the organism is sensitive to the bactericidal agent, then the addition of a bacteriostatic drug is likely to have an antagonistic action. If, on the other hand, the organism is resistant to the bactericidal drug but can be inhibited by a large dose, then a combination of the two drugs may have a synergistic effect. Thus, if a combination of penicillin and chloramphenicol is used against a penicillin-sensitive streptococcus the anti-streptococcal activity may be reduced; but if this combination is used against a penicillin-resistant proteus bacillus a synergistic action may be expected. This reversal of combined activity from the use of a bactericidal and a bacteriostatic drug may be seen also in resistant mutants of organisms, such as the staphylococcus, that are ordinarily susceptible to the group-1 drugs. To what extent these findings are applicable to clinical practice is not yet known; in experimental infections dosage has to be carefully adjusted in order to demonstrate the antagonistic action of two drugs, and indeed contradictory findings have been reported.[4] There is, however, some clinical support for the laboratory findings, as in the disappointing results from the combined use of penicillin and aureomycin in pneumococcal meningitis.[5] It would therefore seem reasonable to avoid combinations of bactericidal and bacteriostatic drugs unless there are good clinical reasons for such a combination.

Another difficulty—and this is particularly evident in hospital practice—is the ever-increasing incidence of drug-resistant variants of the common pathogens. Penicillin-resistant staphylococci are now well established in most hospitals, and there are reports of an increasing incidence of streptomycin-resistant staphylococci and a high proportion of streptomycin-resistant gram-negative bacilli, including proteus and pyocyaneus. Interest in this regard is now focused on the newer antibiotics. While there is little evidence in this country that the pathogenic staphylococci are naturally resistant to these new antibiotics,[6]

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1. Daniels, M., Hill, A. B. *Brit. med. J.* 1952, i, 1162.
2. Jawetz, E., Gunnison, J. B., Speck, R. S., Coleman, V. R. *Arch. intern. Med.* 1951, 87, 349. Speck, R. S., Jawetz, E., Gunnison, J. B. *Ibid*, 88, 168. Jawetz, E., Gunnison, J. B., Speck, R. S. *Amer. J. med. Sci.* 1951, 222, 404.
3. Jawetz, E., Gunnison, J. B. *Antibiotics Chemotherapy* 1952, 2, 243.
4. Bliss, E. A., Warth, P. T., Long, P. H. *Bull. Johns Hopk. Hosp.* 1952, 90, 149.
5. Lepper, M. H., Dowling, H. F. *Arch. intern. Med.* 1951, 88, 489.
6. Linsell, W. D. *J. clin. Path.* 1952, 5, 165.

resistance can be induced fairly readily in the test-tube and there are reports from this[7] and other countries of resistant strains in clinical practice. Thomson[7A] and his colleagues in Australia have found an increasing incidence of resistant coliform organisms as well as of staphylococci in hospital, where cross-infection undoubtedly plays a part. Cross-resistance between aureomycin and terramycin, which are closely related, is common; but resistance between these two substances and chloramphenicol is more irregular. Strangely enough, increased resistance to this group of drugs may be accompanied by enhanced sensitivity to streptomycin or penicillin.

The latest observations on the synergistic and antagonistic activities of drugs and the development of resistance[8] and cross-resistance should stimulate further study of their mode of action on bacteria, about which we still know remarkably little. Meanwhile, what has already been learnt should serve as a deterrent to the indiscriminate use of these drugs; for they are not only very expensive but have a selective action against infections, most of which terminated satisfactorily in the pre-antibiotic era.

Intracranial Thrombophlebitis

In the past twenty years thrombosis of cerebral veins and of the dural sinuses, particularly the superior longitudinal sinus, has been increasingly recognised as a cause of sudden episodes of focal neurological disturbance and raised intracranial pressure.

In 1912 Passot[9] described a syndrome which occasionally followed otitis media and was characterised by headache, drowsiness, and papillœdema without pyrexia or signs of meningeal irritation; the pressure of the cerebrospinal fluid was raised but its constituents were normal. The condition was not, however, generally recognised until 1931 when Symonds[10] described again the clinical features, emphasised that the prognosis was good, and named the disorder otitic hydrocephalus. A few years later he suggested[11] that the cause of the raised intracranial pressure was thrombosis of the superior longitudinal sinus, basing this view on the presence of thrombosis of the lateral sinus on the side of the affected ear in a high proportion of the cases in which the mastoid was explored, and on the necropsy findings in a case described by Bailey and Hass[12] in which thrombosis of the lateral sinus had spread to the superior longitudinal sinus with resulting papillœdema and raised intracranial pressure. This view of the pathology of otitic hydrocephalus is now generally accepted. The raised intracranial pressure with thrombosis of the superior longitudinal sinus may be due to either of two mechanisms. The clot may spread from one lateral sinus to the torcula and in this way shut off the opposite lateral sinus and obstruct the main venous return from the cranial cavity, with subsequent œdema of the brain; or, alternatively, clot in the superior longitudinal sinus may block the arachnoid villi and in this way impede the absorption of cerebrospinal fluid. Ventriculography has shown that in the great majority of patients with otitic hydrocephalus the ventricles are of normal size, the hydrocephalus being a communicating one with an equal rise of cerebrospinal-fluid pressure inside and outside the brain. The prognosis in these cases is almost uniformly good; the papillœdema and raised intracranial pressure gradually subside, owing to recanalisation of the thrombus. Occasionally, however, optic atrophy with failure of vision takes place before the natural recession of the papillœdema. The usual treatment is repeated lumbar puncture to reduce the intracranial pressure; commonly the pressure falls after two or three punctures, but in some cases puncture may have to be repeated for several weeks. In general this treatment is safe, but Symonds[13] has recently described a patient with otitic hydrocephalus who died shortly after lumbar puncture. Probably this was a result of cerebral œdema with tentorial herniation due to withdrawal of cerebrospinal fluid; and he advises that the fluid should be withdrawn slowly and the pressure not be allowed to fall below 150 mm. water.

Another complication of otitis media, which may arise in association with otitic hydrocephalus or apart from it, is Gradenigo's syndrome, in which a sixth-nerve palsy develops on the side of the infected ear. This condition is probably also due to thrombosis of a sinus—the inferior petrosal sinus.[13] This sinus and the sixth nerve pass from the posterior to the middle fossa through a tightly fitting dural sheath—Dorello's canal—and the palsy results from compression of the nerve by the thrombosed sinus, the nerve recovering its function as the sinus becomes recanalised.

Thrombophlebitis of superficial cerebral veins may occur in association with infection in the ear or nasal sinuses or with localised or generalised infections elsewhere in the body[14,15]; and here the usual clinical picture is of focal epileptic attacks followed by loss of function of the parts of the body involved in the attack. More rarely hemiplegia or aphasia may develop suddenly without preceding epilepsy. Often there are general symptoms of infection, and the cerebrospinal fluid may show a cellular reaction, unlike the state with sinus thrombosis where the fluid is usually normal. The diagnosis from a cerebral abscess may be difficult, and indeed an abscess may occasionally follow cerebral thrombophlebitis. With the administration of antibiotics, however, the majority of patients make a good recovery, though there may be residual hemiparesis or hemianopia, depending on the part of the brain involved and the extent of brain damage.

Intracranial thrombophlebitis also occasionally comes on during the puerperium[16]; and possibly the sudden cerebral vascular catastrophes after childbirth described by Ménière[17] in 1828 were of this nature. Martin[18] has suggested that in these puerperal cases the starting-point may be thrombosis in a pelvic vein, and that a detached fragment of clot may pass as an embolus up the extrathecal vertebral plexus of veins, which is largely without valves and communicates with the intracranial venous sinuses. Kendall,[15] on the

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7. Clarke, S. K. R., Dalgleish, P. G., Gillespie, W. A., *Lancet*, 1952, i, 1132.
7A. [illegible] *lin. Path.* 1952, 5, 169 ; *Med. J. Aust.*
8. [illegible] R., Levy, M., *J. Bact.* 1952, 63, 623.
9. [illegible] ris, 1912.
10. Symonds, C. P. *Brain*, 1931, 54, 55.
11. Symonds, C. P. *Ibid*, 1937, 60, 531.
12. Bailey, O. T., Hass, G. M. *Ibid*, p. 293.
13. Symonds, C. P. *Ann. R. Coll. Surg.* 1952, 10, 347.
14. Symonds, C. P. *Brit. med. J.* 1940, ii, 348.
15. Kendall, D. *Brain*, 1948, 71, 386.
16. Martin, J. P., Sheehan, H. L. *Brit. med. J.* 1941, i, 349.
17. Ménière, P. *Arch. gén. Méd.* 1828, 16, 489.
18. Martin, J. P. *Proc. R. Soc. Med.* 1944, 37, 383.

other hand, has pointed out that in the puerperium some factors favour "primary" thrombosis. There is an increase of blood-platelets,[19] especially if there has been severe postpartum hæmorrhage; the plasma-fibrinogen is raised [20]; and there is increased "stickiness" of the circulating blood,[21] possibly owing to an increased number of newly formed cells. These factors would all enhance the tendency to thrombosis in the presence of damage to the endothelium of intracranial veins or sinuses, which might occur during labour. In this connection it is interesting that thrombosis of intracranial venous sinuses has been reported following combined insulin-induced hypoglycæmia and electric convulsive therapy [22] in the treatment of schizophrenia. The suggestion was that the endothelium was damaged during the fits, and thrombosis was precipitated by the dehydration from sweating and salivation during hypoglycæmia.

Stillbirth and Social Conditions

PROGRESS, like growth, is a thing of fits and starts—and stops; and no better illustration of this can be found than the behaviour of the stillbirth-rate in recent years. Whereas during the nine years 1931–39 the rate scarcely declined, falling from 41 to 38 (7%), in the next nine years 1939–47 it fell from 38 to 24 (37%). This change was all the more remarkable because it took place mainly during the years of war and because it has not continued during the years of relative peace; in the last four years, 1948–51, the stillbirth-rate has remained constant at 23.

There are two ways of looking at these changes. On the one hand it may be said that what has happened is no more than was to be expected. The improvement in the technical quality of the maternity service consequent on the better control of sepsis, the use of antibiotics, and the improved facilities for blood-transfusion was bound to reduce the number of stillbirths just as it lowered maternal mortality [23]; and delay of a few years between cause and full effect need not surprise us. Though the beneficial effect of the antibiotics, &c., were soon apparent, obstetricians had to tread warily when it came to testing the many other new measures that were the logical outcome of these changes. For example, the expectant treatment of some cases of antepartum hæmorrhage, and the extended use of cæsarean section to include cases potentially or actually infected, were to become part of obstetric practice; but during the years under review these methods were still on trial, and no material decline in the number of stillbirths could have been expected until they were firmly established. Such might be some of the arguments supporting a close relation between the quality of obstetric practice and the stillbirth-rate. On the other hand, it may be argued that this is only half the picture. The stillbirth-rate of late years has failed to keep pace in its decline with the maternal-mortality rate, and there are other findings which together suggest that social conditions and change are also important and that the influence of environment on the stillbirth-rate should be examined in some detail.

It seems reasonable to suppose that those enjoying a high standard of living will show a better reproductive performance than those with a low standard of living. If this is so, may it not be that most of the decline in the number of stillbirths during the war and immediate post-war years should be ascribed to the social changes in the years in question? This period saw the virtual elimination of unemployment, with an increase in the amount of money spent on food, which, together with food rationing and the system of priorities, ensured for the expectant mother her fair and proper share. Such a hypothesis could explain the abrupt check in 1948 to the rapid decline in the stillbirth-rate. The previous year, 1947, it will be remembered, was a disastrous year of prolonged winter, severe flooding, and drought, in which dairy produce, meat, eggs and egg products, and oils and fats were all scarce.[24] The main question to be answered in regard to stillbirths may well be not so much whether social conditions are important as whether they are more or less important than those matters of a more technical or strictly obstetrical nature; and there is perhaps some urgency in seeking an answer, because the stillbirth-rate is no longer declining, and because further striking improvements in the technical quality of the obstetric service are improbable—at least such as those we have witnessed in the last fifteen years.

Stillbirths have been registered in England and Wales since the Births and Deaths Registration Act, 1926, which came into force in 1927, and in Scotland since 1939, and many trends in the national figures have been detected. For example, it is known that the stillbirth-rate is adversely affected by low social class and, broadly speaking, by advancing age after 25, by primiparity, and by increasing multiparity after the second child; it is also known [25] that the stillbirth-rate is similarly affected by decreasing height (or more particularly leg length) of the mother—a physical characteristic which in its turn is closely related to expenditure on food. Illegitimacy increases the likelihood of stillbirth, especially if the mother is under the age of 30, as also do unemployment and poorly paid work, though not overcrowding [26]; and there are striking geographical differences in the stillbirth-rate.[27] A poor environment and consequent lack of proper food and amenities can only be harmful to reproductive function, and may well be more harmful than factors more strictly obstetrical. It is not yet clear, however, at what age the woman is most vulnerable. Is it when she is a growing girl (if this be the case we have to look back many years for the explanation of recent trends), or is the environmental effect more harmful when acting during pregnancy? Whatever the answer, it is clearly important that a constant watch be kept on the diet of growing girls and adult women. As the first report of the Expert Committee on Maternity Care [28] says, "where food is in short supply the expectant and nursing mother and the child are the first groups in the community to suffer."

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[19] Dowburn, R. Y., Earlham, F., Evans, W. H. *J. Path. Bact.* 1928, 31, 833.

[20] Gilligan, D. R., Ernstein, A. C. *Amer. J. med. Sci.* 1934, 187, 552.

[21] Wright, H. P. *J. Path. Bact.* 1942, 54, 461.

[22] Donnelly, J., Radley-Smith, E. J. *Lancet*, 1950, ii, 904.

[23] See *Lancet*, 1952, i, 85.

[24] The Urban Working-class Household Diet. H.M. Stationery Office, 1951; p. 56.

[25] Baird, D. *New Engl. J. Med.* 1952, 246, 561; see also *Lancet*, 1947, ii, 531; 1949, i, 1079.

[26] Sutherland, I. Stillbirths. London, 1949; see also *Lancet*, 1946, ii, 953.

[27] Munro Kerr, J. M., Moir, J. C. Operative Obstetrics. London, 1949; p. 927.

[28] World Health Organisation. Geneva, 1952.

Annotations

PREREGISTRATION YEAR

THE appointed day for the introduction of the preregistration year of house-appointments required by the Medical Act of 1950 has been fixed as Jan. 1, 1953. The Act requires all newly qualified men to spend a time, now fixed as 12 months, in approved appointments before full registration is granted. The responsibility of approving hospitals for this purpose has been placed on the universities and other "licensing bodies" giving qualifying diplomas. On the advice of these bodies, the General Medical Council is preparing a list of hospitals and institutions in which house-appointments will qualify for full registration. It is hoped that the list will be completed and published by Sept. 30.

The basic machinery of the Act is simple. A student who qualifies after the end of this year will apply for an approved house-job in the usual way. When he has been offered a place he will notify the G.M.C., and the licensing body in whose area he is going to work will provide a certificate of acceptance which will entitle him to provisional registration. He will then spend 6 months in a medical post and 6 months in a surgical post, or, as an alternative to either of these, he may do an obstetrical appointment for 6 months. At the end of the year the licensing body will certify to the council that the applicant has been employed in the prescribed way, and that his service has been satisfactory. He will then become fully registered. The conditions of service and remuneration will be the same as those at present applying to house-officers in their first year. As the scheme gradually comes into full operation, the aim will be to restrict the approved posts to preregistrands, and only to appoint fully registered doctors in exceptional circumstances.

STAPHYLOCOCCAL ENDOCARDITIS

BACTERIAL endocarditis is usually due to streptococci, but not uncommonly the cause is a staphylococcus. Thayer[1] in 1931 found that staphylococci accounted for 8·2% of 536 cases; and Perry,[2] reviewing 1000 cases in 1936, recorded that 10·3% were due to this cause. Dowling and his colleagues[3] in the University of Illinois suggest that the proportion of cases of endocarditis due to staphylococci may have increased in recent years—possibly because patients with staphylococcal septicæmia are now kept alive with antibiotics long enough to develop endocarditis.

The staphylococcus is not always highly pathogenic; thus *Staph. albus* was the cause in 1% of the cases recorded by Thayer and by Perry. In these early studies tests for pathogenicity, such as coagulase or hæmolysin production, were not carried out; but since then workers[4–7] have recorded cases due to coagulase-negative staphylococci. The majority of such cases ran a protracted subacute course; but the case recorded by Cunliffe and Gillam[5] was a fulminating septicæmia with death in less than a month. Dowling et al. found that of 77 cases studied by themselves or reported by others 64 were due to *Staph. aureus* and 13 to *Staph. albus*; the coagulase test, done in 26 instances, was positive in 19 and negative in 7. Rather surprisingly they discovered no significant correlation between the biological characters of the organisms and the type of disease or the underlying condition of the heart. In addition to pathological conditions of the heart the predisposing causes of staphylococcal endocarditis are infection elsewhere in the body and practices likely to introduce bacteria. Dowling et al. believe that of recent years in America the injection of narcotics into a vein has become such a practice. Of 25 cases studied by them, 11 (6 in patients under thirty years of age) were heroin addicts.

The prognosis of staphylococcal endocarditis has been transformed by the introduction of antibiotics. Dowling et al. estimate that 47% of all cases treated with antibiotics recover. Where the infecting staphylococcus is sensitive to penicillin, this is the drug of choice. High dosage—5–10 million units a day—is necessary to penetrate to the site of infection. They recommend that the sensitivity of the infecting staphylococcus to penicillin should be estimated and the dose adjusted to maintain in the blood *at all times* at least four times the minimum concentration necessary by this estimate. It is noteworthy that in the striking case of streptococcal endocarditis described lately by Dr. Baker and Dr. Pilkington,[8] there was no response to heavy and sustained dosage with penicillin, streptomycin, aureomycin, and chloramphenicol; but apparently complete cure resulted from the very high blood-penicillin levels achieved with the aid of 'Benemid.' If improvement does not take place within five days, combination with other antibiotics (aureomycin or chloramphenicol) should be considered. For penicillin-resistant infection most workers recommend aureomycin in doses of 4–8 g. daily. In view of recent observations on chloramphenicol,[9] however, this antibiotic might be tried.

TWO HUNDRED YEARS

TWO HUNDRED YEARS ago, on Monday, July 27, the Manchester Infirmary in humble premises in Garden Street opened its charitable doors. A scrofulous youth, John Boardman by name, was the first and only patient on that day. At its second meeting the weekly board was able to record the attendance of four more outpatients and of the first inpatient, a 12-year-old lad with "sordid ulcers on the leg."

As twelve beds did not long suffice, the governors built a new infirmary on the "Daub-hole field" belonging to Sir Oswald Mosley. It was opened in the summer of 1755, but a few years later wings had been added and the handsome building was adorned by a fine blue-faced clock with large gilt letters. With a lake in front and flanked by trees, it was a haven of rest for the victims of accident and disease in a rapidly growing industrial area. But the discipline was strict, even at meetings of the governors, where it was laid down that only one person might speak at a time. Swearing by patients was prohibited, and one might not play the flute or the hautboy. In 1765 the farsighted governors built on a lunatic asylum wherein no patient could be beaten or put in the bath without order of the physician: these patients were promised "that humane treatment and that judicious advice which they had no encouragement to expect in private madhouses." The two hospitals seem to have functioned as one, for we learn that on Sunday evenings the apothecary was wont to assemble the patients and "other members of this Family" to read such practical books as might be appointed by the chaplain. After a visit of John Howard, who included infirmaries in his survey of prisons, there were improvements in the ventilation and cleanliness of the wards. Cold, warm, and vapour baths were also provided, which proved popular with the Mancunians. Prices were reasonable, including it would seem the fine of sixpence for spitting in the bath. In 1792 the enterprising physicians instituted a system of recording cancer cases "together with the collateral helps to be gained by an

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1. Thayer, W. S. *Edinb. med. J.* 1931, 38, 237.
2. Perry, C. B. Bact [illegible] istol, 1936.
3. Dowling, H. F., [illegible] E. R., Spies, H. W. *Medicine, Balt.* [illegible]
4. Spink, W. W., Vivino, J. J. *J. clin. Invest.* 1942, 3, 353.
5. Cunliffe, A. C., Gillam, G. G. *Lancet*, 1943, ii, 355.
6. Glaser, R. J., Smith, R. O., Harford, C. G., Wood, W. B. *J. Lab. clin. Med.* 1946, 31, 291.
7. Matthew, H. *Lancet*, 1951, i, 116.
8. Baker, G. P., Pilkington, T. *Ibid*, July 5, 1952, p. 17.
9. See leading article, *Ibid*, 1952, i, 550.

enquiry into constitutional habits and disease not strictly cancerous but probably connected with it."

In telling this story Dr. William Brockbank[1] portrays the growth of the Manchester Infirmary vividly and with affection. We see its environs changing decade by decade, with gardens giving place to busy thoroughfares, but inside always the same story of Christian charity, prudence in matters of expenditure, enlightened outlook of the doctors, and a growing sense of responsibility in affairs of public health and in the teaching of medical students. In 1810 Robert Peel conveyed to the governors his Majesty's gracious approval of the Infirmary being designated " Royal." And so the hospital continued to grow and to prosper, the comfort of the sick being foremost in the minds of the governors; in 1860, for instance, engravings were purchased " depicting cheerful subjects for the purpose of conveying agreeable impressions to the minds of the sick to break the monotony of their suffering existence."

The fountains which had welcomed the young Queen Victoria were dismantled in 1866, and soon it was proposed to move the hospital to a more commodious site. The patients were eventually translated to a fine new infirmary on Dec. 1, 1908, and soon afterwards began the work of demolishing the Georgian building, which many today will recall with affection. The site where the gracious charity stood is happily now a garden, while the new medical citadel, justly proud of its heritage, claims a foremost place among our teaching hospitals.

SEROLOGICAL TESTS IN LEPROSY

It has long been known that serum from patients with leprosy is apt to give non-syphilitic reactions with various standard serum tests for syphilis (S.T.S.). Most reports on this subject have dealt with few cases; but Kvittingen et al.[2] have now investigated 821 patients with leprosy, using three serological tests—the Meinicke (M.K.I.R.), the V.D.R.L. slide-test (Venereal Disease Research Laboratory, Chamblee, Ga., U.S.A.), and the Kahn test. The sources of the sera examined covered a wide area, including Ceylon, Rangoon, Bombay, Mandi (India), Simla, Sabathu (India), and Tarataran (India). 31 sera from Mandi and Simla are omitted from this analysis because " the number of sera collected was too small for the results to be of much significance."

Unfortunately the data are not very clearly presented; but, taking the figures as a whole, it would seem that of 790 sera examined by the M.K.I.R. test, 87 (11·1%) reacted positively; of 787 sera examined by the V.D.R.L. test, 189 (24·1%) yielded positive results; while of 500 examined by the Kahn test, 169 (33·8%) were positive. From patients who were positive reactors to one or more of these tests, 62 were selected as representative of the whole group and were classified as follows: (*a*) neither history nor clinical evidence of syphilis (41); (*b*) indeterminate signs of syphilis (6); and (*c*) either history of venereal disease or clinical indications of syphilis (15). Assuming that these 62 patients were truly representative and that groups (*b*) and (*c*) were undoubtedly syphilitic, one can expect that of the positive S.T.S. reactors among patients with leprosy 66% may be non-syphilitic.

Three further points emerge from this report. Firstly, the percentage of positive S.T.S. reactors varies widely in patients with leprosy from different areas. Thus in Ceylon the M.K.I.R. test was positive in only 3·2%, whereas in Bombay this test was positive in 21%. Secondly, a cardiolipin antigen, as in the V.D.R.L. slide-test, yields a greater proportion of positive reactions than the " crude " antigen M.K.I.R. test when the same sera are tested in parallel. Thirdly, the sensitivity of two batches of V.D.R.L. antigen may vary considerably when used in parallel tests on sera. Thus with the same sera one batch of antigen yielded a positive-reaction rate of 16·9%, and another batch a positive-reaction rate of 40·2%.

THE DENTAL CONGRESS

THE 11th International Dental Congress, under the auspices of the Fédération Dentaire Internationale, is being held in London at the Royal Festival Hall from July 19 to 26. This is the first time that the congress has been held in this country; but we trust that it is not the last, for never before has there been a chance to learn so much about recent developments in dental surgery. The congress was due here in 1914 and again in 1941, but on each occasion arrangements had to be abandoned because of the outbreak of war. However, all has gone well this time, and the congress, which is the largest gathering of dental surgeons ever held in Great Britain—no less than 58 nations being represented—was opened last Saturday by the Minister of Health, Mr. Iain Macleod. The proceedings began with the induction of Dr. E. Wilfred Fish as president of the congress by Dr. Ch. F. L. Nord, president of the Féderation Dentaire. Then came the ceremonial presentation of three international dental prizes.

The scientific sessions were opened on Monday by Sir Alexander Fleming, F.R.S. The programme was so extensive that the congress had to be divided into twenty sections, and during the week over twenty international reports will have been presented and discussed. These reports, covering advances made in dentistry during the five years since the last congress, have already been published in the *International Dental Journal*, and résumés only are now being given, so that more time can be devoted to discussion. For the benefit of the many foreign delegates, simultaneous translations in the basic languages of the congress are being given over headphones attached to the seating in certain parts of the auditorium of the Festival Hall.

During the week, no less than sixty table demonstrations have been given each day, some of which were repeated over closed-circuit 1000-line television in the Tele-kinema on the South Bank. Incidentally, this is the first time that a television screen as large as 18 × 16 ft. has been used. Some twelve scientific films have been shown daily, and there has been a scientific exhibition of photographs, photomicrographs, and apparatus. A trade exhibition was also held in the hall.

In connection with the congress, a special exhibition, open to the public, is being held in the County Hall. Opened last Saturday afternoon by Miss Pat Hornsby-Smith, parliamentary secretary to the Ministry of Health, it represents an endeavour to bring home to the general public how much they themselves can do to keep their teeth healthy. The emphasis is on prevention, and the exhibits show how various countries are trying to foster public interest in preventive dentistry. The exhibit of the United States is of particular importance because it presents some of the results of the only long-term work so far done on the fluoridation of water-supplies—a matter attracting much attention in this country at the moment.[1] Two films on dental health, both specially prepared for the public, were shown for the first time on Saturday. One of them, made chiefly for children, is concerned with the training of a girl dental student and is meant to familiarise children with the appearance of dental instruments and the awe-inspiring surroundings of a dental surgery. The other presents by means of animated diagrams the structure of the teeth, and also reviews some of the problems of dental health. It is to be hoped that these films will be widely shown—especially as it appears that even in this country only one person in five owns a toothbrush, while even fewer know how to use one correctly.

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[1] *Portrait of a Hospital.* By WILLIAM BROCKBANK. London: Heinemann. 1952. Pp. 217. 25s.

[2] Kvittingen, J., Cutler, J. C., Guevara, J. A., McCullough, J. C., Rose, E., Ford, V., Tampi, R. B., Sen, S., Lakshwir, Khan, J., Dass, P. *Bull. World Hlth Org.* 1952, 5, 481.

[1] Mackenzie, E. F. W. *Lancet*, 1952, i, 961.

During the week most dental schools and hospitals have organised special demonstrations, and a series of lectures on recent dental research were given in the County Hall. The closing ceremony takes place in the Royal Festival Hall on July 26, and there will be a banquet for the members of the F.D.I. at the Savoy Hotel in the evening.

THE SEWAGE SWAB

IT has proved difficult in the past to isolate enteric bacilli from sewage, because the material is usually much diluted and the pathogens are greatly outnumbered by other bacteria. However, overgrowth by non-pathogens can now be largely averted with the modern highly selective culture media; and the ingenious sewage swab devised by Moore[1] has gone far to overcome the difficulty of sampling large volumes of sewage in which the pathogen is present only intermittently. Moore's method consists in lowering folded pads of gauze through the manholes into the sewers and securing them with string so that they trail in the flowing sewage. Rivers and streams may be similarly sampled. After a suitable interval—usually 48 hours—the swabs are transferred in sterile jars to the laboratory. For the isolation of paratyphoid-B bacilli, swab washings are incubated in a selenite-F enrichment medium from which platings are made next day on a deoxycholate-citrate medium containing also mannitol and lead acetate. The colonies have a characteristic appearance. Typhoid bacilli proved more troublesome to isolate, but success was eventually achieved by a combination of selenite enrichment and direct plating of successive fivefold dilutions of the swab washings on Wilson and Blair's bismuth-sulphite agar.[2]

There are now a number of records of the use of this method in tracing the source of outbreaks of enteric fever and elucidating the cause of sporadic cases. Moore[1] has described an interesting investigation in North Devon; and Lendon and MacKenzie[3] have traced infection back from a river which had been responsible for a number of cases of typhoid fever, through a storm-water overflow to the sewerage system of a residential area and ultimately to a single house, where a chronic carrier of *Salmonella typhi* was located. An essential part of these investigations is the precise typing of the isolated strains by means of Vi-bacteriophages.[4, 5] The determination of Vi antibodies in the serum of an excreter of typhoid or paratyphoid bacilli may also be of value in deciding whether the person is in fact a true chronic carrier.

Moore et al.[6] now give an account of their epidemiological findings during the field work by which Moore's technique was developed, and of a limited survey designed to give an estimate of the number of separate foci of enteric infection in a town of 10,000 people. They describe the regular isolation of paratyphoid-B bacilli from the river passing through this town, the identification of two different strains by Vi-phage typing, and the subsequent tracing back of infection—in one instance through a tributary stream—to groups of houses and sometimes (where the inhabitants coöperated) to an individual carrier. From such observations and the general survey it is inferred that there are in this town at least nine, probably distinct, foci of infection. 2 chronic paratyphoid carriers (type 2) and 1 typhoid carrier (type F1) have been located; these are the types that have been found in clinical cases in the area. The evidence suggests broadly that sporadic notific cases and the occasional epidemic may represent a outcrop from a deeper substratum of subclinical infection The key to the local problem may be the river. know to be subject to pollution with enteric bacilli, which ma reach the residents through vegetables watered from th river, or in other ways.

The report shows that enteric organisms can l regularly isolated from the sewage of communities of u to about 100 houses harbouring a single carrier; and single carrier of paratyphoid-B bacilli has been locate from the sewage of 1500–2000 people. The sewage swa method is already being used to detect poliomyelitis viru in bulked sewage, and it may also prove useful in th study of the epidemiology of bacillary dysentery an salmonella infections, and as a check on the prevalenc of intestinal infection in the staffs of establishment handling food.

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1. Moore, B. *Mon. Bull. Min. Hlth, P.H.L.S.* 1948, 7, 241.
2. Moore, B. *Ibid*, 1950, 9, 72.
3. Lendon, N. C., MacKenzie, R. D. *Ibid*, 1951, 10, 23.
4. Felix, A. *Brit. med. J.* 1943, i, 435.
5. Felix, A., Callow, B. R. *Lancet*, 1951, ii, 10.
6. Moore, B., Perry, E. L., Chard, S. T. *J. Hyg., Camb.* 1952, 50, 137.

VITAMIN D AND ENZYMES

IN-VITRO studies of the biochemical reactions of fa soluble substances are complicated by the difficulty o measuring their interaction with water-soluble enzym systems. Thus, though we know a great deal about th effects of vitamin D in the body, we know much less abou how these effects are brought about. Now, howeve Zetterström[1] has prepared phosphorylated vitamin D, which, being partly soluble in water, can be used fo enzyme studies. The alkaline phosphatase group o enzymes are known to be concerned with ossification and with the metabolic actions of vitamin D[3]; i rickets the alkaline phosphatase level commonly rise before symptoms or signs appear,[4] and administratio of the vitamin restores this level to normal.[5] Vitamin D also promotes the utilisation of phosphate by increasin its reabsorption in the renal tubules[6]; and Zetterströn suggests that it exerts this action through alkalin phosphatase, which it releases from bone, kidney, an intestine. These findings may help to explain the mechanism by which vitamin D prevents rickets; for it i known that for normal ossification sufficient phosphat has to be supplied to the bone-forming tissues. Zetterström[7] has also gone some way towards explaining th action of vitamin D in promoting growth generally and in impairing the oxidative phase of carbohydrat metabolism,[8, 9] by correlating the presence of the water soluble vitamin-D compounds with that of the respirator enzyme complex from the mitochondria of renal cells.

This work seems to suggest that the effects of vitamin-D deficiency may turn out to be due to associated change in enzyme function.

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Dr. Catherine Chisholm, consulting physician to th Manchester Northern Hospital, and one of the founders of the Duchess of York Hospital for Babies, Manchester, died on July 21.

ON July 21 the Duke of Gloucester opened the 10th International Congress of Dermatology, which is being held in London this week under the presidency of Sir Archibald Gray.

Prof. George Macdonald, director of the Ross Institute for Tropical Medicine, London, has left England to lead a commission delegated by the World Health Organisation, to report on the medical condition of civilians in South Korea and the measures necessary for the maintenance of their health.

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BRITISH MEDICAL ASSOCIATION

Scientific Sections

(Concluded from p. 136)

OBSTETRICS AND GYNÆCOLOGY

President: Prof. JOHN CUNNINGHAM

Cardiac Disease in Pregnancy

Dr. ALAN THOMPSON (Dublin) pointed out that the management of the pregnant cardiac patient did not differ greatly from that of the non-pregnant patient. He described the physiological changes in the circulation in pregnancy; these changes were the result of fluid retention, gain in weight, hydræmia, and the reduction in venous return caused by the respiratory embarrassment of the elevated diaphragm. They subjected the heart to a prolonged strain, which any complication of pregnancy could only aggravate, not to mention the hazards of labour itself. This strain was greatest at about the 32nd week, after which it lessened; this was a particularly useful time therefore for assessing the outlook for the forthcoming labour. During antenatal supervision, anæmia should be corrected, and radiological estimation of the heart-size should be made as early in pregnancy as possible while the measurement was still reliable. Auricular fibrillation was not a bar to pregnancy, provided it could be controlled by digitalis, but there was a danger of embolism. Adequate rest, admission to hospital at the first sign of failure, digitalis, fluid restriction, and mercurial diuretics formed the basis of treatment. The main risks were acute pulmonary œdema, respiratory infection, progressive failure with fibrillation, embolism, and subacute bacterial endocarditis.

Dr. ARTHUR BARRY (Dublin) thought that early diagnosis of the cardiac lesion went a long way towards ensuring safe delivery. If the lesion was missed at the first antenatal examination, it was unlikely to be found until calamity threatened. In his series of 266 cases, there was a significant history in 50%, and rheumatic heart-disease accounted for 90%, with mitral stenosis predominating. The mortality-rate was only 0·75%; no revolutionary treatment had been given, but supervision had been thorough. Cæsarean section was only used in 1·5%. The fœtal mortality of 6·6% was only slightly above the general rate. Pregnancy was only a temporary complication in the disease and, provided the immediate dangers were avoided, life was not shortened by child-bearing. There was no case either for sterilisation or for termination of pregnancy; the latter was absolutely contra-indicated as an emergency measure, and if the patient recovered from failure, it was then unnecessary. When asked if he would carry the argument to its logical conclusion and encourage rapidly repeated child-bearing, he said that future pregnancies, if necessary spent wholly in hospital, would do less damage than the tasks of looking after the other children at home. He graded his cases into the usual four groups; groups 3 and 4 were kept at absolute rest. Induction of labour was both futile and dangerous; gas-air, trilene, and ether anæsthesia were taboo because the hyperventilation they caused was harmful. Uncorrectable cardiac failure, far from calling for active obstetrical intervention, positively contra-indicated it, and when failure developed during labour, he preferred incision of the cervix and extraction of the child, using local anæsthesia with 'Hyalase,' to cæsarean section. After delivery the patient was kept in bed until her cardiac grading improved. Breast-feeding was, as far as possible, permitted in accordance with the patient's wishes.

Dr. WALTER SOMERVILLE (London) discussed valvulotomy, and he gave the criteria for deciding whether to operate during pregnancy. Mitral incompetence, other associated valvular lesions, enlargement with significant systolic expansion, and active cardiac failure were the main disqualifications. The stage of pregnancy made no difference and the operation had been performed as late as the 36th week.

Vaginal Discharge

Dr. IAN DONALD (London) dealt with the causes and investigation of this symptom, drawing his facts and figures from the Chelsea Hospital for Women. He gave some sound reasons for segregating the cases into one large clinic where investigation could be properly carried out. Sexual intercourse was a prominent cause in the large number of trichomonas infections. The ratio of pus cells to squamous cells in a fresh saline-drop preparation was a better guide to prognosis and progress than any other observation. Because relapses often followed menstruation, and because both pregnant and post-menopausal cases responded so well to treatment, he felt that menstruation was the greatest single unfavourable factor. The maximum therapeutic effort should be made during the menstrual period itself, allowing, in favourable cases, a welcome respite from treatment in between. He pointed out that careless technique in hospital can spread infection, and he condemned the slovenly practice of not changing gloves for each case. Monilia infections were more common than was generally supposed, quite apart from glycosuria and pregnancy, and spores should be looked for in the cervical canal. Considering how many patients complained of discharge but were in fact more frightened than ill, he thought that empirical treatment, given without proper assessment and diagnosis, did the patient a great psychological disservice.

Prof. WILLIAM KEARNEY (Cork) outlined the many kinds of treatment in use. He preferred antibiotics to œstrogens for vulvovaginitis in children, and in treating cervicitis he used appropriate chemotherapy after identifying the organisms responsible. Surgery was dangerous in acute cervicitis, but it was very useful in the chronic case. In treating gonorrhœa, streptomycin had the great advantage over penicillin that it did not mask concomitant syphilis.

Prematurity

Dr. J. K. FEENEY (Dublin) gave a review of cases treated at the Coombe Lying-in Hospital. Important social factors affected both the incidence of premature birth and the chances of ultimate fœtal survival. In the management of labour, the membranes should be preserved as long as possible, and episiotomy should be freely used. Forceps, applied to the aftercoming head in breech delivery, minimised the risk of intracranial hæmorrhage, particularly if they were kept in position until the head was completely born and therefore safe from sudden decompression. Anæsthesia, either local or spinal, gave the best results, especially in cæsarean section. Early clearance of the infant's air-passages by suction and gentle intubation were invaluable resuscitative measures.

Dr. MARY CROSSE (Birmingham) dealt with the physiology of the premature infant. Its greatest handicap lay in poor development of the lung alveoli, which weak respiratory muscles and an unreliable respiratory centre did nothing to help. Fœtal hæmoglobin liberated oxygen indifferently, although its affinity for oxygen was high. The presence or absence of a cough reflex really determined whether or not it was safe for a baby to be looked after at home, because of the great dangers of inhalation of mucus and regurgitated material. The control of body-temperature was all important, and it should be stabilised at 96°–97°F. Hæmorrhagic diathesis and the liability to œdema were additional risks; starvation during the first day or two was of great value in œdema, quite apart from avoiding the dangers of regurgitation. Anæmia was prevalent and might need transfusion. Unfortunately the administration of iron, though sorely needed, was useless before the child was 10 weeks old and was likely to upset digestion. Dr. Crosse showed that the rate of extrauterine growth should run parallel with what might be expected had the baby continued in its intended environment. The backwardness of the premature infant appeared exaggerated unless one, in fairness, discounted the many weeks by which its birthday was antedated in reckoning its age in comparison with full-term children. However, all such signs disappeared by the 6th year.

Dr. J. N. O'Reilly (London) outlined the management and care of the premature infant, and referred to the dangers of oxygen concentrations of over 50% which may cause retrolental fibroplasia. The climate of England, and of Ireland too, was bad enough to make fussing about humidity superfluous. Overheating was as dangerous as refrigeration, and an immediate environment of 90°F was desirable. Posture was important; propping up after feeds discouraged regurgitation, and the stomach emptied more easily if the infant was laid on its right side for a short time after feeding. Infection was a great bugbear, and septicæmia might be heralded by no more than a disinclination for food. He endorsed an initial period of starvation. Tube feeding was on the whole the best method. Hæmoglobin levels often fell to 55% but seldom beyond, and he did not advise transfusion until that level was reached. Dr. W. R. F. Collis (Dublin) disagreed with keeping the body-temperature at 96°–97°F, and he recommended giving thyroid extract to raise it.

Habitual Abortion

Dr. E. W. L. Thompson (Dublin), discussing the many causes, stressed the importance of the random factor or the chance of spontaneous cure, which was as high as 60% after a sequence of two abortions, but was only 16% after three. Any therapeutic measure had to be reviewed against this background. Rhesus iso-immunisation played no part in habitual abortion. In investigating these cases, he preferred to confine elaborate tests, over and above the routine W.R., analysis of urine, hæmoglobin estimation, and vaginal examination, to patients who had had three unsuccessful pregnancies. He then resorted to hysterography, B.M.R. and blood-cholesterol estimations, and tests of renal efficiency and pregnanediol excretion.

Dr. P. M. F. Bishop (London) referred critically to the intramuscular implantation of progesterone, which he himself had popularised. He wondered seriously whether pregnancy was not sustained by the sheer psychological force of the mumbo-jumbo which his and other impressive lines of treatment involved. This question could, of course, be put to the test by a control series of patients who were either implanted with inert substances or told that there was no help for them; but he was reluctant to carry out such an experiment, and preferred, in the absence of more definite knowledge, to stick to his own methods and their results, whatever the mechanism.

SURGERY

President: Prof. A. A. McConnell

Dysphagia

Prof. F. J. Henry (Dublin), reviewing the commonest causes of difficulty in swallowing, said that dysphagia could be classified as painful, paralytic, or obstructive. *Painful* swallowing was associated with four conditions: inflammatory lesions of the mouth and pharynx, infections of the neck, impacted foreign bodies, and peptic ulceration of the œsophagus. In the obstructive dysphagias the impediment could be extrinsic or intrinsic. In the adult, the common extrinsic obstructing lesions [illegible]nd retrosternal goitre, and enlargement [illegible] lymph-nodes by secondary malignant disease or by lymphadenopathies, such as Hodgkin's disease or leukæmia. The intrinsic obstructions were more important. The four common causes were cardiospasm, fibrous stricture of the œsophagus, a pharyngeal pouch in its later stages of development, and tumours of the pharynx, larynx, œsophagus, and cardiac end of the stomach. Professor Henry pointed out that in carcinoma, when difficulty in swallowing was marked, the disease was so advanced as to be incurable. In the earlier and more hopeful stages, the complaint was often one of only slight and transient sticking of food during deglutition. Finally, there were two important and surgically remediable causes of dysphagia in the newborn. The first was congenital atresia of the œsophagus, and the second, a good deal rarer, was vascular compression of the œsophagus in association with anomalies of the great vessels. The latter was the condition sometimes alluded to as "dysphagia lusoria," and the obstruction could be caused either by a reduplicated aortic arch encircling the œsophagus, or by compression of the gullet by a right subclavian artery arising far back on the aortic arch.

The radiological investigation of dysphagia was reviewed by Dr. C. P. Pickard (Dundee). There was seldom any difficulty in recognising gross œsophageal disease, but the detection of slight alterations in motility and in mucosal pattern demanded observation in different positions and postures, especially when some abnormality at the gastro-œsophageal junction was suspected. Barium should not be used in the neonatal atresias, or in the aged, because of its toxic effects on the bronchopulmonary tree. One of the iodised oils was a satisfactory and safer substitute.

Mr. R. R. Woods (Dublin), discussing endoscopy in the diagnosis of dysphagia, thought that direct laryngoscopy would establish the diagnosis in most cases of pain during the act of swallowing, and that œsophagoscopy would do so in most cases of obstruction. He strongly believed that the thoracic surgeon should be his own endoscopist, for in no other way could he obtain sufficiently accurate information about the size, position, and nature of a growth to enable him to determine the best treatment. In the management of inoperable malignant disease of the gullet, Mr. Woods advocated the insertion of a flexible tube of stainless steel wire.

Mr. R. H. Franklin (London) spoke on the diagnosis and treatment of congenital atresia of the œsophagus. A number of varieties had been described, but the commonest (80%) and the most important surgically was the type in which the upper part of the œsophagus ended blindly at the level of the arch of the azygos vein, and the lower part opened into the trachea at or near the bifurcation. This error of development could be expected once in every 2500 births, and the symptoms to which it gave rise were so characteristic that diagnosis should be simple. The infant had recurring attacks of choking and cyanosis when the accumulated œsophageal mucus spilled over into the larynx. This phenomenon became worse when attempts were made to feed the child, and eventually a fatal pulmonary infection developed. The diagnosis could be made by noting the arrest of a well-lubricated rubber catheter at a distance of 10–12 cm. from the alveolar margin. X-ray examination showed the presence of air in the stomach and intestine, indicating the fistulous communication with the trachea, and the introduction of 1–2 ml. of 'Lipiodol' into the upper œsophageal segment demonstrated the block. Mr. Franklin thought that the most rational and successful of several alternative operations was early primary anastomosis after extrapleural exposure of the œsophagus. In the rarer type in which the distal segment did not communicate with the trachea, he had found the area of obliteration so extensive that anastomosis was virtually impossible.

Prof. John Morley (Manchester) dealt with the treatment of pharyngeal pouch. He thought that operation should be avoided until the pouch was large enough to produce such "nuisance" effects as audible gurgling after meals, and attacks of choking caused by overflow when the patient lay down. On the other hand, too great a delay led to serious malnutrition, for the distended pouch and the distortion of the œsophagus made the passage of adequate food impossible. A further danger of delay was the development of squamous epithelioma in the pouch, a complication he had twice encountered. In his view there was no place for such palliative measures as inversion or suspension of the pouch; it should be removed in one stage, and the pharynx repaired. He doubted whether the fashionable two-stage resection had really ever been necessary; it was now certainly outmoded, and the common approach along the anterior border of the sternomastoid was much more unsightly than a transverse collar type of incision. The operation was carried out under a cover of penicillin. If the patient was seriously emaciated, a preliminary gastrostomy two weeks before operation allowed the nutritional state to be corrected. In his series of 33 cases, Professor Morley had had no fatalities, and a transient postoperative fistula on only 2 occasions.

Mr. Geoffrey Wooler (Leeds) gave an account of the management of cardiospasm and the other disturbances at the cardio-œsophageal junction. Cardiospasm could give rise to symptoms at any age, and lead to emaciation as profound as in cancer. The development of the complete radiological picture was preceded by a change in the motility of the lower part of the œsophagus, and this change could sometimes be detected on X-ray examination. In the majority of cases the symptoms of cardiospasm were relieved, and the size and motility of the œsophagus restored, by dilatation of the cardia, under anæsthesia, with Negus's hydrostatic bag. The Heller type of operation should be reserved for patients in whom the gullet was grossly elongated or had prolapsed through the hiatus, or in whom there was an accompanying hiatus hernia. When there was a hernia, this was repaired as well; and occasionally a deliberate repair of the hiatus had to be carried out after dilatation, because of secondary incompetence, with reflux œsophagitis or peptic ulceration. Hiatus hernia as a cause of dysphagia was nearly as common as carcinoma. The type most often requiring surgery was the sliding hernia of the stomach into the thorax; the para-œsophageal type was seldom associated with reflux of gastric juice. Mr. Wooler believed that all fibrous strictures of the lower œsophagus were secondary to peptic ulceration of the gullet; the stenosis could involve a very long segment of the tube, and, particularly in children, could supervene very rapidly. For this reason, early operation was indicated in children with symptoms of reflux œsophagitis. In adults, the necessity for operation was determined by the severity of the symptoms. Repair should be carried out through the chest, and if there was active ulceration at the time of operation, the ulcer should be resected.

Mr. Vernon C. Thompson (London) discussed the treatment of primary carcinoma of the œsophagus. The surgical ideal was resection of the tumour and restoration of the continuity of the alimentary canal, in most cases by gastro-œsophageal anastomosis within the chest after mobilisation of the stomach. Multiple-stage operations and the elaboration of an ante-thoracic œsophagus were outmoded. Resection should be attempted as a palliative measure, even in the presence of obvious glandular enlargement; but if it was quite impossible, a short-circuit should be established. It was most important that the patient should be able to swallow when he regained consciousness. Except for growths actually involving the cardia, he preferred a right-sided thoracotomy, preceded by a mid-line laparotomy through which the stomach was completely mobilised from the œsophagus to the pylorus, the œsophageal hiatus was stretched, and the anterior part of it divided between sutures. The results of resection were depressing. The operative mortality was high, and the recurrence-rate was also high because of the essential malignancy of the lesion and the usual delay in diagnosis.

In the discussion, Mr. Norman Tanner (London) considered that in the repair of a hiatus hernia, an abdominal approach was preferable to a thoracic operation; it was easier and allowed a more adequate exposure of the defective diaphragmatic crus. He reserved the thoracic approach for cases in which there was considerable shortening of the œsophagus.

Mr. Franklin thought that there were still many controversial points about hiatus hernia and œsophageal regurgitation. He pointed out that regurgitation was usual in infants after overfilling of the stomach, but, on the other hand, œsophagitis, ulceration, and stricture were rare. He had also encountered spontaneous recovery in cases of quite extensive œsophageal stricture in children. He too had found a right thoracotomy excellent for the resection of tumours of the middle part of the thoracic œsophagus. He believed that short-circuit operations gave just as good results in the elderly as resection.

Mr. A. M. Abrahams (Liverpool) had noted the persistence of dilatation and flaccidity after Heller's operation for cardiospasm. Mr. Wooler considered that if œsophageal motility was not restored, the failure was due either to incomplete division of the circular muscle fibres of the lower end of the œsophagus or to degeneration of Auerbach's plexus. He believed that the abdominal repair of hiatus hernia was often inadequate and was attended by a considerable recurrence-rate.

SOCIAL MEDICINE AND OCCUPATIONAL HEALTH

President: Dr. Andrew Topping

Necessity for Preventive Approach to Medical Practice

The subject of this discussion might well have been "the need for simplification and coördination," so closely did all the speakers agree on this.

Prof. Leslie Banks (Cambridge) opened with a description of the history of local-authority health services, and asked whether we still believe that the prevention and cure of disease are distinct entities. He suggested that prevention, diagnosis, and treatment and aftercare must now form one continuous process, and that we should revise our undergraduate and postgraduate teaching accordingly. Professor Banks continued:

"To question the need for maternity and child-welfare services and the school medical service in their present form is to invite a storm of protest and the confident assertion that the facts speak for themselves. Indeed they do. An infant-mortality rate of 26 and a maternal-mortality rate of 0·7 show that the years of endeavour have at last borne fruit. They also show that having defeated the enemy the great army of workers could now be demobilised retaining only a highly skilled skeleton staff. These sentiments may be unpopular, but I do suggest quite seriously that the time has come to merge the maternal and infant-welfare services with the hospital obstetric and pædiatric services. A similar case could be made for the aftercare of tuberculous and mental patients to be conducted from the hospital rather than by the local health authority."

The many local administrative bodies might well be replaced by an all-purpose health and medical care authority with executive responsibility for local health services and for hospital and general medical services. The hospital has become the focal point of our medical services and is likely to remain so for a number of years to come. Health centres should be associated with the hospital. He deplored the past neglect of the salaried medical officer in central and local government service by his clinical colleagues, for this has resulted in a dearth of competent medical administrators when they are most needed. The work of the deans of the great medical schools has shown that it is possible for a doctor to be a good administrator, and Professor Banks thought that the medical officer of health could play a similar part in the coördination of local medical services. An effective first step would be to give him an honorary contract on the staff of the local hospital group as home care physician, charged with the coördination of the many agencies responsible for prevention, home care (especially of the chronic sick), and aftercare. Such an appointment would be of great value both to the general practitioner and to the consultant. The cure of disease has now become a major interest of the State. If the practice of medicine is to be kept at an economic level, and incorporate the benefits of progress, the medical profession must pay more than lip service to the adage that prevention is better than cure, for this applies to the health of the medical profession as well as to the health of the nation.

Dr. RICHARD SCHILLING (Manchester) also emphasised that prevention is better and cheaper than cure, and asked for a broader approach to the problem of the burden of sickness. He thought that the general practitioner, in particular, should play a much greater part in the prevention of disease, both in the individual and in the group. The toxicological hazards in industry have been solved by engineering techniques, and the present-day problems are, indeed, more social than medical. We have, perhaps, too many diplomas, and the time has come to consider whether the teaching of public health and industrial medicine should be unified. In factories curative and preventive medicine must be combined, and Dr. Schilling produced evidence of the benefits of immediate treatment by the industrial medical service, and, incidentally, of the value of keeping good records. In the small industry the bulk of the work should be done by the general practitioner, but he must be trained from the day he starts his medical studies.

Dr. JOHN McCANN, in a speech remarkable for its breadth of vision, pointed out that the good doctor has always been concerned with prevention and treatment. The State, he said, exists to serve society, and mere materialism is not a philosophy. Man's human dignity and spiritual nature must be recognised. He thought the time would come when the patient would say "keep me in good health, doctor"; and no government agency could possibly replace the family doctor, with his detailed knowledge and the confidence of the patient. The doctor is not a diagnostic machine, and Dr. McCann hoped that the time would never come when the public regarded health as a commodity to be supplied on demand. He insisted that the general practitioner and the personal health services must be brought together in the future. The general practitioner should be a key worker in the whole scheme of health, and he hoped that modern society has not made that relationship impossible. Although the world has changed and the tempo of life has changed, human nature has not changed.

Dr. J. A. HARBISON (M.O.H. for Dublin) agreed that the general practitioner should play his part in prevention, but he must have the help of the whole team and become part of it. The team also must take an interest in the general practitioner. Dr. Harbison had some pointed comments to make on health education, and said that the risk is that we are now producing a half-educated community. The remedy, full education, requires the help of the general practitioner. He thought that the medical curriculum for the embryo general practitioner might well be changed to include less major surgery and more knowledge of home conditions of the patients.

Dr. BRIAN PRINGLE (Dublin), speaking from the viewpoint of the industrial medical officer, said that the practice of medicine in the factory was a good experiment in social and preventive work. Just as the cardiologist relied on exercise tolerance tests so could society accept work tolerance tests carried out by the industrial medical officer.

The PRESIDENT pointed out the dangers of a wrong orientation of medical education, and called on Miss Ethel Cohen to describe her experience in the United States. Miss COHEN said that at Tufts Medical College, Boston, it was recognised some years ago that there was a need to teach social philosophy, and for the medical student to recognise the personal problems of the patient. This teaching should not be limited only to home visits, because this may lead to a false emphasis on economics and poverty, whereas interpersonal problems may occur at all levels of society.

Dr. JOHN EUSTACE (Dublin) also spoke as an industrial medical officer, and referred to the value of industrial sick absence records, particularly in revealing the causes of psychosomatic disorders, both at home and at work. In his view the contribution of world unrest to the increased incidence of this type of illness could not be ignored by doctors.

PSYCHIATRY

President: Dr. DESMOND CURRAN

Psychiatric Disorders in Later Life

Dr. R. S. ALLISON (Belfast) emphasised the importance of toxic factors and biochemical disturbances in producing acute though reversible states of confusion or delirium. As ætiological agents, anoxæmia and dehydration were apt to be overlooked; yet after long operations they were often responsible for a severe confusional episode. The prompt treatment of postoperative vomiting was important in prophylaxis. Though most cases in this group were potentially reversible, long-continued anoxæmia could result in permanent dementia: thus in one patient repeated hæmatemeses had caused cortical atrophy. In elderly diabetics fre

attacks could lead to symptoms

senile dementia, and in these cases insulin dosage should be adjusted so as to keep the blood-sugar at a relatively high level. Elderly hypochondriacs might become confused after taking too many stomach powders, but they recovered rapidly with treatment. Cerebral tumour presented difficulties in diagnosis because papillœdema and headache were often absent. The grandiose form of general paralysis was uncommon nowadays, and as the blood Wassermann reaction was sometimes negative the cerebrospinal fluid should be investigated in every case of presenile dementia. A history of head injury was rarely obtained in subdural hæmatoma, but the characteristic fluctuations in the clinical picture usually suggested the diagnosis. The separation of cases of presenile dementia with focal signs, such as Pick's and Alzheimer's disease, from the main body of dementias in old age was justified—if only because it drew attention to the group of disorders, resembling the presenile dementias in their focal symptomatology, which could be alleviated by treatment. Yet he was doubtful whether the parieto-occipital syndromes such as disturbances of spatial orientation and of the body image, reported in these conditions as well as other organic psychoses, ever occurred in the absence of clouding of consciousness.

Dr. **Martin Roth** (Chichester) described an investigation of 386 patients over the age of 60. They fell into five groups which were distinct in their natural history: affective psychosis (forming over half the cases), senile psychosis (about a quarter of the cases), and three smaller groups—paraphrenia, arteriosclerotic psychosis, and acute confusion. Within six months of admission to hospital almost 60% of patients with affective disorder were discharged, while about the same proportion of senile psychotics were dead. Most paraphrenics remained as inpatients, while the acute confusional group showed an equal proportion (42%) of dead and discharged. Cases of arteriosclerotic psychosis were mostly dead or inpatients, in approximately equal proportions. These distinctive patterns of outcome in the five groups were sustained in four of the disorders at two years after admission. The discharges had risen slightly among affective illnesses, while deaths in the senile group had risen to 80% of the total admitted. Most paraphrenics remained as inpatients, and there had been a slight rise in the proportion of discharges among patients with confusion. Only cases of arteriosclerotic psychosis revealed a change in pattern; the deaths had risen steeply to 70% to make the two-year outcome only a little better than that of senile psychosis. The figures had been derived from patients consecutively admitted during three separate years, and the trends described had been consistent. Dr. Roth felt that these differences in the natural history of the clinical groups should be taken into consideration in the planning of units designed for cases of mental disorder in old age. The theoretical interest of the findings was that they showed clear differences in the natural history of the functional group (affective and paraphrenic psychoses) on the one hand, and the organic group (senile and arteriosclerotic psychoses) on the other. These differences in outcome were shown to be independent to a large extent of age differences between the groups, and psychological tests had also been shown to differentiate sharply between them. The combination of functional symptoms such as depression and mania with dementia certainly occurs, but in the case-material studied, the proportion was small enough to make it probable that in such patients there is a coexistence of two relatively distinct disease processes. Much evidence had recently accumulated to support this interpretation.

Prof. **J. Dunne** (Dublin) supported Dr. Allison's plea that more attention be paid to the acute recoverable conditions in old age produced by toxic factors. He had recently studied a patient who had become acutely disturbed after taking excessive doses of ephedrine to cope with his asthma.

Dr. **K. C. Bailey** (Taunton) believed that myxœdema was often a cause of apparently irreversible dementia in late middle and old age.

Dr. **E. A. Bennet** (London) had often met in this age-group patients with psychoneurosis who had made good adjustment to life after neurotic breakdown in adolescence. The recurrence of neurosis in old age often responded to psychotherapy.

Dr. **R. H. Moore** (London) wondered whether the high mortality in cases of senile psychosis could be due to the use of heavy sedation in such cases. Dr. **Allison** in reply agreed that heavy sedation was fraught with risk in old patients.

OTORHINOLARYNGOLOGY

President: Mr. T. O. **Graham**

Antibiotics

Mr. **R. B. Lumsden** (Edinburgh) said that in all infections of the ear, nose, and throat, penicillin was the antibiotic of choice, despite the disadvantage of parenteral administration. Maximum dosage should be used from the start because the formation of resistant organisms was thereby discouraged. Staphylococci, normally the most sensitive organisms, can become the most highly resistant to penicillin. Penicillin could often be usefully combined with sulphonamides especially in meningeal infections. Toxic reactions to penicillin were uncommon, but local lesions may develop in the mouth after the use of penicillin lozenges, which should not be given for longer than 48 hours. The newer antibiotics more commonly produced these oral lesions by inducing a fungus overgrowth. Antibiotics also had their place in prophylaxis—e.g., in operations on patients with rheumatic carditis or nephritis—and he had found that they gave useful cover to a fenestration operation. Though these drugs were a great help in acute otitis media, fundamental surgical principles still applied, and operation had its place. The day-to-day appearance of the drumhead and the evaluation of hearing were important guides; myringotomy should not be delayed when indicated. Whenever possible the infecting organism should be identified, otherwise treatment was empirical. If there was no improvement after 48 hours, treatment should be changed. Acute mastoiditis has become much less common and complications were rare. Chronic suppurative otitis media was little improved by the antibiotics, but active treatment of the acute infection should reduce the number of chronic cases in time.

Mr. **T. G. Wilson** (Dublin) thought that the great improvement which coincided with the introduction of antibiotics might be due, in part at least, to a decline in virulence of the causal organisms. Virus diseases continued to increase however, and acute laryngotracheobronchitis had replaced diphtheria as a dread disease of children. Penicillin, the first antibiotic, was still the best and the least likely to promote drug resistance. The incidence of laryngeal complications in pulmonary tuberculosis had been spectacularly reduced, partly by streptomycin, but he did not think streptomycin should be used in very early tuberculous laryngitis until rest and calciferol had been tried. Streptomycin should be combined with *p*-aminosalicylic acid; each blocked a different metabolic pathway, and resistant strains were less likely to develop. The recommended dosage of streptomycin was 1 g. daily for 3 months. Vestibular responses should be tested at least once monthly during treatment. Dihydrostreptomycin often caused cochlear degeneration, and Mr. Wilson thought its use was unjustified.

Discussing the topical use of antibiotics, Mr. M. A. O'BRIEN (Cork) said that 10% chloramphenicol in propylene glycol was very effective in *otitis externa* and meatal furunculosis. Local treatment might helpfully be supplemented by parenteral penicillin for 72 hours. Local chloramphenicol may be useful in chronic suppurative otitis media without cholesteatoma formation. Terramycin was rather unstable for topical application. 5% aureomycin in lactose was valuable for ridding mastoid and fenestration cavities of secondary infection. Local treatment of the nasal cavity was seldom successful in the early stages of an acute infection, but when localisation had taken place autodisplacement with solutions of penicillin or aureomycin could be used. Chronic sinus infections, especially of the maxillary antrum, responded well to weekly lavage and instillation of 10% sulphathiazole and 20% sulphanilamide in a suitable base. He had found this a useful method in children. The results of local application in infections of the mouth and pharynx were disappointing, presumably because the antibiotic was only in contact with the lesion for a short time.

In the discussion Mr. W. H. B. MAGAURAN (London) said that radical surgery was seldom necessary nowadays. He described a treatment of sinus infection which he had found successful: a small opening was made in the floor of the sinus, the infective exudate was aspirated and replaced by the appropriate antibiotic as determined by bacteriological examination. This simple manœuvre was generally effective, and if reinfection occurred, irrigation and instillation of antibiotics could be performed through the scar.

Mr. R. R. WOODS (Dublin) said that though penicillin was invaluable in acute otitis media, it must be given early and before pus was present. When pus had formed, drainage was necessary to avoid the danger of an adhesive type of infection and deterioration of hearing.

Ménière's Syndrome and Simulating Conditions

Mr. C. S. HALLPIKE (London) said that for information upon the symptomatology and natural history of Ménière's disease it was seldom necessary to go beyond Ménière's original papers. Since Ménière's time, however, we had acquired additional knowledge about the histopathology of the disease and its physical signs. It was now well established that the essential lesion consisted of a distension of the endolymphatic sac without evidence of infection or trauma. In a number of cases in which the difficulties of histological examination had not been too great, it had been possible to show changes in the hair cells of Corti's organ which seem to explain the deafness and characteristic distortion of hearing. In addition we now had at our disposal a number of valuable new tests of vestibular and cochlear function; particularly useful were the caloric tests, carried out according to a technique described by Fitzgerald and Hallpike in 1942, and the loudness-recruitment test. This latter test always gave positive results in Ménière's disease and was, therefore, considered to be pathognomonic of a lesion of the end-organ of hearing. Histological examination of the temporal bones in cases of Ménière's disease had not always been successful in demonstrating a lesion of the hair cells owing to the presence of post-mortem histological artefacts. Recent technical improvement, however, had reduced these artefacts, and Mr. Hallpike showed slides illustrating early pathological changes in the hair cells in a case of Ménière's disease. Although the clinical and pathological identity of Ménière's disease had now been clearly established, it was still the practice to include under the undiscriminating title of Ménière's syndrome various other types of organic vertigo which conformed only vaguely to its established symptomatology and pathology. It was hoped that further knowledge would enable these types of vertigo to be separated from Ménière's disease. Mr. Hallpike referred to a recent investigation by Dr. M. R. Dix and himself into the clinical features and morbid anatomy of a particular form of positional nystagmus originally described by Bárány. They had been able to show, on clinical evidence alone, that the disorder was caused by a lesion of the otolith apparatus within the labyrinth. The condition was typically unassociated with deafness or vestibular dysfunction, objective or subjective, apart from a particular type of paroxysmal nystagmus occurring in certain critical positions of the head. Other evidence of neurological disease was invariably absent, and the disorder nearly always ran a benign course. The lesion therefore, was thought to be a self-limiting one confined to the otolith apparatus; its possible causes were chronic infection, trauma, or vascular changes. The paroxysmal character of the nystagmus and the benign course of the disease suggested that this condition should be known as the benign paroxysmal type of positional nystagmus. Mr. Hallpike's slides of histological preparations of the labyrinth from a typical case showed chronic tissue changes in the maculæ of the saccule and utricle, thus confirming the clinical evidence and the view of Bárány.

Mr. E. R. GARNETT PASSE (London) discussed the syndrome from the point of view of the vascular system and its nerve-supply. The increased labyrinthine tension in Ménière's syndrome was difficult to explain because there was no secreting layer, but it may be due to an increase in permeability of the labyrinthine blood-vessels which are under the control of the sympathetic-parasympathetic balance. He had performed 200 sympathectomies, the results of which seemed to support this view. Further work was being done to see if sympathetic stimulation did increase the production of endolymph. The sympathetic supply to the internal auditory artery came from the second thoracic segment, and the parasympathetic supply from the geniculate ganglion.

Mr. F. A. MCLAUGHLIN (Belfast) mentioned some of the conditions which could cause confusion in diagnosis. Trauma may produce symptoms like those of Ménière's syndrome: syringing of the ear, fractures of the base of the skull, and blast injuries were the commonest types. Acoustic neuroma and other tumours in the cerebellopontine angle may also cause difficulty. Vestibular nystagmus could often be differentiated by the history and the absence of signs of aural disease. There was no doubt that strong emotional upset could produce prostration and vertigo, and the mechanism here was probably vasomotor. Certain toxic substances—e.g., quinine—could produce a similar picture, but here the change was peripheral, and perceptive deafness developed in time. Streptomycin was a well recognised cause of vertigo and deafness. Doses of over 2 g. a day seemed likely to produce damage, but if the drug was stopped at the first signs, recovery could be complete in many cases. Mr. McLaughlin suggested a dose of 10 mg. per lb. body-weight per day. He thought the use of dihydrostreptomycin was quite unjustified. Treatment in Ménière's syndrome should start with sedatives, rest, and belladonna. Any focus of sepsis in the ear, nose, throat, or elsewhere should be dealt with. The anti-histamine drugs could help some patients. Finally, surgery had to be considered if conservative measures failed. Sympathectomy, as suggested by Mr. Garnett Passe, might prove to be the best surgical treatment.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE

THIS was the first congress to be held under the uspices of the International Federation which had onferred the honour of arranging it on the British ssociation of Physical Medicine. Its organisation was n the hands of a British board of management, with he Duke of Gloucester as patron, Lord Horder as resident, Dr. Philippe Bauwens as chairman, and Dr. A. C. Boyle as honorary secretary of the executive ommittee. National representatives were nominated y 14 countries, and some 20 countries were represented.

The congress was officially opened at King's College, ondon, on July 14 by Marshal of the Royal Air Force ord TEDDER. He said that life was not merely to be live, but to be well and to live in harmony with one's urroundings. He thought that the quickest road back o health lay through physical medicine. He had seen ehabilitation at work in the Armed Forces, and he elieved that its success lay in self-help and in the fact hat the layman had been made a partner rather than a atient. He then lit the ceremonial lamp presented y Lord Horder. Mr. IAIN MACLEOD, Minister of Health, welcomed the delegates. He had been particularly mpressed by the way in which physical medicine prevented chronic suffering and ill health among the aged, and enabled them to remain within their own family circle. Prof. FRANK KRUSEN (United States) spoke for the International Federation, and paid tribute to Lord Horder, Mr. Bernard Baruch, and the late Dr. Richard Kovacs for their part in stimulating interest in physical medicine. He then invested Lord Horder with the presidential badge presented by Mr. Bernard Baruch.

Lord HORDER reminded his audience that young men see visions, old men dream dreams. For physical medicine "the sky's the limit," but only if its practitioners realise that physical medicine is an integral part of medicine and must remain so. He then used the gavel presented by Mrs. Kovacs in memory of her husband. Dr. S. CLEMMESEN (Denmark) and Prof. K. M. WALTHARD (Switzerland) expressed the thanks of the foreign delegates for their welcome.

Scientific Discussions

PHYSICAL MEDICINE IN THE PAST DECADE

Professor KRUSEN, speaking of the amazing advances in the last ten years, said that the practice of physical medicine was no longer founded on an empirical basis. The new specialty of physical medicine and rehabilitation has been integrated. The wisdom, foresight, and generosity of Mr. Bernard Baruch had been a major force in bringing into being the new specialty, in which his father, Dr. Simon Baruch, had been a pioneer. Advances had been made in dosiometry, the techniques of thermotherapy and electrotherapy, the use of microwaves, ultrasonic energy, and electromyography, of progressive-resistance exercises, occupational therapy in rehabilitation, and the teaching and training of young men in the specialty and in research work.

Dr. CLEMMESEN, reviewing progress in Denmark, emphasised the need for thorough diagnosis and proper prescription for treatment. Rheumatology and physical medicine could not, he thought, be separated.

Dr. V. E. KLARE (Vienna) mentioned research work done in his country on low- and high-frequency therapy and on ultrasonics. The work of rehabilitation and resettlement had been stimulated by the visit of Dr. Howard Rusk.

Dr. F. D. HOWITT (London) described the rôle that physical medicine played during the late war in the fighting services and the Emergency Medical Service. He showed how it had helped to make use of every available man and woman by upgrading the substandard youth to fighting capacity, by the creation of physical-development centres, by advising on the medical aspects of physical training and of purposeful training for the specific requirements of different arms, and by restoring to maximum capacity in the minimum of time the military and civilian casualties. In the modern hospital service the physical-medicine specialist takes full clinical control of such conditions as chronic rheumatism and other medical disorders of the locomotor system, and also advises his hospital colleagues on the value and application of physical treatment.

A profitable liaison had been established with the medical and social services of industry. Physical medicine had been translated from a therapeutic to a clinical specialty, and was established as an integral part of general medicine.

REHABILITATION AND RESETTLEMENT

Certain aspects of this concept were discussed by Dr. F. S. COOKSEY (London), who spoke on vocational settlement in Great Britain. He stressed the need for greater interest on the part of medical practitioners; they must initiate appropriate measures for rehabilitation and resettlement at the onset of the illness, and give guidance until the process is complete. He pointed out the need for closer integration between the hospital and the industrial health services, and for treatment facilities outside working hours to avoid unnecessary loss of wages and production. The resettlement of the disabled housewife and the chronic sick in their homes makes them independent of the help of others and frees workers for industry.

Dr. A. J. MARTIN (London) described the resettlement conferences conducted by the physician in charge of rehabilitation at the Royal Free Hospital. It was important to establish a close and personal relationship between the patient, the medical officer, the medico-social services, and the district resettlement officer of the appropriate labour exchange.

Squadron-Leader C. B. WYNN-PARRY described the duties of medical officers in charge of medical units in the R.A.F. both in obtaining the greatest functional recovery, and in guiding the patient in the selection of suitable civilian employment. He discussed the method employed, and he too emphasised the need for close personal contact between the doctor, the district resettlement officer, and the patient. The function of resettlement and rehabilitation is to guide the patient in the making of his own decisions.

Dr. G. GINGRAS (Montreal) described the working of a rehabilitation centre operating under the auspices of the Rehabilitation Society for Cripples.

Mr. LIONEL COSIN (Oxford) described the rôle of physiotherapy in the treatment of the aged. He pointed out that only by the repeated assessment of the pathological, psychological, and sociological factors and their inter-relationship can an accurate estimate be made of the physical factor in the disability of old people. On this basis an accurate economic and therapeutically sound programme of rehabilitation can be drawn up, and individual contentment, independence with social integration, and often some degree of economic freedom can be obtained.

The same problem was dealt with by Dr. V. A. PORSMAN (Copenhagen) who discussed the causes of invalidism among old people, and gave examples of successful rehabilitation. He also pointed out the need for close coöperation between physiotherapists, nurses, occupational therapists, and specialists in physical medicine.

THE RHEUMATIC DISORDERS

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Dr. J. M. Poal (Barcelona) showed a new device for the localised treatment of the cervical spine. By using traction alone, or in conjunction with other therapeutic measures, he claimed excellent clinical results. His apparatus consisted of a U-shaped tube resting on the patient's shoulders. This applied traction by means of two gears, with a lever to each, joined to two slings, adapted to the occipent and the inferior part of the maxilla—an ingenious invention of modern Spain.

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Studies on the permeability of the synovial membrane were described by Dr. W. D. Paul and Dr. J. R. Routh (Iowa City).

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An electromyographic investigation on muscular fatigue in man was presented by Dr. Arne Lundervold (Oslo). The muscles in the upper extremities were examined electrographically in 37 healthy persons performing tapping movements. The duration and force of contraction in separate muscles, as well as the number of muscles taking part in the movement, were dependent on the rate of tapping. The more rapid the tapping the greater the number of muscles brought into play, and the more forceable the contraction of each muscle. If the subject became tired and the rapidity of movement decreased, there was an increase both in the number of muscles and in the force of contraction of each individual muscle engaged in the operation. Muscle fatigue was assumed to occur when the restitution phase in the muscle cells became too long in proportion to the time available, so that the contractability for that reason was reduced.

Dr. J. Lefebvre (Paris) read a valuable paper on chronaxie in electrodiagnosis, and Dr. E. Kugelberg (Stockholm) discussed electromyography in the differential diagnosis of neuromuscular disorders. Dr. Bauwens described some technical advances in electrodiagnosis.

PHYSICAL MEASURES IN DIAGNOSIS AND TREATMENT

Dr. Howard Rusk (New York) read a paper on Physical Medicine and Rehabilitation: A Service to Medicine and the Community. He stressed the responsibility of the medical profession to the community. Mr. Bernard Baruch had said that the increase in a man's life span during the past 50 years had had more profound medical, economic, and social implications than such things as atomic energy, air transport, and modern communications. Medical science has added years to life, and now we must add life to those years, said Dr. Rusk. We must help the people whose years we have lengthened to lead useful and dignified lives. He described the rôle of the general practitioner, the diagnostic clinic, and the hospital. One in five of our hospital beds can profitably be used for rehabilitation and convalescence. The hospital should be the centre of the rehabilitation services, and with these services should be linked others providing for or leading to full or selective employment, sheltered workshops, home care, housekeeping services, industrial homework, and colonies for the disabled. The needs of the ageing patient can add to the nation's productivity if he is placed in a job within his capacity. Keeping the elderly population as an active part of our economy will be one of the concerns of preventive medicine of the future. He quoted a hospital administrator as saying that 30% of the jobs in his hospital could be done by disabled people. He believed that these people should be in hospital as workers leading happy and contented lives, not as patients.

Dr. Harold Balme (London) spoke about rehabilitation and its international relations.

Other Activities

Delegates paid a visit to Aldershot where they saw a demonstration of physical education by boys and girls from London County Council schools. Lieut.-Col. J. B. M. Milne described the Pulheems method of physical assessment, and a demonstration of battle physical training was given.

An historic and scientific exhibition had been planned by Dr. C. Shields. The Wellcome Medical Museum showed a fascinating exhibit illustrating the developments of hydrotherapy, massage, and remedial exercises, and the therapeutic use of electricity and radiant energy. Among the other exhibits were electronic equipment developed at St. Thomas's Hospital, shown by Dr. Bauwens, and self-help devices and mechanical aids for the disabled from Dr. Rusk's centre in New York. Mrs. Guthrie Smith showed a bed-chair made of light tubular steel, and consisting of a back and two long arms designed to support the patient in comfort and security and yet afford enough mobility to allow change of posture and increased range of knee and leg movement—an ingenious apparatus which can also be used for rehabilitation and transport. A kitchen unit developed at King's College Hospital for the assessment and training of the disabled housewife aroused much interest.

A series of very interesting films was shown; to name only one, Dr. G. D. Kersley showed a film on hydrology which had been made in the Bath area group of hospitals. After a general summary of rehabilitation methods, the film showed how hydrology could be used to supplement these methods.

The Congress in Retrospect

The congress demonstrated that physical medicine has been accepted as a specialty within general medicine. It does not detract from orthopædics, neurology, or psychiatry, but gives something new to medicine. The speeches of Sir Cecil Wakeley, F.R.C.S., and Sir James Paterson Ross at the dinner given to the national representatives by the council of the Royal College of Surgeons, and those of Sir Lionel Whitby and Sir Russell Brain, F.R.C.P., at the congress banquet, showed that physical medicine was welcomed by the leaders of medical thought and action as a young and dynamic partner. Physical medicine, it was said, is a discipline which aims above all to help human beings to achieve harmony with their surroundings. Rehabilitation, as a part of physical medicine, was defined as the preparation of the patient, mentally, socially, and vocationally, for the fullest possible life compatible with his abilities and disabilities. Rehabilitation is only as sound as the basic medical services of which it is part. The diagnosis and prognosis must be accurate for it is upon them that the feasibility of retraining is determined.

The physical medicine specialist needs to be a "good doctor" as well as a trained clinician. He is looking at humanity, and particularly at his patient, from what may appear to many of his colleagues to be a new angle. At this meeting there were physicians whose chief interest lay in electrodiagnosis, others whose lives were spent in the day-to-day work of a hospital physical-medicine department, others mainly interested in what used to be termed rheumatology, others who studied the problems of the aged, and others engrossed in administration; but all of them were specialists in physical medicine. There were also a number of young men, already good doctors, who were eager to play their part in the medicine of the future, and there were physiotherapists, occupational therapists, and almoners—all essential members of the team on which successful rehabilitation depends.

The personalities of Lord Horder, Dr. Frank Krusen, and Dr. Howard Rusk will remain vividly in the minds of everyone who attended this congress. This is the medicine of the future, but its disciples must remember and live the warning of their president: *Le malade, toujours le malade.*

F. J. B.

CONGRESS OF OBSTETRICIANS AND GYNÆCOLOGISTS

The 13th Congress of Obstetricians and Gynæcologists was held in Leeds on July 8–11, under the presidency of Prof. A. M. Claye.

In a guest paper on Cancer of the Body of the Uterus Prof. M. A. van Bouwdijk Bastiaanse (Holland) discussed the advantages of operation by the vaginal route. He had an operability-rate of 96·2% and an absolute ten-year cure-rate of 65·1%.

The two whole days and two half-days of the meeting were each devoted to discussion of a single subject, with the aim of enabling a large number of members to speak.

Abnormal Uterine Action during Labour

Prof. G. H. Bell (Dundee) as a physiologist reviewed the means for recording uterine action, and found no method satisfactory for deciding whether the lower uterine segment or cervix behaved passively or actively during labour. He thought it unlikely that progesterone caused the uterus of any species to become quiescent. He accepted the evidence that the pregnant and non-pregnant human uterus reacted differently to the posterior-lobe hormones, but remarked that the cause of the difference required investigation. In animals at parturition both the cervix and body responded to pitocin; but the cervix reacted for only a short time while the body continued to respond, thus suggesting a normal action by the cervix to prevent precipitate delivery. If this applied in man it suggested that exaggeration of this effect would lead to cervical dystocia.

There was no objective evidence that in labour pethidine exerted an antispasmodic effect on the cervix. Any benefit from pethidine might be due to augmentation of activity in the uterine body. Among drugs investigated for antispasmodic activity on the rabbit cervix, isoprenaline and dihydroergotamine were effective, the latter however being inconstant in action. The antispasmodic action of isoprenaline was consistently more distinct on the cervix than on the corpus: but this drug would not be suitable for clinical trial until it had been modified to avert its dangerous vasodepressant effect.

Prof. W. C. W. Nixon (London) showed the histology of the pregnant cervix to demonstrate that about half the tissue was muscular and therefore capable of pharmacological response. He thought it possible that incoordination of uterine action was related to abnormal muscle-collagen distribution. The constant feature in incoördination was prolonged labour; and his standard was labour lasting more than thirty-six hours. Comparison of the incidence of prolonged labour in London with seven different racial groups in other parts of the world showed the influence of age and parity. In all centres there was a higher incidence of prolonged labour in primigravidæ; in London a relatively small proportion had their first pregnancy before the age of 22 years.

In a series of primigravid women judged to be at term the position, length, dilatation, and consistence of the cervix was noted at the time of artificial rupture of the membranes. Where the cervical tissues were softened and the canal short and open, the subsequent induction-delivery interval appeared to be generally short. When, however, the cervix was directed towards the sacrum—the "sacral os"—a prolonged labour always ensued. Whenever labour had lasted longer than twenty-four hours a careful review should be made. For cervical dystocia a drip infusion containing pitocin or glucose or 'D.H.E. 45' had not given constant results. During recent years he had found an increase in the incidence of cæsarean section for labours lasting over forty-eight hours; he now felt that unfavourable cases should be detected earlier, thus shortening the interval before section.

Mr. E. A. Williams (Oxford) described a method of recording intra-uterine pressure changes by 'Polythene' tubing introduced into the amniotic cavity past the presenting part through a Drew-Smythe catheter. An ample portion of tubing lay within the uterus; and the portion outside might be strapped to the thigh, thus allowing complete freedom of movement to the patient in the intervals between pressure recordings. The base-for close coöperation between physiotherapists, nurses, occupational therapists, and specialists in physical medicine.

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Dr. HAROLD BALME (London) spoke about rehabilitation and its international relations.

Other Activities

Delegates paid a visit to Aldershot where they saw a demonstration of physical education by boys and girls from London County Council schools. Lieut.-Col. J. B. M. Milne described the PULHEEMS method of physical assessment, and a demonstration of battle physical training was given.

An historic and scientific exhibition had been planned by Dr. C. SHIELDS. The Wellcome Medical Museum showed a fascinating exhibit illustrating the developments of hydrotherapy, massage, and remedial exercises, and the therapeutic use of electricity and radiant energy. Among the other exhibits were electronic equipment developed at St. Thomas's Hospital, shown by Dr. BAUWENS, and self-help devices and mechanical aids for the disabled from Dr. Rusk's centre in New York. Mrs. GUTHRIE SMITH showed a bed-chair made of light tubular steel, and consisting of a back and two long

line for fluid-pressure readings was taken from the level of the symphysis pubis with the patient recumbent. Tracings showed the commencement of labour with normal rhythm; the interference caused by bladder distension; the impetus to uterine action of an enema; and the effect of posture on labour, where the optimum effect was observed with the patient sitting. Failure of relaxation between contractions was observed in association with fœtal distress. It was noteworthy that no instance of hypertonic uterine action had been observed.

Dr. C. N. SMYTH (London) proposed the formation of a committee, national or international, to standardise the meaning of terms employed in obstetric records and to design a labour-record chart suitable for mechanical sorting which could have a world distribution and form the basis of a central file of information. He emphasised the vagueness of words such as "labour." By way of illustrating the value of collected information he showed a graph of the expected duration of labour for patients who had already been in labour for various lengths of time. Dr. Smyth also referred to the controlled "pitocin labour" and emphasised the need for tocographic control of the drip-rate. He pointed out the effect of pressure on the cervix, either manual or from the presenting part, in stimulating uterine contractility.

Prof. R. CALDEYRO-BARCIA (Montevideo) described the experimental methods which he uses with his colleague Prof. H. ALVAREZ to record uterine tension simultaneously in both cornual areas and in the lower body and cervix. The pressure inside the bladder with less than 35 ml. of fluid was recorded to assess the influence of intra-abdominal pressure on the total intra-amniotic pressure. Thus the intra-uterine tension could be estimated. When uterine contractions on both sides were simultaneous and equivalent in force, labour proceeded satisfactorily. With asynchronous activity the contractions were ineffective and labour was slow. The effect of 'Nupercaine' spinal anæsthesia in relieving asynchronous activity, and of adrenaline in increasing irregular activity, was shown. This method was the most satisfactory yet developed for the study of uterine action and for testing new drugs, such as dihydroergotamine.

Miss JEAN HALLUM (Birmingham) reported satisfactory results from dihydroergotamine 0·25 mg. intramuscularly in 40 cases.

Mr. K. S. RICHARDSON (Sydney) reported that dihydroergotamine was suitable, not for the lazy uterus, but for the uncommon incoördinate type, and that dosage should be cautious. Prof. T. N. A. JEFFCOATE (Liverpool) agreed with this distinction. Like Prof. J. CHASSAR MOIR (Oxford) he held that all oxytocics were potentially dangerous. Probably administration in high dilution by a closely supervised drip was the least dangerous method of determining individual dosage.

Pædiatrician's Place in a Maternity Unit

Prof. W. F. GAISFORD (Manchester) as a pædiatrician welcomed the obstetric skill which caused a decline in the number of infants born with intracranial damage liable to produce backwardness. He remarked that the contribution of the pædiatrician to this improvement had been the diminution of pelvic rickets. It was necessary for the pædiatrician to undertake the resuscitation, care, and investigation of the normal newborn infant, in order to acquire skill and knowledge in detecting the earliest signs of disorder and in preventing disease.

His investigations had shown that a binder could contribute to atelectasis; that faulty cord dressings could spread infection; that vernix caseosa should not be washed off; that the routine use of vitamin K reduced the risk of hypoprothrombinæmia; and that early immunisation against tuberculosis and whooping-cough could save lives. He desired control of breast-feeding and believed that preparation should begin early in pregnancy. To this end he advised that a pædiatric sister should attend the antenatal clinic to instruct mothers in preparation for breast-feeding. In the antenatal period the pædiatrician should be consulted in the management of such problems as prematurity, fœtal malformations, hæmorrhagic diseases of the newborn, and toxæmia. Antenatal pædiatrics was an aspect of child health which offered more promise of future development than any other branch.

Mr. F. E. STABLER (Newcastle upon Tyne) said that without definition of status he had for many years found complete harmony in working with pædiatricians. He welcomed the pædiatrician's aid from the earliest stage of pregnancy—indeed on occasion before conception—and his advice on the structure and management of the hospital. In his hospital, at least once a week obstetricians and pædiatricians together went round their departments in consultation. At monthly staff meetings they were joined by the general physician, anæsthetist, surgeon, and pathologist for joint discussion. Mr. Stabler defined the ideal pædiatrician colleague as a good doctor fully acquainted with the physiology and pathology of pregnancy and labour. He must be an obstetrician lacking only manipulative skill in delivery.

Dr. BERYL CORNER (Bristol) said that pædiatricians desired to concentrate on problems of the newborn in maternity units with four main objects: (1) to acquire knowledge of function; (2) by the supervision and care of the newborn and control of the obstetric house-surgeon, to implement the new knowledge; (3) to detect the early signs of disease; and (4) the least important—to treat the sick baby. Should the need for treatment of the sick be common, the control of the pædiatrician had failed.

Mr. A. AMBERY SMITH (Leeds) described the effect of the pædiatrician taking charge of the baby at birth on the experience and training of the young obstetrician. Eight obstetricians trained at his hospital under this system were now consultants; and of these, six had charge in large areas where a pædiatrician was not available. There was also a serious gap in the training of house-surgeons proceeding to the diploma examination of the Royal College of Obstetricians and Gynæcologists before entering general practice.

Prof. G. GORDON LENNON (Bristol) said that obstetricians must bear the responsibility for neglect of baby-care in the past. Pædiatrics was a new specialty that, in the asphyxial stage some twenty to thirty years ago, had been treated by the obstetrician with a liberal supply of oxygen and left alone. As a child it had done as children did, when unchecked, and taken liberties. Now that it had become a man it should put away childish things. Its sphere of influence should be limited and defined. Antenatal pædiatrics was obstetrics. Why should the obstetrician hand over a baby for resuscitation to a houseman untrained in obstetrics? The consultant pædiatrician was never seen in the labour-room during the night. The specialty of obstetrics and gynæcology was being assailed on all sides—in this case by the pædiatrician, in other cases by the radiotherapeutist over the treatment of uterine cancer, by the radiologist indicating when to do a cæsarean section for disproportion, or by the midwife for the care of normal labour. The wealth of attraction of the specialty was becoming apparent to all. Obstetricians must protect their interests.

Prof. W. I. C. MORRIS (Manchester) was aware of friction arising over infrequent visits by the pædiatrician, the management of breast-feeding, and the methods of resuscitation of the newborn. It should be remembered that pædiatricians were too few to provide a complete service to specialist-staffed maternity hospitals, while many maternity units were staffed entirely by general practitioners. It was therefore still vitally necessary to train obstetric house-surgeons and registrars in neonatal pædiatrics. It was also highly desirable that trained obstetricians—both general practitioners and specialists—should have opportunities to refresh their pædiatric knowledge. In a fully staffed maternity unit, usually in a teaching hospital, some rules could be made with advantage, such as:

1. The obstetrician delegates labour-room duties only to a colleague of equivalent professional status.

2. The pædiatrician takes complete control of babies in wards or nurseries—and of breast-feeding of all lactating mothers.

3. The obstetrician resumes complete control of all mothers when the general physical or mental condition makes this desirable, as when fever occurs.

4. The obstetrical house-surgeons should be made responsible for some agreed portion of the pædiatric duties.

High standards of professional behaviour would ensure good relations between colleagues.

Stress Incontinence of Urine

Dr. **Albert H. Aldridge** (New York) discussed the conditions which may create an abnormally high intravesical pressure, including reflex irritability due to inflammatory lesions; and he does not regard leakage of urine from this cause through a normal urethra as true stress incontinence. Leakage of the stress type occurred in the presence of fairly gross anatomical changes involving the urethra and bladder and their supporting structures. From clinical experience and limited knowledge of the mechanism of control of micturition, it seemed important in surgical treatment to do three things: (1) to reduce the lumen of an overstretched urethra to normal and to restore the shortened urethral canal to its original length; (2) to repair the damaged, overstretched, and retracted urethral sphincter-muscles; and (3) to construct a support from the surrounding tissues to hold the urethra and vesical neck as high as possible in the pelvis. Care should be taken to exclude or discover and correct symptoms due to urge incontinence. In general, operations should not be undertaken until at least six months after the original injury or a previous operation for the same condition.

In Dr. Aldridge's experience vaginal operations of the type devised by Kelly (1911) cured about 80% of patients; and the modification introduced by Kennedy had somewhat improved the results. There remained some 10–20% of partial or complete surgical failures. In 1941 he treated a patient in whom leakage of urine had not been cured by three vaginal plastic operations. After another plastic operation by the Kennedy method and transplantation of fascia to form a supporting sling beneath the proximal end of the urethra, this patient had now been continent and free from bladder symptoms for more than ten years. Further experience had shown that this method was relatively simple and safe if dissections were carried out in natural planes of cleavage. The procedure might fail if the sling was not made sufficiently taut, if the abdominal wall was too relaxed, or if the urethra and vesical neck could not be freely mobilised on account of dense scar tissue.

Commenting on the Millin and Read report of only 1 known failure after 140 operations using a fascial sling by the suprapubic route, Dr. Aldridge said that the results were remarkable if the assumption was correct that many women in this series had vaginal birth injuries which were not repaired. Another suprapubic procedure which, used alone without attempt to repair birth injuries to the urethra and bladder, had produced good results was the Marshall and Marchetti operation, which pulled the urethra and bladder-wall forward and upward to be fixed to the pubic bone and anterior abdominal wall.

At a recent meeting of the New York Obstetrical Society, Ball, of Cornell, reported 94% cures from treatment of stress incontinence by combination of a vaginal plastic operation of the modified Kelly type, tightening of the vesical neck on its anterior surface, and fixation of the urethra and bladder-neck to the pubic bone and anterior abdominal wall.

Speculating on why sling operations or suprapubic fixation of the urethra and bladder will cure some women in whom plastic vaginal operations have failed, Dr. Aldridge said that it is apparent that to restore function of the urethral-sphincter mechanism the urethra and vesical neck must be supported high in the pelvis. The success of the Millin-Read sling technique and the Marshall-Marchetti vesico-urethral suspension operation as single procedures—that is, without a preliminary vaginal plastic operation—underlined the importance of this step in any surgical technique for relief of stress incontinence.

If Jeffcoate had found the explanation of the present vaginal plastic failures and the success of the suprapubic procedures, a satisfactory vaginal operation might eventually be found.

Professor **Jeffcoate** reported the results of cysto-urethrography in relation to stress incontinence. He showed the limitations of anteroposterior and oblique studies. By his lateral studies he had discerned important anatomical changes in 90% of cases. In a control group of nulliparous women, and in parous women without prolapse or incontinence, with the bladder full and the patient standing, the bladder-base normally lay parallel with, and 1–2 cm. above, a line joining the lower border of the symphysis pubis to the last piece of the sacrum. The urethra was straight and made a clearly defined and angled junction with the bladder. There was no suggestion of a "neck" to the bladder. The internal urethral meatus was 2–3 cm. away from the symphysis pubis. The posterior urethrovesical angle, which normally measured about 100°, was especially important. A strong bearing-down effort moved the bladder-base and upper urethra slightly downwards and backwards, this displacement being sometimes as much as 1 cm. in multiparous women. The angle and shape of the urethrovesical junction were unchanged by stress. During micturition the bladder became ovoid in shape; the bladder-base and the upper urethra moved downwards and backwards, but the lower urethra remained fixed at the level of the triangular ligament. As the movement exceeded that noted during stress, a relaxation of the pelvic-floor musculature was assumed to bring about this descent. Along with this movement the urethrovesical angle was obliterated, and both urethra and trigone were seen to lie in a straight line, the meatus and upper urethra becoming funnel-shaped, and the remainder of the urethra running straight to its lower fixed point where it was angled to take a downwards direction. The upper movable part of the urethra lay parallel to the plane of the pelvic brim.

In cases of stress incontinence the most striking and constant finding was loss of the normal urethrovesical angle, so that the base of the bladder and urethra were in line. In most this change was present at rest; in some it became apparent only on straining. Funnelling of the urethrovesical junction was seldom seen without a coincident change in the urethrovesical angle. Increased downward movement of the bladder-base, except as related to loss of angulation, was probably insignificant in that it appeared to be related to the degree of prolapse rather than to the severity of the incontinence. During micturition the appearances were essentially the same as in normal controls.

In cases with prolapse without loss of the posterior urethrovesical angle, incontinence was caused only when the trigone was involved. If cystocele involved the bladder-base behind Mercier's bar, incontinence did not result. From this evidence it might be concluded that any operation which was to cure stress incontinence must aim above all at restoring the urethrovesical angle and correcting any funnelling of the internal meatus, the former being the more important. This conclusion was strengthened, and the significance of the anatomical changes found in stress incontinence confirmed, by radiological examination of patients before and after operative treatment.

Dr. **Henry Roberts** (Liverpool) showed lateral cysto-urethrograms in 3 cases after successful Marshall-Marchetti operations which had restored the posterior urethrovesical angle. The inference was that continence depended on a satisfactory condition in the intrinsic musculature about the bladder-base and urethral junction, and not on the state of the pelvic-floor musculature and fasciæ.

Dr. **A. G. I. Ingelman-Sundberg** (Stockholm) and Mr. **J. H. Mulvaney** (Surrey) reported on their operations. Prof. **E. Bracht** (Berlin) showed a film of a new method of elevating the bladder-neck region. Dr. **John R. Upton** (San Francisco) described his adaptation of the Le Fort operation in the aged.

Several speakers referred to the need for care in diagnosing and selecting cases for operation, and for examination by the surgeon in assessing the late results of treatment. Mr. **W. R. Sloan** (Bangor, Northern Ireland) referred to difficulties and unsatisfactory results after sling operations. Professor **Lennon** had seen ill results from sling operations. He was now trying the Mulvaney operation, so far with promising effect. Mr. **J. A. Chalmers** (Worcester) was trying the Marshall-Marchetti operation, and had so far cured all but 1 of 30 cases.

Mr. **L. G. Phillips** (London) did not agree that the failure-rate with vaginal plastic operations was as high as others estimated, provided that the operator was experienced and he made a careful deliberate dissection. Prof. **Chassar Moir** agreed with Mr. Phillips. He referred to the merits of the Millin and Aldridge sling techniques in cases where the vaginal operation had failed. He preferred the Aldridge operation, although it took more time to perform and required two openings; there were few dangers, and the sling tension could be accurately adjusted. He gave a caution concerning the psychological element in assessing the patient before and after operation. In a follow-up, at least six months should have elapsed and the patient should be examined with her bladder full.

Genital Tuberculosis

Dr. **Magnus Haines** (London) believed that pelvic tuberculosis arose by blood-stream infection from extragenital foci. Many of his patients had earlier manifestations of tuberculosis, including pleurisy, cervical adenitis, iritis, peritonitis, and pulmonary, renal, and bone infections. He questioned the belief of some physicians that genital lesions were uncommon among sanatorium patients, and cited Jedburgh's finding on menstrual culture of 5 women with latent genital lesions among 100 sanatorium patients. There was also ample evidence of genital tuberculosis in 7–8% of women who died of pulmonary tuberculosis.

Concerning morbid anatomy, in some cases the uterus, fallopian tubes, and ovaries might appear normal on naked-eye examination. In addition to the exudative and adhesive types of tubal disease, both hæmatosalpinx and hydrosalpinx might be tuberculous. The ovaries were involved in about a quarter of the cases. In early cases the endometrium might look normal. When involved, the myometrium was invaded from the endometrium. The diagnosis by histology had so many limitations that investigators required to find the tubercle bacillus for confirmation. A small portion of suspected tissue might be implanted in the thigh muscles of the guineapig; the organisms obtained might then be used for sensitivity tests with antibiotics and for typing of strain. He believed that nearly always female genital tuberculosis was due to a human-type bacillus.

Mr. **John Stallworthy** (Oxford) dealt with clinical features in his 78 proven cases. The only patient who died was an infertile woman with unsuspected endometrial disease who refused treatment and died one year later of miliary tuberculosis. He believed that there were more women with unsuspected tuberculous pelvic disease than there were with symptoms or signs. Infertility was a complaint in more than half his cases: there were associated gynæcological symptoms in one-fifth of these. Menstruation was normal in half his patients; menorrhagia occurred inconstantly in some, but amenorrhœa was rare. This emphasised the importance of endometrial studies before initiating hormone therapy for menstrual disorders. Pain was not usually prominent. Peritonitis might heal, leaving tubal function unimpaired; and in 1 case pregnancy followed. Deterioration was usually insidious, and ascites might develop with other pelvic signs. Fistulæ might complicate extensive pelvic disease or follow imperfect surgery.

In treatment striking success followed painstaking preparation followed by total hysterectomy and excision of fistulous tracts and diseased bowel; in some instances such success was obtained before the introduction of streptomycin. By contrast, a patient with a unilateral pyosalpinx, colovesical fistula, large posterior myoma, and heavily infected bladder and endometrium was treated with streptomycin 1 g. daily for three months; the tuberculous infection was clinically cured, but the fistula persisted. The patient was anxious to avoid hysterectomy. The affected colon was excised, a myomectomy performed, and the uterine hood used to extraperitonealise the indurated bladder fistula. At eighteen months the patient was well.

Mr. **A. M. Sutherland** (Glasgow) reported on 46 patients receiving 1 g. of streptomycin daily, and 3 g. of P.A.S. four times daily, for eighty-four days, and 29 patients observed as a control group. These 75 patients had histologically proved disease. The endometrium had remained positive in most of the control group. Of the control patients, 1 was later found to have a tuberculous infection of the urinary tract, a 2nd was subsequently brought under treatment because of clinical deterioration, and a 3rd failed to report regularly and now had tuberculous meningitis. Among the treated patients no permanent ill effects had been noted. Treatment was discontinued for slight vestibular disturbances in 2 patients at 52 and 27 g. streptomycin; and a third patient had treatment discontinued at 22 g. because of skin eruption and hair loss. One patient with disease apparently limited to the cervix was six months negative to biopsy test. 3 patients developed peritonitis after the original diagnostic procedures. This complication rapidly subsided with commencement of treatment; repeat biopsies had, however, been omitted. In the remaining 39 cases, premenstrual endometrial biopsies were performed half-way through treatment, at the end of treatment, after three and six months, and at the end of a year, with guineapig inoculation. So far the endometrium had remained negative in most of the treated cases.

Mr. **Linton Snaith** (Newcastle upon Tyne) presented evidence that genital tuberculosis should be regarded as one of the earliest postprimary infections occurring within three years of effective exposure to the disease, judged by the appearance of an obvious primary manifestation such as erythema nodosum. If the primary infection occurred in childhood, when the genital tract was inactive, this escaped infection, resistance was established, and the genital tract rarely suffered. With adolescence the genital tract was active and vulnerable, and school-leaving increased the risk of exposure to infection.

Dr. E. **Rabau** (Israel) reported the treatment of a *bacteriologically proved case of genital tuberculosis* by streptomycin 100 g., followed by insufflation. In this case there was subsequently a successful pregnancy.

The transactions of the congress will be published in the *Journal of Obstetrics and Gynæcology.*

Special Articles

LENGTH OF STAY IN HOSPITAL OF THE AGED SICK

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M.A., M.D. Camb., F.R.C.P.
PHYSICIAN

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UNIVERSITY COLLEGE HOSPITAL, LONDON

It has long been the custom for the aged sick to be cared for in hospitals which cater chiefly for chronic illness. This association has led to the belief that any old person who falls ill will need a long stay in hospital. As a result, in the present scarcity of hospital beds, it has become increasingly difficult to obtain admission for old people even when they are suffering from acute illness.

While we recognise that a small proportion of elderly sick will require a long stay in hospital (often for social rather than medical reasons), this is not true of the majority, as will be seen from our analysis of a year's admissions at University College Hospital.

A YEAR'S EXPERIENCE

The hospital's unit for the care of the aged sick has been described already (Exton-Smith and Crockett 1949, Amulree et al. 1951). There are now 120 hospital beds and a further 30 in a hostel (the Barlow Home) which serves in part as a "half-way house" and in part, inadvertently, as a long-stay annexe. We still have 45 patients who were in the hospital when it was taken over from the London County Council in July, 1948; a further 32 beds are blocked by patients admitted since July, 1948, who have been in hospital for over six months. Of these 77 long-stay patients, 23 are in the Barlow Home.

Most patients admitted come from the borough of St. Pancras, requests being received from general practitioners and also through the Emergency Bed Service. Nearly all of them are first seen by one of us in their own homes to assess their claim to priority of admission.

A great variety of diseases has been treated; cerebral vascular lesions and cardiac and chest conditions were the most common. There were several patients with skin disorders and a few with *pulmonary tuberculosis*. Nearly all were over 65 years old; the average age of the men was $74^1/_4$ years and of the women $76^1/_2$ years.

RESULTS

During the year from July 1, 1950, to June 30, 1951, 340 patients (180 men and 160 women) were admitted; of this total, 40 (11·8%) remained in hospital for more than 6 months and are regarded as long-stay patients. The average stay in hospital of the remaining 300 was 40·2 days; any part of a patient's stay which was in the Barlow Home is included as part of the stay in hospital (see table).

PATIENTS ADMITTED TO THE GERIATRIC UNIT 1950–51

—	Remained in hospital over 6 months	Stayed less than 6 months			Average length of stay in days of groups a, b, and c	Average age in years
		(*a*) Died	(*b*) Discharged	(*c*) * Transferred		
Males (180)	17	54	90	19	38·9	$74^1/_4$
Females (160)	23	51	79	7	41·6	$76^1/_4$
Totals (340)	40 (*11·8%*)	105 (*30·9%*)	169 (*49·7%*)	26 (*7·6%*)	40·2	...

* Some of these patients were transferred for surgical treatment. Others showed mental changes with antisocial habits which made it difficult to nurse them in a general ward; they were not certified, but, after a period of observation, went to hospitals provided for such cases.

The average length of stay of adult patients admitted to the medical wards of University College Hospital during the year 1950 was 35·1 days. When those with tuberculosis and skin diseases were excluded the average length of stay was reduced to 32·6 days.

DISCUSSION

Our survey thus shows that the stay in this hospital of the great majority of elderly sick is not much longer than that of younger medical patients. Many of our acute cases were accepted after the Emergency Bed Service had failed to get them into other hospitals. Our experience suggests that admission officers are often unduly apprehensive of having their beds blocked by old people. Graham (1951) gained the same impression from a study of elderly patients referred to the Emergency Bed Service.

We have not confined our patients for admission to those whose prognosis seemed relatively good; even those with obviously terminal diseases were not rejected. Thus the number of deaths, most of which occurred within a month of admission, is high—105 (or 30·9%).

We do not yet know how long those patients who remained in hospital for over 6 months are likely to stay; of the 40 such patients admitted in the year ended on June 30, 1951, 16 were still in hospital on May 31, 1952.

SUMMARY

Of 340 elderly patients admitted to this unit during one year, 300 stayed in hospital for less than 6 months. The average length of stay of these 300 patients was 40·2 days.

The average length of stay of adult medical patients in the wards of the rest of University College hospital was 35·1 days.

When admitted to hospital, the great majority of elderly sick occupy a bed little longer than do younger patients.

We wish to thank Miss A. Cocks of the secretarial staff for her help in the preparation of our figures and Mr. D. M. Iles, the records officer, for providing the figures for the general medical wards.

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Amulree, Lord, Exton-Smith, A. N., Crockett, G. S. (1951) *Lancet*, i, 123.
Exton-Smith, A. N., Crockett, G. S. (1949) *Ibid*, i, 1016.
Graham, W. L. (1951) *Ibid*, ii, 931.

rather than to the severity of the incontinence. During micturition the appearances were essentially the same as in normal controls.

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Mr. JOHN STALLWORTHY (Oxford) dealt with clinical features in his 78 proven cases. The only patient who died was an infertile woman with unsuspected endometrial disease who refused treatment and died one year later of miliary tuberculosis. He believed that there were more women with unsuspected tuberculous pelvic disease than there were with symptoms or signs. Infertility was a complaint in more than half his cases; there were associated gynæcological symptoms in one-fifth of these. Menstruation was normal in half his patients; menorrhagia occurred inconstantly in some, but amenorrhœa was rare. This emphasised the importance of endometrial studies before initiating hormone therapy for menstrual disorders. Pain was not usually prominent. Peritonitis might heal, leaving tubal function unimpaired; and in 1 case pregnancy followed. Deterioration was usually insidious, and ascites might develop with other pelvic signs. Fistulæ might complicate extensive pelvic disease or follow imperfect surgery.

In treatment striking success followed painstaking preparation followed by total hysterectomy and excision of fistulous tracts and diseased bowel; in some instances such success was obtained before the introduction of streptomycin. By contrast, a patient with a unilateral pyosalpinx, colovesical fistula, large posterior myoma, and heavily infected bladder and endometrium was treated with streptomycin 1 g. daily for three months; the tuberculous infection was clinically cured, but the fistula persisted. The patient was anxious to avoid hysterectomy. The affected colon was excised, a myomectomy performed, and the uterine hood used to extraperitonealise the indurated bladder fistula. At eighteen months the patient was well.

Mr. A. M. SUTHERLAND (Glasgow) reported on 46 patients receiving 1 g. of streptomycin daily, and 3 g. of P.A.S. four times daily, for eighty-four days, and 29 patients observed as a control group. These 75 patients had histologically proved disease. The endometrium had remained positive in most of the control group. Of the control patients, 1 was later found to have a tuberculous infection of the urinary tract, a 2nd was subsequently brought under treatment because of clinical deterioration, and a 3rd failed to report regularly and now had tuberculous meningitis. Among the treated patients no permanent ill effects had been noted. Treatment was discontinued for slight vestibular disturbances in 2 patients at 52 and 27 g. streptomycin; and a third patient had treatment discontinued at 22 g. because of skin eruption and hair loss. One patient with disease apparently limited to the cervix was six months negative to biopsy test. 3 patients developed peritonitis after the original diagnostic procedures. This complication rapidly subsided with commencement of treatment; repeat biopsies had, however, been omitted. In the remaining 39 cases, premenstrual endometrial biopsies were performed half-way through treatment, at the end of treatment, after three and six months, and at the end of a year, with guineapig inoculation. So far the endometrium had remained negative in most of the treated cases.

Mr. LINTON SNAITH (Newcastle upon Tyne) presented evidence that genital tuberculosis should be regarded as one of the earliest postprimary infections occurring within three years of effective exposure to the disease, judged by the appearance of an obvious primary manifestation such as erythema nodosum. If the primary infection occurred in childhood, when the genital tract was inactive, this escaped infection, resistance was established, and the genital tract rarely suffered. With adolescence the genital tract was active and vulnerable, and school-leaving increased the risk of exposure to infection.

Dr. E. RABAU (Israel) reported the treatment of a bacteriologically proved case of genital tuberculosis by streptomycin 100 g., followed by insufflation. In this case there was subsequently a successful pregnancy.

The transactions of the congress will be published in the *Journal of Obstetrics and Gynæcology.*

Special Articles

LENGTH OF STAY IN HOSPITAL OF THE AGED SICK

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IT has long been the custom for the aged sick to be cared for in hospitals which cater chiefly for chronic illness. This association has led to the belief that any old person who falls ill will need a long stay in hospital. As a result, in the present scarcity of hospital beds, it has become increasingly difficult to obtain admission for old people even when they are suffering from acute illness.

While we recognise that a small proportion of elderly sick will require a long stay in hospital (often for social rather than medical reasons), this is not true of the majority, as will be seen from our analysis of a year's admissions at University College Hospital.

A YEAR'S EXPERIENCE

The hospital's unit for the care of the aged sick has been described already (Exton-Smith and Crockett 1949, Amulree et al. 1951). There are now 120 hospital beds and a further 30 in a hostel (the Barlow Home) which serves in part as a "half-way house" and in part, inadvertently, as a long-stay annexe. We still have 45 patients who were in the hospital when it was taken over from the London County Council in July, 1948; a further 32 beds are blocked by patients admitted since July, 1948, who have been in hospital for over six months. Of these 77 long-stay patients, 23 are in the Barlow Home.

Most patients admitted come from the borough of St. Pancras, requests being received from general practitioners and also through the Emergency Bed Service. Nearly all of them are first seen by one of us in their own homes to assess their claim to priority of admission.

A great variety of diseases has been treated; cerebral vascular lesions and cardiac and chest conditions were the most common. There were several patients with skin disorders and a few with pulmonary tuberculosis. Nearly all were over 65 years old; the average age of the men was 74¼ years and of the women 76½ years.

RESULTS

During the year from July 1, 1950, to June 30, 1951, 340 patients (180 men and 160 women) were admitted; of this total, 40 (11·8%) remained in hospital for more than 6 months and are regarded as long-stay patients. The average stay in hospital of the remaining 300 was 40·2 days; any part of a patient's stay which was in the Barlow Home is included as part of the stay in hospital (see table).

PATIENTS ADMITTED TO THE GERIATRIC UNIT 1950–51

—	Remained in hospital over 6 months	Stayed less than 6 months			Average length of stay in days of groups a, b, and c	Average age in years
		(a) Died	(b) Discharged	(c) *Transferred		
Males (180)	17	54	90	19	38·9	74¼
Females (160)	23	51	79	7	41·6	76½
Totals (340)	40 (11·8%)	105 (30·9%)	169 (49·7%)	26 (7·6%)	40·2	..

* Some of these patients were transferred for surgical treatment. Others showed mental changes with antisocial habits which made it difficult to nurse them in a general ward; they were not certified, but, after a period of observation, went to hospitals provided for such cases.

The average length of stay of adult patients admitted to the medical wards of University College Hospital during the year 1950 was 35·1 days. When those with tuberculosis and skin diseases were excluded the average length of stay was reduced to 32·6 days.

DISCUSSION

Our survey thus shows that the stay in this hospital of the great majority of elderly sick is not much longer than that of younger medical patients. Many of our acute cases were accepted after the Emergency Bed Service had failed to get them into other hospitals. Our experience suggests that admission officers are often unduly apprehensive of having their beds blocked by old people. Graham (1951) gained the same impression from a study of elderly patients referred to the Emergency Bed Service.

We have not confined our patients for admission to those whose prognosis seemed relatively good; even those with obviously terminal diseases were not rejected. Thus the number of deaths, most of which occurred within a month of admission, is high—105 (or 30·9%).

We do not yet know how long those patients who remained in hospital for over 6 months are likely to stay; of the 40 such patients admitted in the year ended on June 30, 1951, 16 were still in hospital on May 31, 1952.

SUMMARY

Of 340 elderly patients admitted to this unit during one year, 300 stayed in hospital for less than 6 months. The average length of stay of these 300 patients was 40·2 days.

The average length of stay of adult medical patients in the wards of the rest of University College hospital was 35·1 days.

When admitted to hospital, the great majority of elderly sick occupy a bed little longer than do younger patients.

We wish to thank Miss A. Cocks of the secretarial staff for her help in the preparation of our figures and Mr. D. M. Iles, the records officer, for providing the figures for the general medical wards.

REFERENCES

Amulree, Lord, Exton-Smith, A. N., Crockett, G. S. (1951) *Lancet*, i, 123.
Exton-Smith, A. N., Crockett, G. S. (1949) *Ibid*, i, 1016.
Graham, W. L. (1951) *Ibid*, ii, 931.

Parliament

W.H.O. and Population Problems

In the debate on the adjournment on July 18, Mr. DOUGLAS HOUGHTON recalled recent discussions at the World Health Assembly, on the Norwegian proposal to set up an expert committee "to examine and report on the health aspects" of the population problem. The resolution was opposed by delegations from Catholic countries on the grounds that if the committee recommended that birth-control were included in the permanent programme of W.H.O., that body might lose not only good will but some members. Eventually the Norwegian resolution was withdrawn. As the United Kingdom delegate, Dr. Mackenzie, did not state what our Government's policy was in this matter Mr. Houghton asked the parliamentary secretary to do so. He admitted that the problem of population had not only health, moral, and social aspects, but also sectarian aspects. But, while we must respect religious opinion that did not mean we must submit to it. He believed that disease, misery, death, and starvation were infinitely more immoral than any form of birth-control.

Miss PATRICIA HORNSBY-SMITH said that from the outset it had been the policy of the World Health Assembly and W.H.O. that birth-control was primarily a sociological and not a medical question and that W.H.O. would be competent to advise only in the medical aspect. It was felt that to introduce the economic or sociological side would do grave harm to a new organisation which had an immense field of work in health welfare which it was doing in the most coöperative spirit. An enormous amount of good was being done in fighting disease throughout the world; and if a matter as violently controversial as this topic were brought into this organisation, it would mean the secession of several of the nations who now worked in coöperation with us.

The subject was first introduced at the conference in May, 1952, by the Food and Agriculture Organisation representative, who pointed out the difficulty of feeding the growing populations of the world. The Indian delegate then reported on the experiment in the "rhythm" method of birth-control, in which W.H.O. had collaborated, and was still collaborating, at the request of the Indian government, giving purely medical guidance. The request for that guidance was conditional upon the experiments being restricted to the use of the "safe period," and without the use of mechanical contrivances. The Norwegian delegate's resolution was supported by some delegations, and was strenuously opposed by a substantial team of delegates who held opposing views. One of the reasons against it was that if such an expert committee produced a report it would undoubtedly be taken as the policy of W.H.O. To avoid controversy the Indian delegate put in an alternative resolution which was followed by one from Belgium, the Lebanon, and Italy. Finally, after heated discussions, only palely reflected in the brief official minutes, with agreement all round and a realisation that W.H.O. was too big to split on this topic at this time the motions were all withdrawn.

Replying to the charges that the United Kingdom delegate took no part in the debate, Miss Hornsby-Smith affirmed that his position was clear. The British Government did not believe that it was any part of the duty of W.H.O. to interfere with, or impose, policy on economic grounds. That was the concern of the individual sovereign governments. The representative of H.M. Government did not enter into the discussion at the conference because he felt it ranged far beyond what he thought could be introduced by W.H.O. We had great responsibilities of our own towards native populations under our jurisdiction, and the Government had set themselves against imposing anything of this nature on any territory under our control. Such a policy could readily be misrepresented as an attempt to control native populations to the advantage of white minorities. In short, she affirmed, the Government did not consider that W.H.O. is competent to discuss or express views on the social, economic, or ethical aspects of birth-control.

Medical Problems of Civil Defence

Speaking in the debate on civil defence in the House of Commons on July 18, Dr. BARNETT STROSS pointed out that methods and techniques of civil defence had changed since the late war. The four things to guard against, he said, were high explosives—now an old-fashioned weapon—fire bombs, particularly of the napalm type—atom bombs, and disease attacks. He did not think the latter would in fact be used, for there was no highly technically evolved people that would not be prepared and able to answer back in a like way. Statements, such as that made by General Alden H. Waitt, chief of the United States Army Chemical Corps, who said

> "Clostridium botulinum is the most poisonous thing known to man, and under ideal conditions one ounce would probably kill 150 million people."

did not mean much, because those conditions did not obtain.

Fire bombs and atom bombs were a different matter, and in his view the essential problem of civil defence, was the treatment of burns. Blood plasma and blood would be needed in huge amounts, and he asked the Home Secretary to what extent these were being stockpiled. In the first three or four days anyone suffering from burns—with a skin area up to 50% involved—would need 20 to 30 pints. After that, if the patient survived he would need the usual 20 to 30 operations over a period of two years. What steps were the Government taking to increase the numbers of skilled medical personnel, plus ancillary services for skin grafting and plastic surgery? There were centres in Birmingham and Glasgow, but he doubted whether there were more than two really efficient teams. If they were working all out probably they could not handle more than three or four cases an hour. If there were 20,000 or 30,000 casualties in one incident—which happened at Hamburg without atomic bombs—this country would need to be much better prepared than it was. At Hiroshima there were 34,000 cases of burns. Besides blood and blood plasma we should need stocks of antibiotics and dressings. If this problem was to be tackled seriously a fairly high but elementary level of training was needed throughout the whole population and in addition a large number of highly and technically trained personnel.

Sir DAVID MAXWELL FYFE, the Home Secretary, said he would see that the suggestions underlying Dr. Stross's questions were carefully studied. The question of stocks of blood was in hand at the Ministry of Health. The Government, he continued, did not believe that the atom bomb had made all civil defence useless, but that did not mean that they underestimated its potentialities. At the same time, the danger of lingering radioactivity had been exaggerated. Except in the area immediately below the burst of the bomb, which would be devastated, the probability of radioactive contamination persisting over any appreciable area for more than a short time would be exceedingly remote. The immediate radioactive effects of an atomic explosion did create a new problem, but the Government did not believe that it was insoluble. A great deal of preliminary planning had been done against the danger of fire—for example, in designing new types of emergency fire appliances and equipment.

Of the 263,458 recruits who had been enrolled for civil defence 25,000 were in the National Hospital Service Reserve. The responsibility for the enrolment and training of auxiliary members of the National Hospital Service Reserve, Sir David continued, had been accepted by the British Red Cross Society and the St. Andrew's Ambulance Association.

QUESTION TIME

Preregistration Period for Doctors

In answer to a question, Mr. IAIN MACLEOD, the Minister of Health, stated that he was informing hospital authorities that the General Medical Council have prescribed a year as the requisite period of employment in an approved hospital or approved institution following the passing of a qualifying examination before a person can be registered under the Medical Acts, and that the necessary draft Order will be laid before Parliament. The new provision would come into operation on Jan. 1, 1953, and the necessary formal draft Order in Council had been submitted for the approval of the Privy Council. He would be issuing a circular to hospital authorities giving guidance on the action to be taken by them.

Trainee Scheme in General Practice

Replying to a question, Mr. MACLEOD, said that no changes were at present under consideration in the trainee scheme for general practitioners. During the quarter ending March 31, 1952, 363 doctors in England and Wales were receiving a training grant, and in the quarter ending March 31, 1951, the number was 359.

Mental Hospital Staff

Replying to a question on the shortage of nursing staff at mental hospitals, Mr. MACLEOD said that during the past year there had been a slight rise in the number of women nurses, but on the men's side the position had worsened. The present shortage was about 3400 men and 7800 women.

R.H.B. Area Committees

Major E. G. R. LLOYD asked the Minister how many of the regional hospital boards, because their regions are too large for effective administration, were working through a number of area committees.—Mr. MACLEOD replied: One board has appointed area committees for the whole region and three for a part of their region. The functions of these committees vary widely, and not all have executive powers.

Military Hospital Services

Replying to questions on the treatment of British troops wounded in Korea, military hospital buildings and services in general with a view to improvements, Mr. ANTHONY HEAD, Secretary of State for War, said that the Commonwealth Division had the normal three field ambulances and one field dressing station for light cases. Casualties were then evacuated to a mobile Army surgical hospital. Thence, when fit to travel, they went by air to the 29th British General Hospital in Japan. From there, serious cases were brought to this country by air, while the remainder passed to a convalescent training depot before returning to duty. He was well aware that much work was needed on hospital buildings but there were many civil and other military claims on the limited resources. The main problem in the hospital services was the recruitment of sufficient regular R.A.M.C. officers, and he was examining this question.

Quality of Milk

Replying to Mr. N. N. DODDS, who asked whether the Minister of Food was aware of the spate of protests by local authorities about the deterioration of the quality of milk, Major GWILYM LLOYD GEORGE said that the standards governing the composition of milk and its cleanliness and safety were laid down in statutory regulations administered by local authorities. The Ministry of Food were also empowered to specify areas in which only milk of special designation might be retailed and they were doing so as quickly as conditions permitted. The minimum standard was not too low; the average fat content throughout the country was above what was laid down by Statute.

Mr. P. L. E. SHURMER: Is the Minister aware that the city analyst of Birmingham recently stated that the milk standard was deteriorating fast and that there should be a standard below which no milk should be sold. Major LLOYD GEORGE: Birmingham is one of the cities which I hope will shortly be among the areas in which only the specially designated milk can be sold.

Poisons Board

In answer to a question Sir DAVID MAXWELL FYFE, Home Secretary, stated that the members of the Poisons Board and the authorities appointing them were as follows:

Bertram Reece (chairman), Metropolitan magistrate, J. M. Barnes, M.B., F. R. Thornton, H.M. Chief Inspector under the Dangerous Drugs Act, 1951, and R. A. E. Galley, PH.D. (Secretary of State for the Home Department); J. M. Johnston, F.R.C.S. (Secretary of State for Scotland); W. P. Kennedy, F.R.F.P.S., and Mrs. J. A. Hauff, assistant secretary, Ministry of Health (Minister of Health); C. T. Gimingham, F.R.I.C. (Minister of Agriculture and Fisheries); J. R. Nicholls, D.SC. (Government Chemist); B. A. Bull, PH.C., W. S. Howells, M.P.S., H. N [illegible] plethorpe, PH.C., and H. Noble, PH.C. [illegible] Britain); C. A. Keele, F.R.C.P. (R [illegible] London); Prof. D. M. Lyon, F.R. [illegible] sicians of Edinburgh); Prof. David [illegible] Council); G. Roche Lynch, M.B. ([illegible] of Great Britain and Ireland); F. ([illegible] ciation).

Public Health

The Nation's Health in 1950

THE Ministry of Health's annual report is an account to Parliament and people of work undertaken on their behalf and at their expense; and the sum of these reports down the years illuminates our medical and social progress. The report should also, however, focus attention on outstanding problems; and if it is to succeed here it must appear without undue delay. The broad problems outlined year by year seldom change quickly; but the reader of a delayed report is apt to forget this, and to regard the difficulties of two years ago as lightly as yesterday's toothache.

Sir John Charles, the chief medical officer, is evidently alive to this; for his report on the year 1950 [1] appears more than a month ahead of last year's publication date. We hope that, with the help of the Registrar-General and the Stationery Office, he can take a further month off in each of the next few years.

Part 1 of the report, dealing with the National Health Service, has not yet been issued.

TUBERCULOSIS

Sir John observes that "the remarkable fall of 20 per cent in the number of deaths from tuberculosis from the number in 1949, which was the lowest then recorded in this country, should greatly encourage us." In a chapter on the disease Dr. Norman Smith points out that the death-rate from this cause in 1950 was 364 per 1,000,000 population, compared with about 3456 in the 1850's.

The report pleads for coöperation between medical officer of health, chest physician, sanitary inspector, disablement rehabilitation officer, health visitor, home nurse, and home-help organiser. "In certain areas these people meet regularly to discuss problem cases and to agree action thereon. This plan might well be imitated by every local health authority in the country."

Since July 5, 1948, more than 3500 tuberculosis beds had been added in England and Wales: and during the year tuberculosis nurses increased by 700 whole-time and 150 part-time.

The position with regard to notifications was less satisfactory. Of deaths from tuberculosis, one in six was of a patient not notified before death; and in 1949 one local health authority recorded a proportion as high as one in three. In 1950 the notification-rate was about 1 per 1000 of the population.

During the year the number of mass miniature radiography units rose by 10 to 53. Of the $5^3/_4$ million people examined since the service was started in 1943, 94·6% were found to have no abnormal chest condition. Previously unsuspected active tuberculosis of the lungs was revealed in 3·7 per 1000.

There is a mistaken impression, says the report, that mass miniature radiography is standing still. Technique is in fact continually improving, and it is only a question of time—and a relatively short time—before mass miniature pictures will become as reliable as full-size pictures.

SOME OTHER NOTIFIABLE DISEASES

Smallpox.—The infant vaccination "acceptance-rate," based on births in the twelve months ended June 30, 1950, was 23·8%. This confirms the earlier impression that the popularity of routine vaccination of infants has declined since the repeal of the Vaccination Acts in 1948; but an increase in the number of primary vaccinations in the combined age-groups under 1 and 1–4 years suggests that the age at vaccination is tending to rise. Substantially less than one-tenth of the school-children primarily vaccinated as infants are now being revaccinated before they reach the age of 15.

Since 1948 complications of vaccination done under National Health Service arrangements have been reported to the Ministry. The complications thus reported in 1950 were: generalised vaccinia 15; postvaccinal encephalomyelitis 4 (none fatal); and 1 death, which was of a 67-year-old man.

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[1] Report of the Ministry of Health; Part 2: On the State of the Public Health, being the annual report of the chief medical officer for the year 1950. Cmd. 8582. H.M. Stationery Office. Pp. 192. 6s.

On the 10th day after successful revaccination the vaccination area became much inflamed; the patient had severe constitutional disturbance with delirium; he became stuporose and incontinent, and died five days later. Necropsy showed purulent bronchitis, chronic bronchiectasis, and changes in the brain suggesting cerebral thrombosis; there was no histological evidence of encephalitis.

Diphtheria.—Notified cases amounted to 962 (1881 in 1949), and deaths 49 (84); and the case-fatality rate was 5·1 (4·5).

Immunisations numbered 517,436, compared with 693,441 in the previous year.

Scarlet Fever.—Deaths from scarlet fever numbered 33 (27 in 1949), and from streptococcal sore throat 61.

Poliomyelitis and Polioencephalitis.—During the year there were 7750 cases with 755 deaths. Notifications approached, and deaths exceeded, those in 1947, the year with the highest incidence recorded. In urban outbreaks the links in the chain of spread are obscured by the complexity of city life. Elsewhere, however, several outbreaks suggested a "chain" spread of infection which seems more or less typical of poliomyelitis in rural or semirural communities.

> "These rural outbreaks seem to give an impression that the infection at first moves through a relatively narrow stream of the population. If this were so it would seem difficult to reconcile it with the normally accepted view, based on certain immunological findings, that the virus of poliomyelitis is widespread, or well nigh ubiquitous, in the community. If the virus be virtually everywhere, there seems little hope of preventing infection, but if its distribution were limited to the patients and their contacts, its spread might perhaps be restricted to some extent by the available methods of prevention."

Dysentery.—Corrected notifications numbered 17,274—the highest total yet recorded. In 1949 the number was 4519. Much of the great increase was due to a greater prevalence in many parts of *Shigella sonnei.*

Food-poisoning.—Notified cases numbered 7506, but from special reports received from medical officers of health there was evidence that more than 17,000 people were affected. 64 deaths, 55 of which were due to salmonella infections, were reported. The foods proved, or thought most likely, to have been responsible for the spread of infection were noted in 435 outbreaks and family outbreaks. Of outbreaks in which the food responsible was known, 48% were due to processed and made-up meat dishes. An investigation of places where infection occurred suggested that "there is no reason to suppose that food poisoning arises less often in restaurants than in canteens."

MALARIA

The country remained entirely free of indigenous malaria. A survey at London Airport indicated that the risk of mosquitoes being introduced from the tropics is negligible, provided that aircraft are regularly sprayed.

VENEREAL DISEASE

The number of patients with syphilis attending clinics for the first time fell from 6812 in 1949 to 4143 in 1950. New cases of gonorrhœa decreased from 24,487 in 1949 to 20,504 in 1950.

COMMON COLD

An investigation in a Wiltshire village by the Common Cold Research Unit showed that school-children experienced about three times as many colds as adults living in households without school-children. The presence of school-children in the household approximately doubled the number of colds caught by both adults, and infants under 5 years of age. The risk of infection by exposure to another infected individual in the same household appeared to be about one in five.

Poliomyelitis

Total notifications of poliomyelitis in England and Wales up to and including the week ended July 12 were 1013. This compares with figures for the corresponding period in the last 5 years as follows:

1947	612
1948	746
1949	748
1950	1659
1951	1027

Weekly notifications from the week ended May 3 have been:

Week ended	*Paralytic*	*Non-paralytic*	*Total*
May 3..	15	9	24
,, 10..	15	6	21
,, 17..	25	12	37
,, 24..	18	19	37
,, 31..	26	18	44
June 7..	41	19	60
,, 14..	28	20	48
,, 21..	49	19	68
,, 28..	58	32	90
July 5..	61	25	86
,, 12..	78	41	119

Notifications (119) for the week ending July 12 were similar to those for the corresponding weeks in 1951 (120), 1949 (117), and 1947 (126). In 1950 the figures for the corresponding week were very much larger (212), and in 1948 considerably lower (38). Since the week ended May 31 inclusive, there have been 108 notifications from County Durham, a considerably higher figure than elsewhere. This total included 48 from Gateshead county borough and 19 from Felling urban district council. Counties with the next largest totals for the same period were: London (43), Northumberland (36), Middlesex (32), Warwick (32), and Lancashire (27).

It is difficult to draw any definite conclusion from these figures as to whether poliomyelitis is likely to become unusually epidemic this year. It is, however, clear that a significant increase in the numbers of notifications is taking place.

Dr. James Grant, medical officer of health for Gateshead writes:

> "Poliomyelitis has been prevalent on Tyneside, particularly on the south bank of the river, since May 3. Up to July 19, 93 cases had been confirmed, 62 in Gateshead county borough, 21 in Felling urban district, 9 in Whickham urban district, and 1 in Hebburn urban district. Prevalence has steadily increased, and reached a maximum last week with 17 confirmed cases on South Tyneside. North of the Tyne prevalence has been very slight.
>
> "The age-distribution of the South Tyneside cases is that of classical infantile paralysis; 64 were under the age of 5, 20 aged 5–9, 2 aged 10–14, and 7 were adults. 44 of the cases showed paralysis; and there were 2 deaths, a child of 3 who died of ascending respiratory paralysis, and an adult of 30 who died of bulbar paralysis. Paralysis involved only the limbs in 23 cases, the cranial nerves in 11, the limbs and cranial nerves in 3, and the limbs and respiratory muscles in 7.
>
> "There has been a certain amount of associated illness in contacts, which may have been abortive attacks of the disease presenting neither symptoms of meningeal irritation nor paralysis."

In the *United States* there were 421 reported cases of poliomyelitis in the week ended June 21, compared with 211 in the corresponding week of 1951.

The First Quarter in Eire

In Eire during the first quarter of this year,[1] the birth-rate was 21·8 per 1000 population, which was 0·9 above the rate for the first quarter of 1951. The equivalent annual rate for the number of deaths in the quarter was 14·4 per 1000 population, being 7·7 below that for the first quarter of the preceding year. The death-rate from all forms of tuberculosis was 0·6 per 1000 population (respiratory 0·5, other forms 0·1), compared with 0·8 (0·7 and 0·1) in the same quarter of 1951. The maternal-mortality rate was 1·2 per 1000 births registered, compared with 0·9 in the corresponding quarter of 1951. The infant mortality was 55 per 1000 births registered, compared with 58 in the corresponding quarter of 1951.

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[1] Quarterly Return of the Marriages, Births, and Deaths. Obtainable from the Government Publications Sale Office, G.P.O., Arcade, Dublin. Pp. 15. 6d.

Infectious Diseases in England and Wales

Disease	Week ended June			
	7	14	21	28
Diphtheria	29	19	23	33
Dysentery	210	188	145	135
Encephalitis:				
Infective	5	3	..	1
Postinfectious	2	2	5	1
Food-poisoning	205	116	104	144
Measles, excluding rubella	6348	7312	6288	6843
Meningococcal infection	23	40	33	30
Ophthalmia neonatorum	36	31	38	36
Paratyphoid fever	13	32	38	19
Pneumonia, primary or influenzal	371	427	384	310
Poliomyelitis:				
Paralytic	42	28	49	58
Non-paralytic	19	20	19	32
Puerperal pyrexia and fever	204	210	269	233
Scarlet fever	843	845	1071	1212
Smallpox	..	..	..	..
Typhoid fever	5	4	6	4
Whooping-cough	2075	2513	2575	2446

Population Estimates

The Registrar-General's estimates of the populations of local areas in England and Wales at June 30, 1951,[1] include figures for standard regions, conurbations, &c., as well as for administrative areas; and in each case the number of children under 15 is shown. These numbered at mid-1951 some 9,738,000 in a total population of 43,800,000: they represent 22·2% of the population, compared with 32·4% fifty years earlier.

Medicine and the Law

Oxygen Fatality

At a recent inquest at Hastings, reported in the *Sussex Daily News* and the *Hastings Observer* (July 5), the coroner's jury, after returning a verdict of death by misadventure, criticised the absence of definite instructions from the anæsthetist to a nursing sister with regard to the administration of oxygen.

An operation had been successfully performed upon an elderly woman for strangulated hernia. Some ten minutes later the surgeon was called to the ward. He found the patient suffering from surgical emphysema, extending from the chest to the eyes. The patient died soon afterwards. Having tested an oxygen tube near the bed, the surgeon found that it had a higher pressure than would normally be applied to a patient. The anæsthetist told the coroner that there had been no difficulty in giving the anæsthetic, apart from regurgitant vomiting. An intratracheal tube was inserted in order that material from the stomach should not enter the lungs. Directions were given that the patient should be taken back to the ward; the sister was told that oxygen would probably then be needed. No instructions were given as to how the oxygen was to be administered. The anæsthetist assumed that the ward-sister would have the necessary knowledge of the routine. The sister concerned assumed that the oxygen was to be given through the intratracheal tube; she fitted the oxygen tube on to the intratracheal tube. She had administered oxygen thousands of times before, she said, but never when a patient had an intratracheal tube in place. In answer to a juryman she replied that she did not know that the intratracheal tube fitted so tightly that the patient would not be able to breathe out. The pathologist's evidence attributed death to excessive pressure of oxygen on the lungs.

The hospital matron, called at the request of the jury, said that B.L.B. masks were kept in a store at the hospital. It might have taken five minutes to get one. She agreed that the masks might be more readily available, but they had never been needed before. The jury added to their verdict a rider that a definite instruction should have been given by the anæsthetist as to what method of administering the oxygen should have been employed.

Fatal Error in Hospital

The evidence at a recent inquest in Westminster, reported in the *Evening Standard* (July 15), explained the fatal consequence of an error in the dilution of an anæsthetic. A 4-year-old boy was admitted to hospital for the removal of tonsils and adenoids. Five anæsthetics had been administered already without trouble; the one for the boy required a greater dilution. The anæsthetist told the coroner what then happened. A small gallipot of spirit was nearly empty; he tipped the rest down the sink and washed the pot out with tap-water. He then poured in thiopentone solution and added about 20 ml. from the bowl which he presumed contained sterile water. He was deputising for the regular anæsthetist and had never been to this particular hospital before. He was used to working with a trolley containing a gallipot of coloured spirit. Thinking it was water, he mixed the anæsthetic with alcohol. Blood-transfusion, oxygen, and artificial respiration were tried but the patient died next morning from alcohol poisoning.

Asked by the coroner if he satisfied himself, by smelling it or dipping his finger in it, that the gallipot contained water, the anæsthetist replied that his mask would have prevented him from smelling it; he thought he had inadvertently dipped in a finger earlier, but he had noticed nothing. The coroner, commending the frankness of the witness, recorded a verdict of death by misadventure, adding that the hospital management committee would no doubt look carefully into the arrangements as regards the colouring of bowls containing spirits.

Self-service Sales of Drugs

In Pharmaceutical Society of G.B. *v.* Boots Cash Chemists (Southern) Ltd. (*Times*, July 17) the legality of "Boots Self Service" was examined in relation to section 18 of the Pharmacy and Poisons Act, 1933. At the company's Edgware premises the customer passed a barrier where he obtained a wire basket. On the shelves drugs, including proprietary medicines, were displayed with retail prices clearly marked. Having selected his purchase and placed it in the basket, the customer would leave the premises by an exit where a cashier would scrutinise the purchase, assess the price, and take the money. The Act prohibits the sale of a part-I poison unless "the sale is effected by, or under the supervision of, a registered pharmacist." The chemist's department at the premises in question was under the control of a registered pharmacist stationed near the poisons section. In all cases of the sale of a drug the pharmacist would scrutinise that part of the transaction which took place at the cash desk; if he thought fit, he was authorised to prevent a customer from removing the drug from the shop. Did these arrangements comply with the statute or was an offence committed?

The Lord Chief Justice said the question was whether the sale was completed before the money was paid and before the customer passed the pharmacist, or whether it was completed at that later moment. It was well-established law that a shopkeeper's exposure of goods for sale did not amount to an offer to sell. The self-service system meant merely that a customer picked up an article and brought it to the shopkeeper with an offer to buy. The shopkeeper could decide whether or no he would then sell. The very fact that a supervising pharmacist stood near the place where the money was paid was some intimation that the shopkeeper was not necessarily willing to make a contract with anyone who might pick up an article. Lord Goddard accordingly gave judgment for the defendant company.

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[1] Registrar-General's Estimates of the Population of England and Wales: Populations of each Administrative Area at June 30, 1951. H.M. Stationery Office. 6d.

In England Now

A Running Commentary by Peripatetic Correspondents

A PHYSIOLOGIST of our acquaintance went through a frightening experience the other night. Returning tired but happy from his daily battle with recalcitrant electrons, he found his wife lying flat on her back in the middle of the living-room floor with one hand on the upper reaches of her sternum and the other on the region of her pylorus. She was hyperventilating strongly, and there was an admiring audience of children on the sofa. The weather was fine and cloudless, the barometer was high, and the hour was 6.15.

Though a physiologist, our acquaintance has not forgotten how to take a case-history, and he shortly elicited the fact that his wife was Breathing, having found out at 5.59 from her guiding women's magazine that Breathing was Life and that Tenseness was caused by Shallow Ventilation. It also transpired that his wife had been Breathing Wrongly and Inefficiently all her life, and that he, a specialist in human function, had never observed this elementary fact; the least he could have done was to have taken the trouble to ascertain whether or not his dependants were Breathing Properly. It was no thanks to him that his children were not yet Tense and that his wife had not contracted Tuberculosis.

Our acquaintance could make but little of the situation, and was therefore glad when, after a few more minutes during which the curtains billowed and swayed in the violent air currents and the shade of the hanging light vibrated dangerously, a knock was heard on the door. Conscious of her social obligations, his wife immediately scrambled up, and, having by this time a serious alkalæmia, fell flat on her nose, scattering the audience on the sofa and disrupting a large pink balloon, the property of the smallest spectator.

Our acquaintance had his supper without further comment.

* * *

Long train journeys are tedious. Small boys can be tedious. Our train journey with our small boy threatened to be most tedious. He was filling in his latency period with what Freud laughingly refers to as *Zugnummerkrankheit*: he had noted the number of our engine before we had started, but once we were in motion he found further material too swift in transit to be recorded without cheating, and a steady flow of questions began.

Why is the smoke from the engine white when the coal is black? Who puts the pictures in the railway carriages? Is the engine-driver sitting down or standing up? My stumbling answers earned his vociferous scepticism and our fellow passengers' silent contempt. I counter-attacked by asking how many people he supposed were on the train. There was a minute of silence, more tense than restful, before he gave his considered opinion that he did not know. Did I know? We were back where we began. We contemplated our ignorance together for a while; then he suggested, "Shall I go and count them?" My wife hastily nodded and he left us to the disapproving stares of the rest of the carriage. Their thoughts were obvious: what callous parents—poor little mite—fall off the train, sure as fate. Feebly my wife and I telepathised back: no he won't—fell out of a train (stationary) last year—learned his lesson.

Presently he returned, triumphant. "145" he announced. "Fine!" we said. He glanced thoughtfully round the compartment. "Do we count these as well?" he asked. "These" registered outraged dignity and I hurriedly said that we mustn't hurt anybody's feelings. "148 and us as well!" he concluded. "What shall we do now?" "Count the ladies," I suggested. Having established that his mother was eligible, he left us once more in peace. "52" he announced on his return. "What's next?" Hopefully I recommended that he count the men and cheerfully he set off once more. But as my wife and I began to point out to each other the gap in his logic, he reappeared in the doorway and glared at us accusingly. "If you take the ladies away from everybody" he said, "the men are left behind." Feeling guilty, we tried to look surprised. I made a fighting recovery, offering him pen and paper with which to work things out. He wouldn't hear of it. "You do it in your head," he said, "It's quicker." Such faith was unnerving and I pretended to have forgotten the original figures. Our fellow passengers, on the point of reminding me and probably, in all their smugness, providing the answer as well, recoiled before my greater wisdom when I suggested that he had better go and count them all again. He considered this briefly. "It's a silly game," he decided. "You didn't tell me why the smoke was white."

Long train journeys are tedious. Small boys . . .

* * *

It is a new and exhilarating experience to sit in on a session of a Conference of Heads of Medical Departments from twenty-five territories, under the Chief Medical Officer of the Colonial Service, and to hear first-hand opinions from the ends of the earth. Development and Welfare: the Motherland must look to her laurels. How well it is understood at the limits of Empire that health campaigns in isolation have little value; they must be integrated with all the related activities—with population problems, with water-supplies, with engineering, with agriculture and indigenous food-supplies, and above all, with education.

It was exciting to hear an experience related by East Africa echoed by one from, say, the Windward Islands; a difficulty described in Malaya which proved no problem for British Guiana; or unanimous opinions from Southern Rhodesia and Trinidad.

There was a general feeling that the erection of fine hospital buildings could be disproportionately overdone—that preventive measures are the essential in the centres of population and education in the rural areas. What use to erect a hundred thousand privies if you haven't taught the people how and why they should be used? How do you set about education? Why, through the Midwifery and Child Welfare Clinics that flourish almost as familiarly as in the L.C.C. area.

But you must be careful! The comic spirit is abroad. When a highly coloured poster, designed to encourage dental hygiene in one Territory, displays an open mouth with a superabundance of dazzling teeth and a toothbrush dangling before it, beware how you transfer it! In another Territory, the local interpretation is that it must be an advertisement for a new kind of bait wherewith to catch the sharks that infest their coastal waters!

* * *

I wonder how many of my peripatetic colleagues, especially those whole-time professors who now tour the few remaining Colonies inspecting prospective medical schools, realise that if they fly more than 15,000 miles in the course of one year they are automatically depriving their dependants of all benefits under their F.S.S.U. scheme should they be involved in a fatal accident? Apparently all the leading life-assurance societies have a clause in their policies which imposes this limit on flying unless an extra premium is paid. Presumably there is a sound actuarial basis for such a restriction, but it seems rather hard lines on Sir Miles Thomas, in his valiant efforts to make B.O.A.C. a paying proposition, that the life-assurance companies consider a return flight to Singapore to carry a greater risk to life than an unlimited number of miles covered by road, rail, or sea. Personally, I would much rather fly a thousand miles with B.O.A.C. (or B.E.A.) than travel one mile in a Chicago taxi.

* * *

Comment on the N.H.S. has frequently been both pithy and pungent, but the following quotation from a North of England newspaper is surely the briefest and fiercest so far:

> "The conference will discuss malaria, tuberculosis, leprosy, cancer and the National Health Service."

No doubt in an attempt to identify the causative parasite.

* * *

". . . but surely, Brain is even more abStrauss?"

Letters to the Editor

BUTAZOLIDINE

SIR,—Now that this substance is generally available we feel it only right to point out that clinical trials in this country have been only on a small scale; and though we have ourselves seen no complications apart from reactions to injection, in the United States peripheral œdema, purpura, skin rashes, and gastro-intestinal upsets have been reported, almost always with the oral preparation and usually after several weeks or months of continuous therapy. These reactions have never to date been serious and have rapidly disappeared on stopping therapy. Kuzell et al.[1] have recently reported four cases where there was activation of pre-existing peptic ulcers; they advise the concurrent use of alkalis and suggest that more than usual caution should be observed in cardiac cases because of the risk of promoting sodium retention and œdema. Although the drug is a member of the pyrazole series no cases of leucopenia have yet been reported.

Until more is known of the drug's uses and toxic effects three general rules should be observed:

1. Careful watch should be kept on blood-counts, including platelet estimations.
2. Especial care is indicated in patients with dyspepsia, alkalis being given concurrently.
3. Sodium restriction is advisable in cardiac patients.

It would be a pity if what promises to be a useful drug should earn a bad reputation early through misuse.

Westminster Hospital,
London, S.W.1.

F. DUDLEY HART.
A. M. JOHNSON.

THE ADRENOGENITAL SYNDROME

SIR,—In your leading article of June 28 you comment on the use of cortisone in the treatment of the adrenogenital syndrome by Wilkins et al., and by Dr. Bishop and his colleagues whose report is printed in the same issue.

It may be of interest to call attention to other studies on the same subject. Thorn[2] has studied the effect of cortisone in one case of virilism. Bartter and his co-workers[3] described the same effect in three cases: Bastenie, Verbiest, et al.[4] in September, 1951, reported on the effect of cortisone in two cases of adrenogenital syndrome; and Laroche et al.[5] studied one case.

The study of Bastenie and his co-workers included chromatographic analysis of the urinary 17-ketosteroid output by Dingemanse's method. Our work has now been extended to four cases (one 14-year-old patient with pseudohermaphroditism, two adults with hirsutism and other masculine features, and one adult with simple hirsutism). In three of the four cases cortisone treatment induced temporary regression of the signs of masculinisation. In each case the various adrenal fractions of the 17-ketosteroid partition chromatogram showed a pronounced drop, affecting principally the 11-hydroxy-17-ketosteroids, which comprise fractions VI and VII in Dingemanse's fractionation and are regarded as katabolites of the glucocorticoids. The excretion of dehydroisoandrosterone (fraction III), generally accepted as a derivative of adrenal androgenic compound, was also depressed but to a smaller extent.

The depressive action of cortisone in cortical adrenal hyperfunction seems to deserve further investigation.

Clinique Médicale, Hôpital Brugmann,
Université Libre de Bruxelles.

PAUL BASTENIE.

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[1] Kuzell, W. C., Schaffarzick, R. W., Brown, B., Mankle, E. A. *J. Amer. med. Ass.* 1952, 149, 729.

[2] Thorn, G. W. *In* Adrenal Cortex: Transactions of the Second Conference, Nov. 16, 1950. New York, 1951.

[3] Bartter, F. C., Albright, F., Forbes, A. P., Leaf, A., Dempsey, E., Carroll, E. *J. clin. Invest.* 1951, 30, 237.

[4] Bastenie, P., Verbiest, M., Flamand, C., De Lannoy, C. Congrès français de Médecine, 25th session, Brussels, 1951; p. 144.

[5] Laroche, G., Chevmol, J., Tremolieres, J., Pellet, M., Corteel, A. *Ann. Endocrinol.* 1952, 18, 58.

DEGENERATION OF THE SPINAL CORD ASSOCIATED WITH CERVICAL SPONDYLOSIS

SIR,—The paper by Dr. Bedford and his colleagues in your issue of July 12 throws new light on the mechanism of the neurological lesions in cervical spondylosis, and the description of a similar case may be of interest.

A single woman, aged 47, who had been suffering from rheumatoid arthritis since the age of 25, had become completely crippled despite several courses of treatment at various hospitals. She had had primary atypical pneumonia in 1949 and infective hepatitis in 1950; she had also suffered from recurrent conjunctivitis and iritis over the past few years.

On admission she was unable to do anything for herself; almost every joint in her body, including the intervertebral joints, was affected and the pain was barely kept under control by 8–10 tab. codein co. *B.P.* daily and amidone at night.

About six weeks after admission she noticed numbness of her left leg, and complete loss of sensation to pain and temperature was found on the left side of her body below the 7th cervical dermatome. There was no evidence of a pyramidal lesion or of muscle wasting. Lumbar puncture revealed clear cerebrospinal fluid not under increased pressure and normal in all respects. Radiography of the cervical spine at this time showed gross changes of cervical spondylosis with almost complete ossification of the disc between the 4th and 5th cervical vertebræ.

Her condition did not change significantly during the remainder of her stay in hospital, except for the development of a pressure-sore on the left buttock which responded slowly to treatment. She was finally transferred to a home for chronic invalids.

The unusual feature of this case is that the lesion seemed to be confined to the right lateral spinothalamic tract. This distribution corresponds neither to that of a vascular lesion nor to that described by Brain et al.[1] as due to disc protrusion. In the case described by Dr. Bedford and his colleagues, one of the lesions was demyelination spreading into the lateral column of the cord from a thickened denticulate ligament. The position of the lateral spinothalamic tract on the lateral aspect of the cord renders it liable to damage by traction from a thickened denticulate ligament, and this may have occurred in this case.

I would like to thank Dr. F. Dudley Hart for permission to report this case.

St. Stephen's Hospital,
London, S.W.10.

PETER R. FLEMING.

BENEMID IN THE TREATMENT OF STREPTOCOCCAL ENDOCARDITIS

SIR,—The report by Dr. Baker and Dr. Pilkington in your issue of July 5 on the use of 'Benemid' (*p*-[di-*n*-propylsulphamyl] benzoic acid) in the treatment of streptococcal endocarditis prompts us to write briefly of a similar case, in fact the one to which Dr. Douthwaite has already referred (July 12).

A machine operator, 35 years of age, had had rheumatic fever at the age of 4. His schooling was subsequently interrupted. Nevertheless, in 1939 he enlisted in the Royal Artillery and saw 6 years' active service.

In August, 1950, he first developed subacute bacterial endocarditis, *Streptococcus viridans* being found in blood-cultures on three occasions. He was treated with 70 mega-units of penicillin over a period of 72 days and responded satisfactorily. For 16 months, despite evidence of mitral valvular disease, he remained quite fit and continued normally with his work.

On March 7, 1952, he had a sudden rigor. Thereafter he felt generally unwell, sweated profusely, and complained of backache and aching in all his muscles. On admission to Guy's Hospital next day he was pale and sweating; the temperature was 99·6°F, the pulse-rate 104 per min., and the respirations 22 per min. The only other abnormalities on examination were petechial hæmorrhages in the buccal mucosa and a short pre-systolic and loud blowing systolic murmur at the apex of the heart.

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[1] Brain, W. R., Northfield, N., Wilkinson, M. *Brain*, 1952, 75, 187.

Investigation showed a white-blood-cell count of 8000 per c.mm., an erythrocyte-sedimentation rate of 6 mm. in the first hour (Westergren), and normal urine. Repeated blood-cultures were negative. Nevertheless, the clinical diagnosis was subacute bacterial endocarditis.

With treatment by saline penicillin, even in doses of 750,000 units intramuscularly every 4 hours, the intermittent pyrexia up to 99·6°F remained unaltered. Chloramphenicol 1 g. 6-hourly and aureomycin 1 g. 6-hourly were thereafter administered as well, but the patient's condition showed no change; these two drugs were accordingly withdrawn. With the penicillin still given in a dosage of 750,000 units 4-hourly the blood-levels were estimated, with the following results:

Relation to administration of penicillin 750,000 units	*Blood-penicillin level (units per ml.)*
Immediately before .. .. .. less than	1/32
1 hour after	8
2 hours after	8
3 hours after	2

Benemid was thereupon given as well, in doses of 0·5 g. 6-hourly by mouth. Repeated estimations then showed:

Relation to administration of penicillin 750,000 units	*Blood-penicillin level (units per ml.)*
Immediately before	1
1 hour after	19
2 hours after	4–8
3 hours after	2

Notably then the patient's temperature fell to normal within 24 hours, and he remained apyrexial thereafter. His general condition improved, and the therapy was maintained thus for 43 days. During this time he received dental treatment, including the extraction of two carious teeth, all without complication. At no time was there any evidence of renal damage as evidenced by examination of the urine or estimation of the blood-urea.

When discharged on May 20, the patient seemed quite fit. His unchanged cardiac signs occasioned him no disability; he has returned to work, and now after nine weeks he seems as well as ever.

We thank Dr. A. H. Douthwaite, under whose care the patient was admitted, for permission to publish these further details, and Messrs. Sharpe & Dohme Inc., for a supply of the drug.

Departments of Clinical Pathology
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Guy's Hospital Medical School,
London, S.E.1.

D. F. V. Brunsdon
Roy Goulding.

STABILITY OF NORADRENALINE

Sir,—We have found that the optimum conditions for stability and storage of solutions of noradrenaline (1 in 1000 of base) when enclosed in well-filled ampoules are: (1) an initial pH of about 3·6, and (2) the presence of a stabiliser such as sodium metabisulphite. When such solutions are autoclaved, the loss of activity is negligible. A solution of noradrenaline bitartrate with metabisulphite ('Levophed,' Bayer Products Ltd.) satisfies these conditions.

Solutions of noradrenaline are now being extensively used for the treatment of acute hypotension,[1] and it is important therefore to know if dilutions (1–10 µg. per ml.) are stable when stored under conditions simulating those in the operating-theatre. Dilutions of levophed were therefore made in normal saline with and without ascorbic acid (10 µg. per ml.), in 5% dextrose solution in distilled water, in plasma, and in whole blood. These dilutions were maintained at room-temperature for periods up to 12 hours and then assayed on the blood-pressure of a spinal cat, using a fresh dilution as the standard solution. Other dilutions were taken to pH 7·9 before storage for 6 hours.

RELATIVE ACTIVITY OF DILUTIONS OF NORADRENALINE
(Fresh dilution = 100%)

Diluent	Hours of storage			
	6	9	12	6 (at pH 7·9)
Saline	83	78	76	80
Saline + vitamin C ..	98	95	90	95
Dextrose solution ..	98	98	90	90
Plasma	98	95	90	90
Blood	88	80	80	80

The results shown in the accompanying table suggest that dilutions should be made in dextrose solution, plasma, or saline containing ascorbic acid; for significant losses were recorded when whole blood and saline were used as diluents. Further work showed that dilutions in an isotonic mixture of 4% dextrose and 0·18% sodium chloride in distilled water were as stable as those in 5% dextrose in distilled water.

Department of Pharmacology and Therapeutics,
University of St. Andrews Medical School,
Dundee.

G. B. West.

CONTROLLED HYPOTENSION

Sir,—Venostasis by means of tourniquets to the four limbs of an anæsthetised patient may be a useful method of producing hypotension. I tried this method some years ago in a conscious subject and was not successful, but recently in an anæsthetised patient (healthy male, aged 33) the pressure dropped from 130 mm. Hg systolic to 70 mm., and rose again rapidly when the tourniquets were released.

Birkenshaw,
near Bradford.

C. G. Blakeley.

SORE THROAT AND RHEUMATIC FEVER

Sir,—May I, once again, plunge *in medias res* on the subject of tonsillectomy? I do so lest last week's letter of Dr. Alice Stewart and Mr. David Hewitt may cause the demon pantonsillectomy again to raise its head. I did not have much experience of acute rheumatism, but that may have enabled one, who gave almost daily thought for nearly forty years to the reasons for refraining from tonsillectomy, to see the problem more clearly.

Near the end of my career, I became attached to a large hospital with a big rheumatic clinic, and on the first day I was asked to go and see a case. The child had a severe attack of very acute rheumatism and there was no question of doing anything to the throat at the time. I began therefore to discuss the problem that was before us as to tonsillectomy and acute rheumatism. But the physician in charge wanted none of that; he wanted the tonsils out, and all he was asking me was "When?" I replied that it was clear that it could not be done for a long time, and when that time was approaching I would discuss with him whether it should be done. I was never asked to see that case again or any other case of rheumatism in that hospital. A "general" surgeon came in and removed the tonsils at the request of the physician when he thought it was time. But though I was debarred from discussing clinical medicine in the wards in *individual* cases, I was able to talk amicably with the physician at the luncheon table, and when I knew him well enough I got him to admit that if his views were carried to their logical conclusion it would be well for the whole population to be tonsillectomised by the age of one. In that way only could acute rheumatism be stamped out, and this disease was *the* foremost problem in national health.

Leaving alone the question of the minimum numbers that should be worked out in percentages before any conclusion is drawn from them, with tonsillectomy it is necessary to know not only that the tonsils have been removed, but into whose hands the patient had got before the operation was done. Was it the rheumatico-pantonsillectomist, or just the enthusiast for the focus-of-sepsis hypothesis? Was it at a station in which the majority or nearly 50% were set aside for operation, or in a clinic in which every aspect of the child's health was carefully inquired into, and a minimum of at least a quarter of an hour was given to the patient before the parent was advised to decide that the operation should be done. The value that can be attached to any statistics

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1. See Swan, H. J. C. *Brit. med. J.* 1952, i, 1003.

very largely depends upon which of these sources they came from.

But there is another thing. Clincial medicine is an art, and must ever remain so; but science must be applied to it, and one way of applying it is by checking the art by the laboratory whenever it is possible to do so. And with tonsillectomy this is possible by sending every tonsil that is removed to the laboratory for investigation bacteriologically. The decision to remove tonsils is an assessment of a bacteriological probability; and I do not think that any statistics today should be put forward unless they include the organisms found in the tonsils after removal.

The first paper I ever wrote was read at the Medical Society in March, 1914, and was entitled Tonsils and Adenoids in Children: a Plan for Fewer Operations. Since then the tonsillectomy-rate, with a few local remissions, has steadily gone up until it reached, in at least one area, 50% of the population by the age of 5. In the last five years, I am told, it has been receding. It would be a pity if a letter from a scientific institute, which carries with the profession and with parents so much more weight than the experience of clinicians, should result in this operation-rate starting to climb again; especially now that it seems that acute rheumatism may be stamped out without operation.

Lingfield, Surrey. T. B. LAYTON.

CALCIFEROL IN PULMONARY TUBERCULOSIS

SIR,—Dr. Jackson (June 7) states: "a controlled trial of calciferol given with streptomycin and P.A.S. has been made." It appears that his cases were treated for six weeks, and then assessed radiologically. The only permissible conclusion (and one may question the value of conclusions drawn at the end of six weeks' therapy in pulmonary tuberculosis) should therefore be that six weeks' combined treatment of unselected cases gave results no different from six weeks' chemotherapy alone. I am not surprised. The cases which we described[1] had been treated for 4–6 months and observed for 12–18 months. It is true that Dr. Jackson says that in a few of the 'Sterogyl' group, chemotherapy was continued for a further 6 weeks, but this presumably applies to the streptomycin-P.A.S., and not to the calciferol. Having taken the trouble to investigate the treatment, it seems a pity that he did not continue for a longer period, which a consideration of the results in lupus vulgaris would indicate to be necessary. He found no contra-indication to the use of calciferol in this way; why then were conclusions drawn after so short a time?

It is worth while emphasising that calciferol is one of the few chemically defined substances known to have an effect on the host reactions in tuberculous lesions. It is difficult to obtain direct evidence of tissue reaction in pulmonary disease. However, in some later cases treated at Paddington Hospital in which 600,000 units sterogyl was injected twice weekly for a month, followed by one injection a week for a further month, an interesting change in the character of the sputum was observed. After the second or third injection, the sputum became uniformly rusty pink. This persisted for 2 or 3 days, then disappeared, to reappear following the next injection. This succession of events was seen for 2 or 3 weeks. It is strikingly similar to the stage of congestion observed in lupus during the early stages of calciferol treatment, and is additional evidence that the reaction in pulmonary disease is of the same kind as that seen in cutaneous tuberculosis. This is the essential point of the case I have presented. The manner in which this phenomenon may be best utilised in therapy still requires investigation.

New-Delhi, India. J. FIELDING.

SUCCINYLCHOLINE

SIR,—We wish to thank Dr. Bourne and his colleagues for their excellent contribution, published in your issue of June 21. Dr. Franks (June 28) says that "there appears to be no indication beforehand of the amount of muscular activity to be expected with the initial dose of the drug." Some of his muscular patients showed only minor muscle-fibrillation, whereas other similar patients had rather severe convulsions. Our experimental and clinical observations over the past two years may be of interest here.

Experiments in animals (cats and rabbits) and in volunteer medical students have shown uniformly that the degree of muscle-fibrillation (twitch) depends primarily on the rate of the injection. In man injection of 20–30 mg. succinylcholine in less than 10 sec. invariably gave rise to a "twitch-reaction" of varying degree. In most cases the same dose administered in the course of 10–30 sec. resulted in less muscle-fibrillation, and in about 25% of the cases no "twitch" was seen. When the same dose was infused (mechanically) in the course of 30–60 sec., almost no muscle-fibrillation resulted.

The "twitch-reaction" was recorded by means of needle electrodes in muscles of the limbs. The potentials were studied on an oscillograph. Muscular and respiratory paralyses were observed in these experiments and measured by means of ergographs and spirometer (Krogh). The muscular contractions were produced by electric stimulation of different motor nerves. In most cases the paralysis following rapid injection was complete and of short duration (1–2 min.). After slow infusion the paralysis was less pronounced, but of longer duration (2–3 min.).

Two years' clinical experience, including patients undergoing general surgery and electric convulsive therapy (about 2000 administrations), has confirmed these experimental results.

Municipal Hospital, Copenhagen. HENNING POULSEN.
G.E.A. Ltd., Copenhagen. WILLY HOUGS.

SIR,—Dr. M. L. Mackay describes in his letter of July 19 respiratory arrest in a woman weighing 12 stone, which lasted six and a half hours after injection of 50 mg. of succinylcholine. He finds this difficult to explain on the basis suggested by Evans et al.[1]—i.e., that succinylcholine sensitivity is caused by a low serum-cholinesterase level.

It may be pointed out that Bourne et al.[2] found a significant difference in the serum-cholinesterase level when they compared 6 patients recovering normally from succinylcholine and 6 whose response lasted beyond eight minutes. Day[3] found that a patient weighing 10 stones responded to a dose of 50 mg. with seven and a half minutes apnœa; 20 mg. produced a reaction lasting three minutes; and after six subsequent injections of 40 mg., there was a reaction lasting 6 minutes.

Dr. Mackay himself suggests that the injection of neostigmine must have played a part in the prolonged apnœa seen in his case, and, in fact, considering his experience from the enzyme-chemistry point of view, one must conclude that injection of neostigmine after 35 minutes must have been the cause of the very prolonged apnœa. If the short action of succinylcholine depends on its rapid destruction by serum-cholinesterase, the injection of a powerful inhibitor of this enzyme—in what was presumably a patient with a very low serum-cholinesterase level to begin with—would delay recovery almost indefinitely.

There may well be other mechanisms of succinylcholine removal: in the absence of the enzymic defence mecha-

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1. Fielding, J., Maloney, J. J. *Lancet*, 1951, ii, 614.

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1. Evans, F. T., Gray, P. S .W., Lehmann, H., Silk, E. *Lancet*, 1952, i, 1229.
2. Bourne, J. G., Collier, H. O. J., Somers, G. F. *Ibid*, p. 1225.
3. Day, B. L. *Brit. med. J.* 1952, ii, 162.

nism, excretion by the kidneys may play a part; but there seems to be no reason at present to consider anything other than serum-cholinesterase activity.

To produce dramatic delay in recovery, the enzyme level must obviously be very low, and Callaway et al.[4] have shown that there is little chance of encountering such cases in an average sample of the population. Bourne et al. found only 5 among 546 patients in whom the reaction lasted longer than eight minutes, and Evans et al. encountered the first case of prolonged response only after they had employed succinylcholine more than 400 times. If patients likely to have a low serum-cholinesterase level (those with liver-disease, anæmia, malnutrition, and possible polyphosphate poisoning) are excluded from succinylcholine treatment, and if it is realised that neostigmine is contra-indicated after this drug has been given, the use of succinylcholine should be quite safe. It is obvious that no drug producing apnœa should ever be given unless facilities for artificial respiration are available.

Once it is quite clear in the minds of anæsthetists that prolonged response to succinylcholine is due to delay in destruction of the drug by serum cholinesterase, *they will stop giving a cholinesterase-inhibitor*, such as neostigmine. The obvious treatment, if any, will be to increase rather than lower the enzyme activity; transfusion of fresh blood or plasma should serve this purpose, and it is noteworthy that even blood stored for several weeks has in its citrated and diluted plasma esterase levels varying from 30 to 50 units.

St. Bartholomew's Hospital,
London, E.C.1.

H. LEHMANN.

SIR,—Following recent articles on the use of ultra-short-acting relaxants, an account of a small series in which repeated doses of succinylcholine chloride ('Scoline') were given may be of interest.

On theoretical grounds it seemed that appendicectomy would be the operation of choice for the exhibition of this agent. It should be possible to maintain light anæsthesia throughout, while providing relaxation when required—that is, until the delivery of the appendix, returning the gut to the abdomen, and closing the peritoneum. Should difficulties be encountered, the relaxation could be prolonged indefinitely by giving repeated doses.

Of 30 cases of appendicectomy in the series, 25 were emergencies. The 11 "difficult" cases included 3 in which paramedian incisions were made; the longest operation lasted fifty minutes, and the shortest ten; the age-limits were 12–58.

Premedication was usually morphine gr. $^{1}/_{6}$ and atropine gr. $^{1}/_{100}$. The *induction* was by *thiopentone*, usually 0·5 g. Maintenance was by nitrous oxide and oxygen from a Boyle's machine delivered via a Coxeter Mushin apparatus. 'Vinesthene' was placed in the chloroform bottle, and the lever left just above the minimum position. A flow of 5 litres per minute of nitrous oxide and 1 litre of oxygen was attempted,[5] but usually it was necessary to reduce the proportion of nitrous oxide to avoid hypoxia. Succinylcholine was given in 5% solution from a 10 ml. syringe strapped to the arm. Assisted or controlled respiration was given when necessary.

5 further patients (i.e., 5 out of 35) were adequately relaxed *without succinylcholine*. Of 4 *cases in which* vinesthene was not given, only 1 was satisfactory.

Recovery was rapid, usually within fifteen minutes. One patient's recovery was delayed an hour. This patient was a fat chronic bronchitic who had an exacerbation lasting four days. One other chronic bronchitic had a temperature of 99·2 F for one day. There was no other postoperative morbidity, apart from that due to preoperative infection of the pelvis.

The technique has so far fully confirmed the theoretical expectations.

The initial dose is 10 mg., and from the response to this the size of subsequent doses is judged. In the "difficult" cases, where prolonged relaxation is required, the optimum relaxing dose and its duration is determined, usually by the second or third dose; and this is then repeated as long as relaxation is required. Each dose is given thirty seconds before the previous dose will wear off. This timing is most important, as the sudden return of abdominal tone may cause the rupture of a friable viscus. The "simple" case usually requires one or two doses before the appendix is delivered, and one for closing. Sometimes it requires one dose only or none.

The usual relaxing dose is 5–15 mg., which causes apnœa or inadequate, shallow respiration. Commonly adequate spontaneous respiration returns before abdominal tone; sometimes respiration remains adequate throughout. Relaxation starts twenty to thirty seconds after injection, and lasts two to four minutes. During a given operation the same dose always has the same effect, plus or minus a few seconds, thus permitting the accurate timing of repeated doses. No additive effects, and no case of prolonged action, have yet occurred.

The doses of succinylcholine suggested are smaller than those previously recommended. This is probably because an attempt has been made in each case to give a dose which provides relaxation without rendering respiration inadequate, while the nitrous oxide and vinesthene anæsthesia will also reduce the dose required. Whether it is possible to retain spontaneous respiration still seems uncertain. Swedish workers, using a drip, claim that this is possible, while British workers doubt it.[6] My own small experience indicates that with the technique described it is possible at least in some cases. It would seem probable that the level of the accompanying anæsthesia, and the degree of respiratory depression that it causes, is the deciding factor.

Whatever the place of succinylcholine in more extensive operations, I suggest that for appendicectomy it is a very useful agent. The advantages are: a light level of anæsthesia accompanied by profound relaxation when required; absence of toxic effects; complete control; and rapid recovery.

County Hospital,
Whiston, near Prescot,
Lancashire.

HAROLD T. KAY
Anæsthetic Registrar.

AS A PATIENT SEES IT

SIR,—Your annotation of July 12 tempts me to write of my all too present experience as a patient.

The untiring kindness of the nurses is beyond praise; but surely the most terrible thing to bear is the deadly monotony of hospital routine. On many occasions I have tried to break through this, but with no success. I give two examples.

Quite early on in my stay in hospital I asked whether the Bible, prayerbook (shortened version), and hymnbook (A and M) which were beside my bed could be moved to the far side of the books (including a Bible) which I had brought in with me. A very serious-faced probationer replied: "It is a rule of the hospital that the Bible, prayerbook, and hymnbook must be next the patient."

The second attempt was no more successful. After many weeks in the hospital I said, rather tentatively, to the nurse who was making my bed: "How would you react were I to ask if, just for a change, I could have my counterpane the other way round?" "Oh," she replied without a moment's hesitation, "we should call you a Socialist."

A PATIENT.

OSTEOPATHY AND ORTHODOXY

SIR,—I have no sympathy for your peripatetic correspondent (July 5) in his chagrin at learning that an osteopath had employed a form of orthodox treatment. If he and some of his colleagues were as quick to appreciate the value of osteopathic treatment, in appropriate cases,

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4. Callaway, S., Davies, D. R., Rutland, J. P. *Ibid*, 1951, ii, 812.
5. Dawkins, C. J. M. *Anæsthesia*, 1950, 5, 81.
6. Bourne, J. G., Collier, H. O. J., Somers, G. F. *Lancet*, 1952, i, 1225. Richards, H., Youngman, H. R. *Brit. med. J.* 1952, i, 1334.

as osteopaths are quick to appreciate good orthodox methods, also when appropriate, we should all benefit—including the patient.

Osteopathic Publishing Company Ltd.,
4, New Zealand Avenue,
London, E.C.1.
A. WILLIAM ELLIS.

PLEA FOR PSYCHOTHERAPY

SIR,—In recent years there has been a spectacular advance in the physical treatment of psychiatric illness. Electric convulsive therapy alone has revolutionised the prognosis of involutional depression. In schizophrenia the chances of a remission are sufficiently good to justify treatment by insulin coma. Leucotomy has undoubtedly made bearable and even useful the lives of patients who have hitherto been a misery to themselves and a burden to their friends. Various abreactive techniques have made it possible to release deeply repressed, painful complexes and thereby, in some cases, have produced a dramatic relief of symptoms and in others have shortened analytic procedures.

On the other hand, the glowing hopes aroused by the pioneer work of Freud for the solution of all psychiatric problems by psycho-analysis have faded after many disappointments, and the pendulum has undoubtedly swung away from treatment along mental lines to treatment by physical methods.

The problem of body-mind relationship has so far been insoluble; but one can perhaps claim that there is no proof that mind has not an autonomy of its own, and that there is a case for attacking some problems along mental lines. In the past psychotherapy has had, as well as many failures, considerable successes. These must depend firstly on correct diagnosis, and secondly on a flexible attitude to the methods of attack to be used in each case. At the present time there would seem to be a danger that in the altogether laudable search for short-cut methods, preferably physical, the value of psychotherapy may be forgotten. Even where physical methods or abreactive techniques relieve symptoms in a dramatic way, relief may not be permanent without a change of mental attitude; and in other cases nothing but a patient understanding and unravelling of the patient's psychological problems can give the help which is required.

London, W.1. MARION GREAVES.

TREATMENT OF ANURIA

SIR,—In referring (July 5) to my short contribution to the discussion on the Treatment of Anuria at the Royal Society of Medicine on June 26, you unfortunately misquoted my remarks on its therapeusis.

I had attempted to show that embryologically the kidney was a "neurile" organ; that the comparative physiology of the salmon and of the eel afforded evidence that change of environment produced prolonged "anuria" from which renal recovery was complete; that controlled experiments had evoked acute tubular necrosis by nervous pathways; that there was considerable pathological evidence to show that cortical renal ischæmia and medullary congestion was the post-mortem change in such states, and that all this could be explained by the Trueta mechanism of whose occurrence under physiological and experimental pathological circumstances I brought strong proof. Especially I emphasised Bykov's conditioned-reflex experiments where antidiuresis could be provoked in animals with diabetes insipidus, indicating the paramount importance of the glomerulus in urine production.

My theme was that anuria was due to the "shunt," and was reversible even at late stages by conduction anæsthesia; also that the disturbance the "shunt" produced in the electrolyte and water environment itself offered a stimulus to renal shut-down. Modern therapeutics were content to deal with the latter alone, whereas the clinical results of Hingson's ('Pavex') caudal technique supported the theory of spasm and recovery from it even in late stages. Since then the remarkable results of Dr. Chatterjee[1] have given the strongest evidence of the correctness of my view.

London, W.1. JOHN SOPHIAN.

THE NORMAL TEMPERATURE

SIR,—What is the normal human temperature? It has been long accepted as 98·4°–98·6°F taken by clinical thermometer in the mouth. For myself, I no longer accept this as correct. I have not kept records, but I long ago came to the conclusion that for most people the normal sublingual temperature is rarely higher than 97·6°F and not infrequently is less by up to a degree and a half. There are, I think, slight environmental variations—due to atmospheric conditions, the processes of digestion, &c.—but these variations are by no means considerable.

I base my contention on observation over many years. In fact I have come to regard a temperature of over 97·6°F in an ambulant patient as a raised temperature requiring further investigation; more often than not I have been justified, although the lesion may have proved to be no worse than a mild gingivitis or a rhinitis.

London, W.C.2. G. RALSTON.

PLACENTAL CONTENT OF A.C.T.H.

SIR,—Dr. Böe and Mr. Salvesen (June 14) describe data which show that adrenocorticotrophic hormone is not contained in the human placenta. These workers have used physiological saline with 0·25% acetic acid to prepare their extracts.

In this laboratory we have attempted to confirm the work of Tarantino,[2] Jailer,[3] and Opsahl,[4] all of whom claim to have demonstrated the presence of A.C.T.H. in the placenta. We have utilised the glacial-acetic-acid extraction method of Payne et al.,[5] followed by oxycellulose adsorption.[6] 20 g. lyophilised tissue (full-term placenta) yielded 40 mg. of solids in the oxycellulose eluate. The material isolated by these procedures was assayed by the ascorbic-acid depletion method of Sayers et al. and was found to contain approximately 0·01 international units (I.U.) of corticotrophin per mg.

Thus placental tissue may be calculated to contain 4–5 I.U. of A.C.T.H. activity per kg. fresh tissue, which represents a much larger concentration of corticotrophic activity than may be ascribed to the blood present in the tissue, inasmuch as Sydnor and Sayers[7] have found the concentration of normal blood to be less than 0·01 I.U. per litre, whereas Granirer[8] has shown that postpartum plasma contains about 1 I.U. per litre.

Research Department,
Princeton Laboratories Inc.
Princeton, New Jersey, U.S.A.
HERMAN COHEN
WILLIAM KLEINBERG.

INFORMATION SOUGHT ON PORPHYRIA CASES

SIR,—I and my colleagues at University College Hospital are making a chemical study of urines from patients with acute porphyria. Our work has come to the stage when we need large supplies of material. I would be very grateful if anyone having knowledge of a case of acute porphyria would contact me as soon as possible.

Department of Chemical Pathology,
University College Hospital Medical School,
London, W.C.1.
C. RIMINGTON.

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1. Chatterjee, H. N. *Lancet*, July 12, 1952, p. 90.
2. Tarantino, C. *Fol. endocrinol. Jap.* 1951, 4, 197.
3. Jailer, J. W., Knowlton, A. I. *J. clin. Invest.* 1950, 29, 1430.
4. Opsahl, J. C. *Yale J. Biol. Med.* 1951, 24, 199.
5. Payne, R. W., Raben, M. S., Astwood, E. B. *J. biol. Chem.* 1950, 187, 719.
6. Astwood, E. B., Raben, M. S., Payne, R. W. *J. Amer. chem. Soc.* 1951, 73, 2969.
7. Sydnor, A., Sayers, G. Endocrine Society Meeting Abstracts, 1952, p. 25.
8. Granirer, L. W. *N.Y. St. J. Med.* 1951, 95, 2767.

Obituary

HUGH WILLIAM BELL CAIRNS

K.B.E., M.A., D.M. Oxfd, M.B. Adelaide, F.R.C.S., Hon. F.R.A.C.S.

ALIKE as a surgeon, a leader, and a friend, Sir Hugh Cairns will be gratefully remembered. His death at the age of 56 must sadden all who appreciated his skill, his vision, his resolution, and his devotion to medicine. But he had done much of what he set out to do; and through his mastery of neurological technique and team-work he had left a deep impression on those he taught. His methodical approach, his self-discipline, and his helpfulness will be continued through them.

The only son of a Scottish father and an Australian mother, he was born and brought up in Adelaide, South Australia, where he did well at the High School and the University. During the first world war he served in the Army, first in the ranks, and then, after qualifying at Adelaide in 1917 at the age of 21, with a commission in the Australian Army Medical Corps. Having seen active service in the Middle East and in France, he came to this country in 1919 as a Rhodes scholar at Balliol, and he rowed in the Oxford boat in 1920. He worked as a demonstrator in the anatomy department, and was house-surgeon at the Radcliffe Infirmary, before going on to the London Hospital in 1921. In the same year he took his F.R.C.S., and after holding house-appointments and working in the pathology department, he became first assistant in the surgical unit. In the next few years his interests were mainly in genito-urinary surgery, and he wrote on tumours of the testicle and on congenital cystic kidney. As an operator he was distinctly slow; and he was intelligent rather than specially clever. But he was alert, inquiring, and entirely dependable—a strong man to whom nothing was too much trouble. With characteristic insight the late George Riddoch saw that these qualities could be put to particularly good purpose in neurosurgery as practised by the school of Harvey Cushing in Boston, and he persuaded Cairns that there was an opening in London for a neurosurgeon who had learnt Cushing's methods. In 1926 the next appointment to the London Hospital staff was anticipated by electing Cairns supernumerary assistant surgeon, and he was given leave of absence to go with a Rockefeller fellowship to the United States, where he became assistant resident surgeon in Harvey Cushing's clinic in Boston.

[Stoneman

The Medical Research Council report [1] which he wrote on his return showed how strongly the elaborate American technique appealed to Cairns: the fullest possible examination, the most careful operation, and the most detailed notes, so that surgery and science might advance—this was the way, he felt, in which medicine should be practised. But he had learnt not only technique but also much else for which Cushing stood. He set himself to become, so far as he could, his own neurologist, and to combine research with practice. He adopted, too, the American plan of conducting his private practice in the building where he did his hospital work, believing (courageously but rightly) that the man tells more than the address, and that, if he made himself good enough, patients would come to Whitechapel to consult him. In fact, however, he was little interested in whether patients were private or not: what he chiefly wanted was the right conditions for his work. Neurosurgery, as he saw it, was a highly coöperative affair, and with his team of assistants and ancillaries, his dictaphones, and his operations lasting hour after hour, he represented the New Model in British surgery. The way was not always easy, and if in dealing with patients Cairns always had the gentleness of strength he could also display some of its ruthlessness when he felt that opposition must be broken down. In the ten years after his return from Boston he gradually earned himself a great reputation; and he was appointed to the two principal London neurological hospitals, at Maida Vale (1931–34) and Queen Square (1934–37). For a long time, however, he had cherished the hope of forming a rather different kind of neurosurgical institute—perhaps out in the country—where the art and the science could be developed more deliberately and without distractions. He was by nature an organiser and planner, of a highly practical kind, and he was interested in education as well as research. When, therefore, he came into contact with Lord Nuffield he was well prepared to advise that potential benefactor on what might be done at Oxford, and his appointment to the Nuffield chair of surgery in 1937 enabled him not only to play a leading part in the development of the clinical medical school but also in due course to create one of the world's foremost neurosurgical clinics.

Too soon, however, the war intervened; and Cairns became first the Ministry of Health's adviser on head injuries, and then consulting neurosurgeon to the Army, with the rank of brigadier. In this capacity one of his best-known achievements was the prevention of many head injuries by compelling Service despatch-riders to wear crash helmets; and another was the field trial he organised with Sir Howard Florey in which the use of penicillin for battle casualties was tested in various theatres of war. Even more benefit, however, came of his steady determination that the treatment of head wounds and injuries by field units should be of the highest possible standard, and he could share the credit for a death-rate for such casualties that was lower than in any other army. In Oxford he was at the same time organising the Head Injuries Hospital in St. Hugh's College, and the wartime organisation for the treatment and reablement of head injuries which he developed with Sir Charles Symonds made many important contributions to knowledge and to the efficiency of the Army and R.A.F. medical services.

After the war there were many claims that took him away from Oxford. As an organiser he was becoming more patient, and in a presidential speech to the Association of Surgeons in 1947 he remarked that "in this university institutions and departments don't mature quickly," but he hoped that the right conditions would develop in the next ten years. On the same occasion he deprecated standardisation of surgical types and spoke of the advantages of a mixture after the English manner; and he also believed strongly in the value of bringing non-medical scientists into medical research teams. In the following year he was visiting Australia and New Zealand as first of the Sims travelling professors; and his later tours in the southern parts of Africa made him plead earnestly that the profession at home should take more interest in the medical needs of the African continent, where action, he thought, could bring such great results. But with these and other obligations, he remained the vigorous head of a department that has been producing valuable work on tuberculous meningitis, on antibiotics in intracranial surgery, and latterly on alternatives to leucotomy.

"He was amazingly easy to work with," writes W. R. R., "for he never bothered with petty matters of prestige, or who should be in charge of this or that. He was always appreciative of the work of his colleagues, and provided every facility to further their researches. He formed the most important training-ground for neurosurgeons in this country, and there must be over a score of his trainees who have themselves formed similar neurosurgical clinics in many parts of the world. He played the game of life with an enthusiasm and an insistence on the highest possible standards which were an inspiration: his work was his life, and holidays were short intervals during which vigorous physical activity strengthened him for the next session. He was always convinced that things could be improved, and his insistent pressure for changes naturally provoked opposition at times; but his motives were so transparently honest and sincere that he usually gained much support. Those of us who were privileged to work with him were accustomed to leave to him the most important administrative aspects of our work, for we had such complete confidence in his judgment regarding such matters. We had looked forward to many more years of happy collaboration, but as this cannot now be we must maintain what he has built."

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[1] *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 125, 1928.

"In Cairns's success," writes W. R. B., "there were many ingredients. An athletic physique, an untiring capacity for work, manipulative skill, and high intelligence all played their part; but a man may have all of these and yet be no more than a first-rate exponent of his art. Cairns added to them an imaginative vision, which served him alike in his everyday activities and in larger affairs. He had an unusual insight into his patients' point of view, which was invaluable both in taking a history and in the management of treatment, and contributed to his minute attention to detail. His approach to larger questions was empirical, and guided by an intuition which led him successfully to explore possibilities in research and treatment. His professional life was a pilgrimage, from general surgery to neurosurgery, and from the London, Maida Vale, and National Hospitals to Oxford, because at each step he saw before him bigger opportunities to use his ability. He lived with a humorous zest, which sprang from some perennial youthfulness. One could not picture Hugh Cairns as an old man; and now he 'shall grow not old, as we that are left grow old.'"

The following is a tribute from one of his pupils.

"Cairns was above all a teacher, not in the didactic sense, but by precept and example. Just as Cushing had left his imprint on him, Cairns left his mark on all of his pupils and he derived the greatest pleasure from watching their progress. During the hectic years in London, he gave the impression of being a stern master, but beneath the surface of hard work and rigid discipline there was a warm heart and keen appreciation of effort. No-one was ever ticked off for an error of judgment or mistaken diagnosis unless it was the result of lazy thought or action. It was in the busy practice of the London Hospital that he established his reputation, and by the standards of those days, in a comparatively short time. He had the gift of investing every case with a particular interest, and his system of records made the material easily available for future reference. Each patient was 'followed up,' and over the years a useful body of information about the natural history of neurological diseases has accumulated. He had a great respect for pathology, and he often spoke of his association with the pathology department at the London as being one of the most valuable parts of his own training.

"When he left London for Oxford, a certain mellowing was soon apparent. He worked as hard—as did everyone else—but it was all done in one place and more efficiently than had been possible in London. There was time for an occasional round of golf at Huntercombe, tennis in his own garden, wooding expeditions on Sunday afternoons, and family holidays at South Stoke and Bamburgh. He enjoyed giving parties and arranging functions, and was an excellent host; one of his happiest memories was the occasion of Cushing's visit to Oxford to receive his honorary degree when they were surrounded by mutual friends from all over the world. But these activities were only adornments of his work, and his output was increasing all the time.

"The war interrupted much of this pleasant way of living. He was thrown into the development of the undergraduate clinical school in Oxford and this remained one of his chief interests. There were difficulties, and it is not surprising that the motives of one with such a dynamic personality should be occasionally misunderstood; but his interests were always the best interests of medicine in general, and the Oxford school in particular, as he saw them. His influence in the councils of his colleagues increased steadily during and after the war. At the same time the war presented the problem of head injuries, and with Sir Charles Symonds he developed an organisation which was unequalled anywhere. The same qualities which had made a success of his departments in London and Oxford found even more fruitful application in the larger field of battle casualties. Even during these strenuous years, he never lost sight of the value of records or the importance of training young surgeons, and there was about St. Hugh's much of the atmosphere of a teaching hospital.

"After the war, he had to spend more time on administration and ambassadorial duties, and there was less time for routine clinical work. This was a considerable loss, because he was essentially a good doctor and was at his best immersed in clinical problems and dealing with ill people and their relatives. But he was able to spend more time on the scientific projects in which he was interested, and his approach became much more philosophical. Although he had had no formal training in research techniques, he had learned a great deal by study and observation, and his own researches were models of thoroughness, clarity, and critical assessment. He was to the end a student, eager to learn from anyone who knew more about a subject than he did, and his interests were by no means confined to his own specialty. It was these qualities, together with his charming personality, which made him such a good representative of British medicine.

"The brisk walk, the flashing eyes, the firm lower jaw, and the quick smile are no longer with us; but none of us can ever forget the indomitable spirit which has been and will remain our inspiration."

Hugh Cairns married in 1921 Barbara, youngest daughter of A. L. Smith, then master of Balliol. They had two daughters and two sons, one of whom received the degree of D.M. at Oxford a few weeks ago.

ROBERT WILLIAM CRAIG

O.B.E., M.D. Edin., F.R.C.P.E., F.R.S.E.

Dr. R. W. Craig, who was for fifteen years Scottish Secretary of the British Medical Association, died at his home in Edinburgh on July 14.

He graduated M.B. at Edinburgh University in 1903, and held various house-appointments before he succeeded to his father's general practice at Pathhead, Midlothian. He remained in practice there until 1931 when he was appointed Scottish secretary to the B.M.A. For nine years he was a member of the Midlothian education authority and convener of its medical committee. Shortly after joining the staff of the B.M.A., he was made a member of the Cathcart Committee, which from 1934 to 1936 studied and reported on the Scottish health services. He was appointed O.B.E. in 1941 in recognition of his work in the organisation of civil defence in Scotland.

[Kemp, Dalkeith

In 1943 Dr. Craig became a member of the Scottish Old People's Welfare Committee and later he was elected chairman. For many years before his death he sat on the General Medical Council as a directly elected representative from the profession in Scotland. At the start of the National Health Service he became a member of the Scottish South-Eastern Regional Hospital Board and he served as its vice-chairman until he retired in 1951. His public appointments thus brought him into close contact with a great many people in Scotland, and the circle of his friends was enormous, for he was an open-hearted and friendly man, with the inestimable gift of always remembering faces and being able to attach the correct names to them.

A memorial service was held on July 20 in Crichton Church, in the district where Dr. Craig formerly practised.

Mr. J. O. D. WADE

T. G. I. J. writes: "All who studied anatomy and surgery at Cardiff will recall 'Jimmy' Wade's phenomenal memory for the minutest detail of anatomy and his remarkable speed and dexterity in operating. He made emergency surgery, especially the acute abdomen, his specialty—indeed, no-one in this country had wider experience in this field. He was always ready—day and night—to respond to the many calls for his skill, and his work for the people of South Wales, particularly in the mining valleys, was colossal. A kind and encouraging chief, he was a great support to his house-surgeons, to whom he was always available. After a night of operating it was a privilege and an education to walk home with him—his arm resting on one's shoulder—while he discoursed on the many facets of the surgery of a vast experience."

Appointments

BRAIN, R. H. F., M.B. Birm., F.R.C.S.: asst. surgeon and asst. thoracic surgeon, Guy's Hospital, London.
CRANE, J. E., M.B. Wales: appointed factory doctor, Carmarthen district, Carmarthen.
DEAN, THOMAS, F.R.C.S.E., M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, St. Helen's Hospital, Barnsley, and Montagu Hospital, Mexborough.
FARQUHAR, J. V. L., B.A. Camb., M.R.C.S., D.P.H.: asst. county M.O. for Staffordshire and M.O.H. for Tamworth.
LUKER, B. C. H., M.B. Camb., F.R.C.S.: consultant surgeon, Montagu Hospital, Mexborough, and Moorgate Hospital, Rotherham.
MCCLEMENTS, D. T., M.B. Edin.: senior house-officer (surgical), Edenhall Hospital, [illegible] ian.
MACLEAN, A. B., M.B. [illegible] L.F.P.S.: asst. surgeon (consultant), East [illegible]
TOLLAND, JOHN, L.R.C.P.E., D.P.H.: M.O. to Newcastle-under-Lyme area health committee, asst. county M.O., and M.O.H. of Kidsgrove Urban and Newcastle-under-Lyme Rural Districts.

Leeds Regional Hospital Board:

BENIANS, R. G., M.A., M.D. Camb.: asst. chest physician (S.H.M.O.), Bradford chest clinic.
BOWEN, W. A. L., M.R.C.S., D.P.M.: consultant psychiatrist and medical superintendent, Naburn and Bootham Park Hospital.
WINN, CECILIA, M.R.C.S.: asst. anæsthetist (S.H.M.O.), Ilkley and Otley, Menston, and Middleton and Grassington groups.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

BARROWCLIFF.—On July 4, at Stratford-on-Avon, to Germaine, wife of Dr. D. F. Barrowcliff—a daughter.
GARROD.—On July 17, at the British Military Hospital, Benghazi, M.E.L.F. 6, to Gwyneth (née Glynne), wife of Captain D. C. H. Garrod, R.A.M.C.—a son.
HERBERT-BURNS.—On July 6, at 18, Edward Road, Dorchester, to Joan (née Jolly) and Dr. Jack Herbert-Burns—a daughter.
IMRIE.—On July 15, at Mount Alvernia, Guildford, to Diana, wife of Dr. David A. Imrie—a daughter.
ODELL.—On July 17, at the South London Hospital, S.W.4, to Ruth (née Licence), wife of Dr. J. R. Odell—a daughter.
PEATFIELD.—On July 13, to Ruth (née Wilson Hall), wife of Mr. Ronald Peatfield, F.R.C.S., the Fairway, Green Lane, Oxhey—a son.
ROWLANDSON.—On July 17, to Rosamund (née Firth), wife of Mr. Richard Rowlandson, F.R.C.S., the Gables, Henlow, Beds—a son.
SHEAHAN.—On July 14, at Central Middlesex Hospital, N.W.10, to Lorna (née Leader Williams), wife of Dr. Christopher Sheahan—a daughter.
YATES.—On July 11, to Alison (née Walker), wife of Dr. P. C. Yates, of 404, Stirling Highway, Cottesloe, Western Australia—a son.

MARRIAGES

DAVIES—VAN LEUVEN.—On July 19, in London, Howard Davies, M.D., to Brenda Van Leuven, M.R.C.P.
LINDAN—JACKSON.—On July 17, in London, Olgierd Lindan, MED. DIP., to Rosemary Jackson, M.B.

DEATHS

BAIRD.—On July 18, in London, Stephen Young Baird, M.B. Glasg., of Assam, India.
CAIRNS.—On July 18, at the Radcliffe Infirmary, Oxford, Hugh William Bell Cairns, K.B.E., D.M. Oxfd, M.B. Adelaide, F.R.C.S., Nuffield professor of surgery in the University of Oxford, aged 56.
MITCHELL.—On July 19, at Ben Mohr, Insch, George Mitchell, M.B. Aberd., L.M.
O'REILLY.—On July 15, Charles Joseph O'Reilly, D.S.O., M.C. and bar, Knight of St. Gregory, M.B. Dubl., lieut.-colonel R.A.M.C., Roseboro', Naas, co. Kildare.

Notes and News

IMPERIAL CANCER RESEARCH FUND

To mark the 50th anniversary of the foundation of th Fund, the president and council held an At Home at th Fund's laboratories at Mill Hill on July 15. Exhibits a demonstrations were arranged to illustrate the story of th Fund's work since 1902, and to show what is going on at th moment.

Dr. James Craigie, F.R.S., director of the Fund, and D A. M. Begg have continued their investigations using tumou preserved as cell suspensions in the frozen state. Some ce have now been kept alive in this way for $3^1/_2$ years. Mr. H. Crabtree presented some of his results with the azo-compoun that he has been synthesising and examining to explore th idea that *p*-aminobenzoic acid may play some part in th genesis of liver tumours. Mr. P. C. Williams's research mammary cancer in mice is designed to answer the questio can hormonal differences account for the different prevalen of cancer in three strains of mice? As a first step, he h studied the effect of subcutaneous injections of stilbœstr on vaginal smears of spayed mice; sensitivity is shown cornification of the epithelium. There are many variabl and the work is necessarily long; for example, some anomali that have turned up may be caused by climatic changes- a factor which can only be taken into account by analysi results for at least a year. When the experiments are extend to intact animals, the further complication of the œstro cycle will be introduced. The next step will be to deci whether mammary and vaginal sensitivity can be correlate Dr. L. M. Franks's demonstration included an account work on the spread of prostatic carcinoma to bone. T injection of a barium suspension in male cadavers has enabl a direct communication between the prostatic veins, t vertebral venous system, and the veins of the pelvic bon to be shown radiographically. Spread along these vei seems a likely cause of bony metastases. The routi investigation of human breast cancer was dealt with Dr. G. D. Lumb and Dr. J. Strotton Young. The "giant section technique, in which sections of frozen tissue are c with a band-saw, enables large areas to be examined micr scopically in one specimen, and is very useful in tracing loc spread of tumour cells.

MEDICINE IN ABORIGINAL SOCIETIES

FINAL students, oppressed by the complexity of mode medicine, may like to know that even in less hackney societies the Art is elaborate, technical, illogical, contradictor uncertain in its results, and long to learn. So much is evide from an exhibition illustrating "The Medicine of th Aboriginal Peoples in the British Commonwealth," open by Lord Webb-Johnson at the Wellcome Historical Medic Museum on July 18. Moreover, as Dr. E. Ashworth Unde wood hints in his informed introduction to the fine illustrat catalogue,[1] the aboriginal curriculum, too, has its burdens.

There are, he says (and it has a homely sound), sever grades or degrees of medicine men in the same area. Studen need a high sense of vocation, amounting in fact to a convictio that they are born for the part; for when a young ma decides to take up medicine he retires to a desert place an falls into a trance, perhaps induced by fasting, and havin thus passed his entrance examination, is admitted to th initiation rites—which, among the Aruntas of Australi include having a hole bored through the tongue, perhap to help him to think before he speaks. He then settles dow to a long period of training in a school for medicine me When he finally gets into practice his daily round does n differ as much as might be expected from that of his mo urbane counterpart, except that he is granted consulta status from the outset. Most aboriginals, in fact, on call in the doctor as a last resort, relying on simple hom remedies to deal with such trifles as colds, measles, toothach smallpox, snake-bite, bee-stings, and jiggers. The medici man is reserved for occasions when an enemy or an ev spirit are thought to be, ætiological factors; and round h comes with his little bag like any other doctor. True th equipment he turns out on the table, is rather differe from that with which Dr. Geoffrey Barber regales prospecti general practitioners at St. Mary's.[2] The outfit of a Nigeria

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1. To be had from the Oxford University Press, Amen Hous Warwick Square, London, E.C.4. Pp. 58. *3s. 6d.*
2. *Lancet*, 1952, i, 495.

medicine man, shown at the exhibition, includes (besides scissors, and materials for dispensing the equivalents—probably—of aspirin or cascara) a bell, the nest of a weaver bird, and an assortment of small animal skulls. Rattles too are popular, and Cetewayo's personal physician habitually carried 13 small horns, and a number of rough knives. These objects are commonly brought round in a wicker basket, but at least one practitioner used a bag composed of a more than part-worn jackal skin, with the head still attached.

Standards of professional integrity sometimes fall rather low, especially among the priests of Shopono—in some parts of Africa the God of smallpox. As so often happens in primitive societies the priests combine their profession with that of medicine, and do very well out of both: not content with holding a monopoly in the treatment of smallpox (by mediating with the god in return for an exorbitant fee) they also claim the property of all who die of it; and are not above furnishing their own epidemics by carrying the virus round in cowrie shells, and leaving it about in other people's houses.

It is a relief to turn from these evidences of malpraxis to a little straightforward surgery. An illustrated account of the cæsarean section seen by Dr. R. W. Felkin in Uganda in 1879, and the very knife with which this successful operation was almost certainly done, show that aboriginals are not always mystical in their medicine. Cupping horns, miniature bows and arrows for venesection, pincers for dentistry, and sharks' teeth beautifully mounted as lancets give a vivid idea of the skilful hands that make and use them. The usual trephined skulls offer their perennial problem to the servants of aseptic surgery.

The centre-piece of the exhibition is a tusk set on a bronze head, and splendidly carved with the ancestors of a king; and round the room are set such masks and figures as puzzle and capture the imagination. Nothing could be more agreeable than the winged top-hatted figure designed by his European authority to scare away spirits; and the seated figure of a woman from the Nicobar Islands is a considerable work of art. But for pure charm the prize must go to the black callipygous lady of unknown provenance—perhaps the Hottentot Venus in person—whose innocent humble face is as haunting as that of the Mona Lisa—and quite remarkably different.

MEDICAL WAR RELIEF FUND

During 1950–51 16 awards were made from this fund, of which 15 were gifts and the other a loan. Of the 15 gifts, 6 were towards the school or university expenses of children whose fathers had been killed in the war, and the remainder were for the maintenance of doctors who have suffered illness attributable to the war, or for other special purposes. Since the fund was started loans to the value of £19,000 have been made. There is still a balance of £15,000 in hand, but it is expected that the calls on the fund, particularly for children's education, will continue. The committee has decided for the time being not to invite further contributions.

BRITISH UNIVERSITIES

The *Yearbook of the Universities of the Commonwealth, 1952*, is the twenty-ninth issue and is published[1] for the Association of Universities of the British Commonwealth (formerly the Universities Bureau of the British Empire). In addition to general information about, and staff lists of, every university in the British Commonwealth, some events of interest during the previous academic year are reported. An appendix includes the five universities of Eire, and another describes Anglo-American academic relations.

THE W.A.M.J.

We welcome the reappearance of the *West African Medical Journal* which has been in abeyance since 1938. The directors of the medical services of the four Colonies sponsor a new 40-page journal which is to be issued quarterly from the University College of Ibadan. The editor, Dr. D. B. Jeliffe, of Ibadan, is to be congratulated on a good first number, to which the African D.M.S. of Nigeria, Dr. S. L. A. Manuwa, writes a foreword. Western medicine is not only acclimatising itself to West Africa but is becoming almost indigenous, and a journal such as this gives expression to the more valuable kind of national endeavour. Some day, no doubt, the *W.A.M.J.* will be printed and produced on the Coast and on African paper, and we hope it will long continue to record things new out of Africa. Orders for the journal (1 guinea per annum, or 6s. for a single copy) should be addressed to Effingham House, Arundel Street, Strand, London, W.C.2, or to the Editor, University College, Ibadan, Nigeria.

MORTALITY FROM GASTRIC CARCINOMA

Prof. Gunnar Nyström,[1] of Uppsala, has lately cast an interesting light on the number of deaths from cancer. Since the beginning of 1948 official Swedish statistics have shown the number of such deaths in people between the ages of 70 and 80, and from 80 onwards; and in 1948 and 1949 deaths after the age of 80 accounted for about one-seventh of all the deaths from cancer. For the City of Stockholm there has been a remarkable fall in gastric-cancer mortality among males. Between 1905 and 1940 this mortality ranged from 55 to 63 per 100,000 population. After 1940 this rate fell rapidly, and in 1945 it was down to 43. For women there has also been a similar fall, though less pronounced. Professor Nyström has explored the possibility that this fall may be due to operative treatment; but he finds that surgeons can claim very little credit for it. In his opinion, it reflects a falling incidence of gastric cancer—a fall that, according to Henschen, may be due to a rising standard of living, with better and more digestible food. Professor Nyström emphasises that generalisations about rising cancer mortality are apt to be misleading if the patients' ages are ignored.

University of Oxford

Dr. Florence B. Seibert of the Henry Phipps Institute, University of Pennsylvania, will deliver a lecture on Tuesday, July 29, at the Dunn School of Pathology on the Isolation of the Tubercle Bacillary Protein Fraction and its Ability to Sensitise Cells.

University of London

At recent examinations the following were successful:

D.P.H.—Mohammad Abbas, Mignon B. S. M. Alexander, P. A. Allsopp, J. D. B. Andrews, C. H. J. Baker, T. D. Blott, W. T. Buckle, L. J. Clapham, James Clarke-Taylor, T. E. J. de Fonseka, W. E. Denbow, N. R. E. Fendall, A. M. Gillespie, G. R. Gunn, A. T. Halliday, C. V. Harries, F. J. W. Hooper, Zein El Abdin Ibrahim, D. N. Keys, H. T. Knights, J. A. H. Lee, J. I. Lesh, J. C. G. Lockyer, Emeric Losonczi, J. F. Lucey, Betty J. McConnell, Sheila C. MacGregor, D. K. MacTaggart, June M. MacTaggart, Sardari Lal Malhotra, Robert Maycock, H. B. M. Murphy, Balbir Ball Greene Nehaul, J. A. B. Nicholson, D. A. Parker, A. G. Poulsen-Hansen, M. J. Rayner, Myrtle V. Richards, J. M. D. Roberts, Kathleen I. Scott, D. F. S. Shaw, J. F. Skone, Frank Summers, V. M. S. Thevathasan, A. L. Thrower, E. H. Todd, J. N. Twohig, A. J. Walker, M. D. Warren, Alfred Yarrow.

D.T.M. & H.—P. A. Cooper, B. O. L. Duke, E. B. Harvey, John Newsome, R. T. Scholes.

Medical Research Council

The council has made the following travelling awards for 1952–53:

Rockefeller Travelling Fellowships in Medicine

Dr. M. de Burgh Daly, lecturer in physiology, University College, London.

Dr. J. E. Hotchin, member of scientific staff, National Institute for Medical Research, London.

Dr. E. L. McDonald, assistant to professor of medicine, Middlesex Hospital, London.

Dr. R. G. Mitchell, lecturer in child health, University of St. Andrews, Dundee.

Dr. N. B. Myant, member of scientific staff, department of clinical research, University College Hospital Medical School, London.

Dr. P. C. Reynell, graduate assistant, Nuffield department of clinical medicine, Radcliffe Infirmary, Oxford.

Eli Lilly Travelling Fellowships in Medicine

Dr. C. J. Earl, junior lecturer, department of chemical pathology, Guy's Hospital Medical School, London.

Mr. P. H. Schurr, senior registrar in neurosurgery, Radcliffe Infirmary, Oxford.

Dr. R. G. White, Freedom research fellow, London Hospital.

Dr. G. M. Wilson, senior lecturer in therapeutics, University of Sheffield, and assistant physician, Sheffield Royal Infirmary.

Dorothy Temple Cross Research Travelling Fellowships in Tuberculosis

Dr. C. N. Hand, lecturer in bacteriology, University of Bristol.

Mr. H. Platt, university research fellow in veterinary pathology, department of pathology, University of Liverpool.

Alexander Pigott Wernher Memorial Travelling Fellowships in Otology

Dr. D. R. Haynes, department of otolaryngology, Johannesburg General Hospital.

Dr. R. F. Naunton, member of scientific staff, Wernher research unit on deafness, Institute of Laryngology and Otology, Royal National Throat, Nose, and Ear Hospital, London.

French Exchange Scholarships in Medical Science (in association with the Centre National de la Recherche Scientifique)

Dr. J. D. Carr, British Empire Cancer Campaign grantee, Poultry Research Centre, Edinburgh.

Dr. M. A. Epstein, assistant pathologist (research), Bland-Sutton Institute, Middlesex Hospital, London.

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[1] London: G. Bell & Sons. 1952. Pp. 1661. 42s.

[1] *Svenska Läkartidn.* June 13, 1952.

University of Leeds

Dr. Winifred Burbury has been appointed senior lecturer in child psychiatry.

Mr. P. J. Moir has been elected dean of the faculty of medicine for 1952–53 in succession to Prof. J. W. McLeod who is retiring. It is expected that Mr. Moir will give about half his time to the duties of the deanship, which have increased in recent years to such an extent as to require more time than can be given by the head of a university department.

University of Edinburgh

On July 16, the following degrees and diplomas were conferred:

M.D.—* Marion B. Bethune, † J. C. Cruickshank, † J. W. A. Duckworth (in absentia), R. A. K. Harper, Runa B. Mackay; * A. R. Muir, Thakur Ram Nath Parhar, C. H. M. Walker.

* Highly commended. † Awarded medal.

Ph.D. (in the faculty of medicine).—Bruce Cruickshank, Zbigniew Godlowski (in absentia), R. H. Girdwood, Autar Singh Paintal.

M.B., Ch.B.—D. H. Adamson, J. C. Aickin, J. A. Aitken, N. C. Allan, H. C. Allen, Anne J. Anderson, Andrew Armstrong, E. F. Auden, Timothy Awuku-Asabre, W. M. Ayles, J. A. M. Bain, Arthur Banks, F. M. Begg, W. D. Bennett, A. J. Berry, H. S. P. Binnie, Sheila H. Birse, G. C. Biss, Alexander Bisset, Allan Black, J. G. Blyth, Heather Bremner, Alison G. H. Brown, Jean F. Brown, Donald Budge, Douglas Cadger, Helen M. Caldwell, H. A. Campbell, D. I. B. Carrie, T. M. Chalmers, D. G. Chambers, Agnes Clark, H. G. Clarke, Allan Craig, Margaret Cramb, F. M. R. Cranston, G. A. G. Crease, * S. H. Davies, K. J. Dennis, Margaret M. Dewar, Agnes M. Dickson, Andrew Doig, P. H. Dootson, Betty Duncan, J. K. Edwards, W. A. Elliott, E. T. Faunch, William Ferguson, J. A. D. Gillies, Joyce Y. Graham, R. W. Graham, M. J. Grayson, W. M. Haining, Daphne V. M. Halliday, William Harrison, Pamela P. Hartley, G. I. Hendry, Rena E. Hogg, James Hood, Margaret Hope, Agnes C. Howie, Constance C. M. Howie, G. A. Ives, T. P. C. Jameson, V. W. Johnson, S. M. Joubert, Lilias Kilpatrick, Christine C. G. Krause, Mairi H. Lack, J. P. Laidlaw, R. B. Laidlaw, Ann L. Langley, A. W. B. Lawson, W. J. H. Leckie, P. B. Lesslie, C. D. Livingstone, Margaret A. Loraine, I. A. Lowe, G. B. McAulay, H. F. MacConnachie, Alexander McDonald, H. J. McDonald, Hugh Macdonald, Isobel Macdonald, Jean M. Macdonald, Robert Macdonald, G. P. McGovern, D. P. McGowran, Duncan MacGregor, Kathleen L. MacGregor, G. M. McLaren, John Macleod, Murdo Macleod, Inez M. McMurray, John McNae, I. S. McRobbie, R. G. Mahaffy, J. M. Main, J. E. Malcolm, C. M. Manson, T. W. Manson, F. P. S. Marriott, J. A. K. Meikle, K. T. W. Miller, W. H. Morgan, J. K. Morrison, N. M. Munnoch, Dorothy Murphy, P. J. B. Murray, G. J. M. Nairn, W. J. Newlands, Paulette O'Dowda, J. N. Park, Morag Parnell, R. A. Parry, A. B. Partridge, Margaret D. Paton, R. W. F. Paul, W. F. Paveley, William Peter, R. C. Phellas, D. E. B. Powell, H. W. S. Rankin, Jean M. Reid, Kathleen M. Robb, M. K. Robinson, A. I. Ross, I. A. B. M. Ross, T. A. Sanderson, P. D. Sears, Marjorie E. J. Shafto, Doreen W. Shennan, J. P. Shutt, B. C. S. Slater, W. D. Smith, A. K. M. Stewart, F. L. Sturrock, J. H. Tait, D. E. M. Taylor, J. A. Taylor, I. M. Thom, C. H. Thomson, E. D. M. Tod, I. C. K. Tough, G. H. Wallace, G. S. Wallace, Alexander Watt, G. O. Way, D. B. Williamson, J. B. Williamson, A. O. A. Wilson, James Wilson, H. W. Wright.

* Honours.

D.P.H.—E. C. B. Bramwell, Isobel B Drummond, R. R. Gillies, R. S. Hardie, Elizabeth C. Nelson, J. H. Nicolson, Robe Krishava Ramadwar, Shafiqur Rehman, W Shearer, C. E. G. Wickham, I. M. Wood, H. W. Woolmer, E. W. Wright.

D.T.M. & H.—Ahmad Mohamed Ishak El Haddad, D. M. Cameron, D. G. Conacher, Aisha Zaki Shafei Hanno, W. K. Lutterodt, Yahia Marzouk, Hareebrun Bunsee Singh, Chengleput Harikrishnan Sivaraman.

D.Psych.—Beatrice M. Allen, David Satya Nand.

The Cameron prize in practical therapeutics has been awarded to Prof. K. P. Link, PH.D., who holds the chair of biochemistry in the University of Wisconsin, in recognition of his work on anticoagulant therapy.

National University of Ireland

The degree of M.D. has been awarded to Prof. Edward J. Conway, F.R.S.

Royal College of Surgeons of England

A three-dimensional film in colour will be shown at the college, Lincoln's Inn Fields, London, W.C.2, on Thursday, July 31, at 5 P.M., of an operation for Radical Resection for Carcinoma of the Stomach.

Royal Institute of Public Health and Hygiene

On July 16 the Harben medal was presented to Prof. E. C. Dodds, F.R.S., and the Smith award to Dr. Andrew J. Shinnie.

St. Charles' Hospital, London

On Wednesday, July 16, Sir Harold Gillies opened the new accommodation at this hospital for the plastic unit. The new unit, which is to bear his name, is in direct continuity with the first plastic unit which he established at the hospital. It includes two new wards

Research Board for the Correlation of Medical Science and Physical Education

The William Hyde award for 1950 (£300) has been given to Dr. R. W. Parnell, of the Institute of Social Medicine, Oxford, in recognition of his work on the application of special physical measurements (*somatotyping*) to students in Oxford.

Postgraduate Course in Public Health Engineering

Enrolment is now going on for the 1952–53 course in public health engineering, given jointly by the Imperial College of Science and Technology and the London School of Hygiene and Tropical Medicine. Further details may be had from the deputy registrar, City and Guilds College, Exhibition Road, London, S.W.7.

Leeds Medical School Dinner

The annual dinner of past and present students of the Leeds School of Medicine is to be held on Nov. 28 at the Hotel Metropole, Leeds.

Stability of the Family

A conference on this subject is to be held in Oxford between Sept. 8 and 13 by the International Union of Family Organisations. Further information may be had from the hon. secretary of the British committee, c/o British Social Biology Council, Tavistock House South, Tavistock Square, London, W.C.1.

Summer School in Health Education

The Central Council for Health Education is holding a course at St. Osyth's College, Clacton, from Aug. 6 to 16. The speakers will include Prof. Fraser Brockington, Sir Allen Daley, Dr. Richard Schilling, and Dr. A. R. Harrison. Further particulars may be had from the medical director of the council, Tavistock House, Tavistock Square, London, W.C.1.

Biology as a Career

The Institute of Biology is holding a one-day discussion on this subject in Birmingham on Oct. 4, at which Sir Harold Himsworth will speak on Careers in Medical Research. Further particulars may be had from the general secretary of the institute, Tavistock House South, Tavistock Square, London, W.C.1.

Manchester Royal Infirmary Old Residents' Club

The 11th reunion of this club will be held at the Midland Hotel, Manchester, on Saturday, Oct. 4, 1952, in the bicentenary year of the infirmary. Further particulars may be had from the honorary secretary of the club at the Manchester Royal Infirmary.

Fellowship in Virology

The British Memorial Fund in Victoria, which was set up as a gesture of "loyalty, gratitude and affection" to the British people in recognition of their rôle in the second world war, is offering a fellowship in virology to a British graduate.

The fellowship (£A1000) provides for ten months' study in Victoria and covers all travelling and living-expenses during the period. It is open to graduates in medicine or science, under 35, who contemplate a career in research or teaching or who have already had some research experience in microbiology or biochemistry. Study will be at the Walter and Eliza Institute Hall, Melbourne, chiefly in the field of virus diseases. Further details can be obtained from Sir John Lienhop, Victoria House, Strand, London, W.C.2. Applications will be received during the next four weeks.

CORRIGENDUM: *National University of Ireland.*—In announcing the honorary degrees lately conferred by the university (*Lancet*, July 19, p. 151) the names of the sponsors were inadvertently included. The list should have read as follows:

LL.D.—Prof. E. P. McLoughlin, Dr. A. W. S. Sichel.

D.Litt.—Mr. William Doolin.

D.Sc.—Sir Henry Cohen (in absentia), Sir John Parkinson.

M.D.—Major P. J. Delaney, Sir Stewart Duke-Elder, Sir John McNee, Dr. Angus Macrae.

M.D.S.—Dr. J. P. Walsh.

On July 19, Major A. B. Kinnier-Wilson, late R.A.M.C., won the Queen's prize at Bisley.

Sir James Learmonth has been elected a foreign correspondent of the National Academy of France.

Dr. F. Avery Jones will be away on a Nuffield Foundation lecture tour in Australia and elsewhere from Aug. 3 to Nov. 3.

THE ARTERIAL LINING*

J. B. Duguid
M.D. Aberd.
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF DURHAM

To anyone who has studied the vast literature on arterial disease it must appear that every conceivable aspect has been covered, and that the principles laid down nearly a hundred years go, having stood the test of time, are beyond question. But I believe this to be wrong; and I would like to submit a conception which, though not new, has been entirely overlooked in the writings of the past century. We have been brought up on the cellular theory, a convenient formula by which to explain the development of morbid processes; but most morbid histologists must, I think, have felt from time to time that it did not quite fit some of the changes they have been called on to interpret. To me atherosclerosis has been a case in point.

PATHOGENESIS OF ATHEROSCLEROSIS

About the middle of last century von Rokitansky attributed atheroma of the aorta to the deposition of layers of fibrinous material on the inner surface of the vessel, the fibrin later undergoing fatty change and sometimes softening. He thus viewed the arterial thickenings as products of the blood. Somewhat later Virchow elaborated his cellular theory which embodied the principle that all morbid structures consisted of cells which were derived from pre-existing cells; and in accordance with this he held that atheromatous thickenings were the products of the connective-tissue cells of the arterial intima. On these two conflicting ideas there ensued a controversy in which Virchow used an argument which has, I think, done lasting harm. He argued that since the thickenings were subendothelial—i.e., external to the endothelial lining—they could not be surface deposits. He thus referred to the endothelium as if it were a fixed landmark by which the tissues of the vessel could be identified, and in so doing established a misconception which has to this day restricted our approach to arterial disease. We are still taught to regard all parts of the vessel wall external to the endothelial lining as belonging to the vessel not only structurally but also as regards development; and this is easily shown to be wrong.

One has only to study a canalised thrombus in a coronary artery (Duguid 1946) to see that a new endothelial lining develops wherever a new channel is formed, and that where this has occurred the thrombus is external to it. Moreover, when the thrombus becomes organised it forms a fibrous mass which is continuous with the intima, and sometimes quite indistinguishable from it. In short the mass which was originally formed in the blood-stream becomes a part of the vessel wall. The same is seen in mural thrombi, which are far commoner (Duguid 1948, 1949) than we have been led to imagine. They also become covered by endothelium and are thus incorporated in the vessel walls, with the result that when they are organised they form fibrous thickenings of the intima. Moreover, they undergo fatty change; and there can be little doubt that some of the lesions we have been accustomed to classify as atherosclerosis have been of this nature. The same process has been recognised in atherosclerosis of the renal artery by Heard (1949) and in the formation of fibrous thickenings in the mitral valve by Magarey (1951).

Experimental confirmation of the existence of this process can be obtained by inducing arterial thrombosis in animals. If one inserts a silk thread into the femoral or carotid artery of a dog, passing it along the lumen for a short distance and out again, a thrombus forms and in two or three weeks is incorporated in the vessel wall as a fibrous thickening. The same effect can be produced by pricking the central artery of a rabbit's ear. More striking confirmation has been provided by Harrison (1948) and by Heard (1952) who injected particles of fibrin into the veins of rabbits and showed that the particles lodging in the smaller pulmonary arteries were converted into fibrous thickenings of these vessels, producing the morbid appearance we associate with pulmonary hypertension. Another confirmation has recently been provided by Rannie (1951) in relation to experimental cholesterol lesions in rabbits. In the development of these lesions Leary (1949) visualised an active penetration of the endothelium of the arteries by cholesterol-bearing phagocytes which circulate in the blood, but Rannie has produced evidence that the phagocytes are merely deposited on the surface of the arteries and in due course covered by a newly formed endothelial layer so that they are passively incorporated in the intima in the same way as mural thrombi.

Thus Virchow, in putting forward his cellular theory against the thrombosis hypothesis of Rokitansky, overlooked one fundamentally important principle—namely that the endothelial lining of the vessel is an adjustable structure. One of its functions is to rearrange itself so that any solid mass adhering to the internal surface of a vessel is covered and becomes part of the vessel wall. Neglect of this principle has undoubtedly retarded progress in the pathology of arterial disease.

DEVELOPMENT OF HYALINE CHANGES IN ARTERIES

It may of course be argued that the organisation of a thrombus is itself a manifestation of cellular pathology, the thrombus being colonised by cells from the adjacent intima and ultimately replaced by them or their products; but a study of mural thrombi will show that this is by no means the whole sequence. When a mural thrombus becomes incorporated in an arterial wall it may not immediately be invaded by capillaries and connective-tissue cells, or attacked by macrophages, as in the classical process of organisation which we have been taught to visualise. Instead it undergoes a gradual metamorphosis which has some interesting features. First its fibrin loses its characteristic fibrillary structure, and also its specific staining properties, so that it is no longer easily identifiable. In time it becomes condensed and more or less homogeneous, taking a deep pink stain with eosin and having that appearance to which the terms "hyaline" and "fibrinoid" have been applied. Ultimately it may be invaded by connective tissue cells and transformed into fibrous tissue; but it is the intermediate hyaline stage which is on the whole the most prominent, and there is little doubt that, in this stage, old mural thrombi have frequently been mistaken for degenerations of the intimal connective tissues. (Here I would emphasise the importance of using frozen sections in a study of this kind, since dehydration and paraffin embedding seems to obscure the finer details of these structures.)

Thus Rokitansky was in a large measure correct in his thrombosis hypothesis, but the hypothesis has been forgotten and we have been so influenced by the cellular theory as to be blinded to the possibility of an alteration in the appearance of an artery meaning anything but a change in its original constituents. With recognition of the existence of a process by which deposits in the blood-stream are converted into thickenings of the vessel walls, a fresh approach to the problem of arterial disease opens, and we must now review the histology in the light of it.

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* Abridged from the Kettle memorial lecture delivered at Cardiff on Nov. 23, 1951.

HYALINE CHANGES IN THE ARTERIOLES

A form of arterial disease in which hyaline change figures especially prominently is the arteriolosclerosis seen in the kidneys, spleen, and other organs in hypertension and in diabetes mellitus. This lesion consists of a hyaline thickening of the walls of the arterioles with narrowing of their lumina, and the orthodox interpretation seems somewhat paradoxical. The hyaline thickening has been taken to be a degeneration, but it is difficult to see how a degeneration could be associated with narrowing. When it is remembered that arterioles are subject to an internal pressure of blood equivalent to 20 mm. Hg or more, a degeneration would be expected to lead to weakening and dilatation, and the fact that they are consistently narrowed seems to suggest that there may be some other explanation. Since hyaline change in the larger arteries can be produced by mural thrombi it seems not unreasonable to suspect that a similar process may be involved in arteriolosclerosis, and with this in mind G. S. Anderson and I have reviewed the histology of hypertensive and diabetic kidneys. Our findings (Duguid and Anderson 1952) seem to support the suspicion.

In the typical hyaline arteriolosclerosis, as seen for example in the afferent arterioles of the renal glomeruli, a layer of hyaline substance, usually much thicker than the original vessel wall, surrounds the narrow lumen and displaces the medial coat outwards. In the vast majority of instances its inner surface is lined with endothelium, so that it has every appearance of being a part of the intima; but if one searches carefully through the more severely affected kidneys one will usually find exceptions in which the hyaline layer is exposed to the blood-stream. In such instances its internal surface is usually ragged, and there may be loose fragments of hyaline substance more or less mixed with the elements of the blood, while sometimes the lumina are actually plugged with the substance. Such formations are particularly well seen in cases of malignant nephrosclerosis where some of the thickenings may be composed of newly formed fibrin, or fibrinoid material as it is called, and where the lumina are represented by irregular clefts entirely devoid of endothelium.

These appearances lend some support to the suspicion that the so-called hyaline degeneration is actually a deposit of fibrin or other coagulum in the lumina of the vessels; for they are what would be expected in the early stages of such a process, before the new endothelial lining has formed. I realise of course that these occasional findings prove nothing—histology seldom provides decisive evidence on a question of this kind—but it must be remembered that the orthodox interpretation, against which they have to be weighed, is likewise without proof. There is no reason to believe that the hyaline substance represents a degeneration of the tissues beyond the fact that it looks like one under the microscope, and then only provided the narrowing is ignored. When the narrowing is taken into account the weight of evidence seems to be all in favour of the deposit hypothesis, for it is obvious that a deposit in the blood-stream must narrow the lumen of the vessel from the outset, whereas a degeneration, which must interfere with the strength and resilience of the wall, would be more likely to lead to aneurysm. There is therefore, to say the least of it, some reason to doubt the long-accepted interpretation of these lesions and to throw the matter open for reconsideration from a fresh viewpoint.

At the present time there is little satisfactory information as to the nature of the hyaline deposits, if such they be. It is perh[illegible] that some of the arteriolar thickenings in [illegible] consist of fibrin, whereas others, [illegible] ion, are hyaline, because it suggests that here, as in the aorta, fibrin may in time form hyaline substance. This does not however imply that all hyaline substance may arise in this way. One often sees small masses of eosinophil coagulum mixed with the blood in the arterioles in such a way as to suggest that protein substances other than fibrin may be precipitated in the circulation and choke the smaller vessels. No doubt with newer methods of histochemical analysis these substances will in due course be identified, but it should be borne in mind that their identification will be of doubtful value so long as their relations to the existing tissues remain uncertain.

NATURE OF THE CONNECTIVE TISSUES

The importance of this latter consideration becomes evident when we refer to some of the problems of connective-tissue change which are now occupying attention. There is for example the question of the ageing of collagen. It has been suggested that the hyaline or fibrinoid change seen in the arteries of old people represents an ageing of the collagen fibres, and attempts have been made to determine the nature of this change. If, however, the hyaline substance is, as I suspect, not collagen but altered fibrin, then the results of such investigations may only lead to further misinterpretations. Similarly the conception of the so-called collagen vascular diseases is involved. This group of diseases, which includes disseminated lupus erythematosus and polyarteritis nodosa, is said to be characterised by certain alterations in the extracellular connective tissues, and hyaline or fibrinoid changes in the renal arterioles are cited as examples. These have been referred to as chemical or physical alterations either of the connective-tissue fibres or of the interstitial ground substance, and special efforts have been made to determine their nature in the hope that some light might be thrown on the development of connective tissue; but if they are altered mural thrombi or some other coagulation product we are again in danger of being misled. Obviously no conclusions as to the nature or development of connective tissue can be based on these arterial thickenings until we know exactly what developmental relation they bear to the vessel walls. It will readily be seen that the same considerations must apply to the non-vascular collagen diseases and any other conditions in which fibrinoid change figures.

CONCLUSIONS

These tentative interpretations of the pathogenesis of atherosclerosis and hyaline arteriolosclerosis have been put forward to show that the orthodox views are not the only possible ones. I do not wish to press them, but rather to bring out the important principle on which they are based. In the past our views on arterial disease have been limited by the notion that all new tissues are the products of pre-existing cells, and that any increase in the thickness of a vessel signifies either swelling or proliferation of its tissues. We must now recognise that the extracellular tissues are not necessarily subject to any such law. The fact that the arterial lining is a labile structure makes it possible for solid matter forming in the blood-stream to be added to the body tissues, and that fact has I think been proved beyond any shadow of doubt.

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THE TREND OF SERUM-CHOLESTEROL LEVELS WITH AGE

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It is increasingly evident that the largest, and perhaps the most difficult, health problems in the Western World are presented by those non-infectious disorders seemingly associated with ageing. It would be over-sanguine to hope for indefinite postponement of ageing in general, but people do not all age at the same rate, and even in the same person there may be well-marked differences in the ageing of different tissues and organs. Not only the relatives and the family physician are outraged when, for example, myocardial infarction strikes a man in full physical and mental vigour, and it is small consolation to have the pathologist report that the victim had the coronary arteries of an old man. Besides the social loss, the medical scientist is chagrined to have no better clue to physiological age—in this case of the arteries—than the number of years from birth.

This justifies, therefore, the most vigorous efforts to explore measurable human characteristics that change with age after the years of growth, particularly if these may be associated in any way with a morbid process, such as atherosclerosis, which tends to anticipate general ageing. So we were interested to find, in a study of clinically healthy men in Minnesota, a distinct difference in the average serum-cholesterol levels between young and middle-aged men.[15] That the serum-cholesterol level is significant in relation to the development of atherosclerosis is now, of course, well established.[5 6 11 12 14 16 17]

PREVIOUS STUDIES

In an expansion of the research in Minnesota observations on 1492 clinically healthy men showed a steady rise in the average serum-cholesterol level from the late 'teens until the mid-50s, the average annual increment being about 2·3 mg. per 100 ml.[20] The analysis of data from smaller series of men studied in New York,[23] southern Minnesota,[1] San Francisco,[4] Boston,[8] and Denmark,[21] showed reasonable agreement. In 46 relatively young men in England there was a mean annual rise of 1·7 mg. per 100 ml.[25]

Though all of these studies show much the same age trend, they are also all in agreement that there is much variation between people of the same age, the standard deviation of the mean being about 30–45 mg. per 100 ml. In other words, the standard deviation of serum-cholesterol for a group of men of identical chronological age is equivalent to something like plus or minus 15 years of age. As the age trend of atherosclerosis varies similarly from one person to another, it is tempting to suggest that the serum-cholesterol level may be a more useful index of vascular age than of mere years. In any case, it is essential to inquire into other factors than age which affect the serum-cholesterol level.

In cross-sectional surveys we found no relation at any age between the serum-cholesterol level and the habitual dietary intake of cholesterol[15 19] and this has been confirmed by others.[9 28] In controlled experiments lasting some months it was found that drastic changes in the cholesterol intake of man are without effect on the serum-cholesterol level if the intake of calories and fats is constant, but that changes in the intake of fat have a profound effect.[18 19] Well-marked changes in the serum-cholesterol level appear when the intake of fat is substantially altered, even when both calorie and cholesterol intakes are constant.[13 19] For example, in healthy men there was an average difference of 64 mg. of cholesterol per 100 ml. of serum in alternating periods of a month each on daily intakes of 11 g. and of 110 g. of vegetable fat, the diet being at all times devoid of cholesterol and animal fat. In identical experiments, in which at all times the diet provided about 700 mg. of cholesterol daily, the serum-cholesterol level averaged 61 mg. per 100 ml. less on the low-fat diet than on the intake of 68 g. of fat (A. Keys and J. T. Anderson, unpublished). The response of serum-cholesterol to diets low both in fats and cholesterol[3 26] is therefore explained by the change in fat, the dietary cholesterol being unimportant.

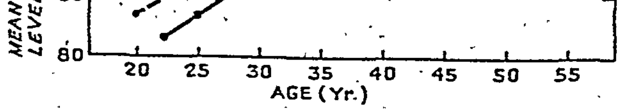
Now, in those countries in which the cholesterol-age trend has been studied so far, the national dietaries are similar as regards the proportion of total calories supplied from all kinds of fats. In 1949 fats supplied about 38% of the calories in the United States, 34% in Denmark, and 32% in the United Kingdom.[7] Studies of actual intake in working-class families in England gave an average of 35% of calories from fats in 1949, and in 1947 (the low point in supplies of fat in recent years) the average for the English families surveyed was 32%.[22] Our cholesterol data so far, then, all pertain to regions of high-fat diets.

STUDIES IN NAPLES

We have now been able to study this question in Naples, where the intake of fat is much less. For the whole of Italy in 1949 the average was 20% of calories from fats,[7] and in the men surveyed by us in Naples we found the same value.

The Neapolitan subjects were 84 clinically healthy men, aged 18–54 (average 35·5), employed by the City of Naples as firemen and as *vigili annonari* engaged on inspection and auxiliary police tasks. To assure comparability with the Minnesota study, we were at pains to use the same cholesterol method[20] in all details and brought the essential apparatus, as well as pure cholesterol standards and acetic anhydride, direct from Minneapolis. Each serum sample was analysed in duplicate, and satisfactory repeatability was obtained. The men were taken for study in a random sequence of ages.

From preliminary inspection of the data it was clear that the Naples data departed widely from a simple linear relation between age and serum-cholesterol level over the entire age-range; so the expedient was adopted of analysing the data for restricted successive age-



Mean serum-cholesterol levels in healthy men in Naples and in Minnesota. For each city the values are expressed as percentages of the average for age 35 in that city. The numbers of Neapolitans in each age-group were as follows: aged 18–25, 13; 21–30, 23; 28–34, 24; 32–39, 25; 37–44, 24; 43–49, 24; and 44–54, 18. The values for Minnesota were computed from data of Keys et al.[20]

groups. The main features of the findings are shown in the accompanying figure.

Up to about the mid-30s the Neapolitans had a similar age trend to that found in Minnesota and elsewhere, but thereafter they did not show any further rise. Whereas in Minnesota there is an average rise of about 40 mg. of cholesterol per 100 ml. of serum from age 35 to age 50, in the Neapolitans the average serum-cholesterol was a plateau over those years. Statistical analysis (see table) showed that the difference between the two population samples is highly significant. The mean annual increments were computed as the slopes of the least-squares regression lines fitted to the data over age-groups in which there is no significant curvilinearity. There is a highly significant difference ($t = 4{\cdot}3$, $t_{0{\cdot}001} = 3{\cdot}3$) between the slopes in the years between 30 and 48, but up to the early 30s the slopes were not significantly different. Beyond age 30 the Naples data show no significant departure from zero age trend.

ANNUAL INCREMENTS OF AVERAGE SERUM-CHOLESTEROL LEVEL IN CLINICALLY HEALTHY MEN OF DIFFERENT AGES IN NAPLES AND IN MINNESOTA

Region	No. of men	Age (yr.)		Rise of serum-cholesterol level per year (mg. per 100 ml.)	
		Mean	Range	Mean	Standard error
Naples ..	58	38·4	30–48	0·37	0·87
Minnesota ..	116	37·3	30–45	3·63	0·69
Naples ..	40	27·9	18–34	3·10	1·00
Minnesota ..	1172	23·7	17–45	2·29	0·18

It would be unwise to draw sweeping conclusions from the Naples findings about the relation between diet and the incidence of atherosclerosis. Other factors besides those considered here require attention, and direct evidence on the incidence of atherosclerosis is lacking. On the latter point we have only the unanimous judgment of the local physicians that coronary-artery disease is less common in Naples than in the United Kingdom and the United States, except, perhaps, in the rich people, who were not represented in our sample. It should be added that coronary-artery disease is understood and recognised by these physicians in the same way as in the United Kingdom and in the United States.

But several facts are clear. The Neapolitans live on a diet far lower in fats than in the United States, Britain, and northern Europe, and they have always so subsisted. The diet is also relatively low in cholesterol and in animal proteins. In spite of these differences the serum-cholesterol level is not low in the young men, and the age trend in early manhood is much the same as in men in the other areas studied. But in the years when, in other areas, a major development of atherosclerosis occurs, the Neapolitans differ in the absence of the expected continued rise in the blood-cholesterol level. So far we can find no reasonable explanation other than the dietary difference. The climatic factor seems unimportant in view of the differences of climate between Minnesota, California, Massachusetts, and Denmark, in all of which the age trend continues at least into middle age. Possible differences in physique and relative obesity [15 25] are currently under scrutiny, but at best only a part of the discrepancy could be explained on this score; the Naples men were neither unduly thin nor unduly fat and were not remarkable in somatotype.

There are a few published reports on serum-cholesterol levels in populations which subsist on diets differing from the U.S.-U.K. pattern in their fat and cholesterol content, but none of these is satisfactory for the present analysis. In India various results suggest a low average level of cholesterol in "healthy" persons,[2 10] but the methods used are faulty, and age was not considered. A recent study [27] on Alaskan Eskimos ignored age but concluded that the serum-cholesterol level is high and that this is related to the carnivorous diet; the averages cited, however, are not unusual for adult populations studied elsewhere.[20] It has been reported that six days' subsistence on fatty pemmican raises the level of all serum-lipids in Canadian Eskimos.[24]

SUMMARY AND CONCLUSIONS

In populations habitually subsisting on relatively high-fat diets—e.g., in the United States and most of northern Europe—the serum-cholesterol level tends to rise steadily with age from adolescence through middle age.

In 84 clinically healthy men in Naples, of ages ranging from 18 to 54, the serum-cholesterol level conformed to the U.S.-U.K. age trend to the early 30s but did not increase thereafter.

The Neapolitans, like most Italians, have a diet which is low in fat, and the peculiarity of their cholesterol-age trend is ascribed to this.

These facts probably have a bearing on the development of atherosclerosis and the incidence of coronary-artery disease.

We are grateful to Prof. Ferruccio di Lorenzo for invaluable coöperation in providing both subjects and clinical assistance; to Mrs. Margaret H. Keys for much aid in the cholesterol determinations; and to Dr. A. del Vecchio for willing help. Our greatest obligation, of course, is to the subjects whose voluntary coöperation was the basis of the work. The investigation was aided by a research grant to one of us (A. K.) from the National Dairy Council acting on behalf of the American Dairy Association.

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"The scientist, conscious of possessing a key that does open the locked doors, of the world-wide agreement of his colleagues, and of new secrets being wrested from Nature almost daily, is likely to ask, 'What have these philosophers ever *discovered*?' It is part of the philosopher's business to listen to criticism with patience and attention; but there are limits even to a philosopher's patience; and there is an immediate answer to this one, which I cannot refrain from offering. The philosophers have discovered science."—Prof. JOHN MACMURRAY, *Univ. Edin. J.* Summer Number, 1952, p. 87.

TORSION OF THE TESTIS AND ITS APPENDIX

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TORSION of the testicle or one of its appendages is still regarded as very rare. I believe, however, that it is by no means so rare as is taught, and that many cases diagnosed as acute epididymo-orchitis are in fact cases of torsion. This particularly applies to boys about the age of puberty and younger.

The first case was published in 1840 by Delasiauve. In 1907 Rigby and Howard described 9 cases seen at the London Hospital and referred to 40 examples in the literature. In 1946 Riba and Schmidlapp described 5 cases and stated that 489 had been published up to 1943. In 1928 Roche reported 3 cases seen by himself within five weeks. Rigby and Howard (1907) and Roche (1928) dealt in detail with the ætiology, symptoms, signs, and diagnosis, and there is in fact nothing to add to their description. They emphasise the frequency with which torsion of the fully descended testicle is diagnosed as acute epididymo-orchitis, and it is the frequency with which this mistake is still being made that makes me think that there is a place for a further paper on the subject.

MATERIAL

I have seen 11 proved cases, but 3 of these have been reported by Kennedy (1948) in his series of 11 cases of torsion of the testicle (not including torsion of the testicular appendix) seen at the London Hospital in twenty years ending in 1948. I have now collected a further 8 cases at the same hospital since 1948. These 8 cases, in 1 of which there was subsequently torsion on the opposite side, together with 2 cases of torsion of the hydatid of Morgagni and a case of torsion of the testicle treated elsewhere, form the substance of this paper. An example of torsion of a boy's only testicle eleven years ago, the other having been removed a year previously for the same condition, is not included, because the notes are not available.

Brief histories of 3 of the 11 cases are given below, and a summary of the remaining 8 is given in the accompanying table.

ILLUSTRATIVE CASE-RECORDS

Case 1.—A boy, aged 11, was first seen on May 15, 1947, with twelve hours' history of sudden pain in the left groin. He had not vomited.

On examination his temperature was 98°F and pulse-rate 72. His left testicle was not felt in the scrotum. There was an extremely tender swelling at the left external inguinal ring, where the overlying skin was red. A diagnosis of torsion of an undescended testicle was made, and he was admitted to hospital.

Operation (three hours later).—Under anæsthesia the testicle was felt in the scrotum and the inguinal swelling had disappeared. Through a left inguinal incision the testicle was delivered, and the tunica vaginalis was opened. It contained a little bloodstained fluid. The hydatid of Morgagni, which was twisted and gangrenous, was removed.

The boy made an uninterrupted recovery and was discharged on the tenth day.

Case 2.—A man, aged 32, was admitted on Nov. 1, 1949, with twelve years' history of recurrent attacks of mild pain and swelling of the left testicle, lasting for an hour or two and occurring about twice a year. Five years ago he had had severe pain in the left testicle. He was sent to hospital with the diagnosis of torsion of the left testicle, but the pain and swelling disappeared in the ambulance. For five hours he had had severe pain and swelling in the left side of the scrotum. He felt ill and vomited. There was no disturbance of micturition and no urethral discharge.

On examination the patient had a temperature of 97°F and pulse-rate 92; he was slightly shocked. The left side of

SUMMARY OF OTHER CASES

Case no.	Age (yr.)	Side	Previous attacks	Duration of present attack	Symptoms, &c.	Temp. (°F.)	Vomiting	Signs	Findings at operation	Operation
4	8	L	Intermittent for 3yr.	5 days	Severe pain in left testicle; off food	98·0	Nil	Tender swelling at external inguinal ring; skin red	Torsion of hydatid of Morgagni	Excision
5	$1\,{}^{7}/_{12}$	L	—	24 hr.	Brother tried to lift by scrotum; developed retention; scrotum red and swollen	98·0	Nil	Swollen red scrotum; skin puckered posteriorly	540° anticlockwise twist; testicle gangrenous	Orchidectomy
6	6	L	Intermittent attacks for a month	18 hr.	Severe pain in left testicle, which swelled	100·1	Nil	Testicle 4 times normal size; skin red but not tender	180° clockwise twist; gangrenous	Orchidectomy
7	13	L	—	4 days	Slight pain on playing football, worse next day, swelling testicle	100·0	Nil	Red swollen œdematous scrotum	Gangrenous. Long mesorchium	Orchidectomy
8	21	L	2 years ago testicle swollen and painful for 1 hr.	5 hr.	Awoken by severe pain	99·4	Nil	Testicle 2 or 3 times normal size, but 1 hr. later normal except for flaccid hydrocele	Long mesorchium (operation 5 days later)	Orchidopexy
9	12	R	—	3 days	Pain and swelling, unable to sleep	99·6	+ +	Red swollen scrotum	Intravaginal twist round lower pole	Orchidectomy
		${}^{11}/_{12}$ later L	—	5 hr.	Mild pain on left side	98·0	Nil	Swollen, untwisted while being examined	Epididymis attached to lower pole only	Orchidopexy
10	2	L	—	12 hr.	Mother noticed tender swollen shiny testicle	97·0	Nil	Four times normal size, shiny, red, and hot	90° twist through upper pole	Orchidopexy
11	42	L	Several milder attacks	3 days	Painful lump in left groin	98·0	Nil	Swelling over external inguinal ring; œdematous skin	Gangrenous undescended testicle	Orchidectomy

his scrotum was swollen and œdematous, with puckered skin. He was admitted to hospital.

Operation (three hours later).—While the patient was being shaved under anæsthesia, the testicle suddenly twisted into its normal position and the swelling disappeared. Through an inguinal incision the testicle was delivered and the tunica vaginalis was found to contain a few ounces of bloodstained fluid. The testicle was congested but viable. The parietal layer of the tunica vaginalis was excised, and the tunica albuginea was sutured to the areolar tissue of the scrotum. The patient was discharged on the ninth day.

Follow-up.—He was last seen on Nov. 1, 1951, when he had had no further pain or swelling of the testicle, which was of normal size and consistence. Testicular sensation was present.

Case 3.—A boy, aged 16, gave a history of having had a sharp pain in his left groin four weeks earlier. This had eased, leaving a dull ache. Two days later the pain had become more severe, and he had vomited. A swelling in the left side of his scrotum was noted, but his right testicle could not be palpated. His temperature was 102°F. Three days later the swelling increased to "the size of an orange" and was extremely painful. Acute epididymo-orchitis had been diagnosed and treated with sulphonamides without improvement, until a week before admission the swelling subsided and the pain disappeared.

On examination the temperature was 98°F and pulse-rate 80. The right testicle was felt just outside the external inguinal ring. On the left side there was a swelling 2 in. in diameter. The epididymis could not be palpated separately from the swelling.

Operation (Feb. 9, 1950).—Mr. Charles Donald delivered the testicle through a left inguinal incision. It had twisted 180° in a clockwise direction. It was removed and a right-sided orchidopexy was performed.

ÆTIOLOGY

Maldescent

The earlier papers said that most cases were associated with maldescent. There is a simple explanation for this. If the testicle lies in or near the inguinal canal, the patient will present with localised pain, sometimes referred to the abdomen, and a tender irreducible swelling in the groin; often there is vomiting. Such cases are almost indistinguishable from strangulation of an inguinal hernia (so often associated with maldescent), and operation is almost certainly advised.

When the testicle is lying in the scrotum, the signs closely resemble those of acute epididymo-orchitis, and conservative treatment is often recommended.

In the present series all but case 11 concerned fully descended testicles.

Anatomical Anomalies

Far more important is the normal anatomy of the testicle, tunica vaginalis, epididymis, and cord. It is agreed that in all examples of torsion of a fully descended testicle there is some anatomical abnormality. The well-known anomalies are as follows:

(*a*) *Intravaginal epididymis.*—In the normal testicle there is a wide bare area behind the epididymis where the visceral layer of the tunica vaginalis is reflected to form the parietal layer, leaving only a small part of the epididymis in the vaginal sac. As Roche (1928) pointed out, the normal relationship is similar to that of the ascending colon to the peritoneum: there is no mesentery. In many cases of torsion there is a mesentery. This anomaly was well seen in cases 8 and 9.

(*b*) The epididymis is attached at the upper or, more commonly, the lower pole only and passes straight back into the vas.

These, I believe, are the common abnormalities. Roche (1928) described others and emphasised the anchoring effect of the entering blood-vessels. The internal spermatic artery is attached not only at the upper pole but also by branches entering the whole posterior margin. These and the artery to the tail and body of the epididymis will counteract any tendency to rotate round the main pedicle (the internal spermatic artery).

The great majority of torsions are intravaginal and some writers deny the existence of an extravaginal torsion. Campbell (1948), however, reporting 2 cases which occurred on the first day of life, states that both were examples of an extravaginal twist, and his photographs show that this is certainly so.

Trauma

What actually starts the twist seems to be quite unknown. In some cases there has been, as in case 5, a most definite insult to the scrotum, but in many others the torsion develops at rest or even in sleep.

Age

Although the condition has been described in the elderly, it is commonest at about puberty. In this series the ages were 19 months, and 2, 6, 8, 11, 12, 13, 16, 21, 32, and 42 years. The youngest patients in the previously published cases were a child aged 4 hours (Taylor 1897) and Campbell's 2, which also had torsion on the first day of life.

Side

It is curious that in this series the left side was involved in 10 of the 11 cases (in 1 case torsion was bilateral). Roche's 3 cases were left-sided, and in Kennedy's series 8 of 11 were on the left. Aird (1949) states that the right side is involved more often in the proportion 7 : 5, but Kennedy (1948) cites Wallenstein and Abeshouse as having collected 144 right-sided and 142 left-sided.

SYMPTOMS

Pain is a constant feature and is usually of sudden onset. Vomiting is often present, but in this series it was noted in only 4 cases. The pain is referred to the scrotum or the groin according to the site of the testicle. It may be referred to the lower abdomen. It may increase in intensity for a day or two and then gradually subside. Should spontaneous correction take place, there is dramatic relief. Sometimes (cases 2, 4, 6, 8, and 11) there is a history of previous milder attacks.

Difficulty of micturition has been reported in some series. Rigby and Howard (1907) reported that 1 of their patients needed catheterisation, and in the present series the mother of the child aged 19 months noticed that he seemed to be unable to void his urine.

PHYSICAL SIGNS

The signs vary according to whether the testicle is fully descended or not. If the testicle is *in the scrotum*, the overlying skin on that side is red, œdematous, and tender. The scrotal skin may be tethered to the underlying structures. This has been described as Dillon's sign. Extreme tenderness may make precise palpation very difficult, but even under anæsthesia it is usually impossible to distinguish the epididymis from the body of the testis.

In the early stage the patient may be mildly shocked, with a subnormal temperature, as in case 2. More often there is pyrexia; in case 3 it was reported to have been 102°F.

If the testicle is undescended but lying at or near the external inguinal ring, the signs will closely resemble those of a strangulated hernia. As in either event operation is urgently called for, distinction between the two is less important.

In case 1 the left testicle could not be felt in the scrotum, and it must be supposed that pain had elicited a violent and prolonged cremasteric reflex. The parents displayed an astonishing ignorance as to whether the testicle was descended or not.

DIFFERENTIAL DIAGNOSIS

When the testis is not felt in the scrotum, it is extremely difficult to distinguish torsion of an undescended testicle from a strangulated inguinal hernia. If the overlying skin is red and œdematous, it is far more likely to be a case of torsion, for with a strangulated hernia this would be a late sign in a desperately ill patient or (as I have twice seen) due to a foreign body ulcerating through the loop of bowel in a hernial sac. In either event operation is called for.

It is when the testicle is fully descended that mistakes are so often made. All the patients in this series with normally descended testicles, except case 2, were at some stage diagnosed as epididymo-orchitis. I think that, if the following points are borne in mind, error can be avoided:

Age.—Apart from the complication of mumps, epididymo-orchitis must be very rare below the age of 18. Dix (1931) states that cases diagnosed as epididymitis in children are probably examples of torsion of the appendix of the testis. I should add here that it is usually impossible to distinguish between cases of torsion of the testicle and torsion of its appendix (hydatid of Morgagni), for, as McFadden (1939) remarks of the latter, the swelling and œdema are out of all proportion to the minuteness of the lesion.

Sudden pain accompanied by vomiting is more suggestive of torsion.

Absence of symptoms of cystitis and of urethritis should make one suspect torsion.

Palpability of Epididymis.—In cases of acute epididymitis it is nearly always possible to distinguish the enlarged epididymis from the body of the testicle. In cases of torsion it is usually impossible to palpate the two separately.

Redness, swelling, and œdema, which are always present in torsion, are also seen in some cases of acute epididymitis, and on local signs alone the two can in fact be indistinguishable. If these signs are found in a boy about the age of puberty or younger, torsion is almost certainly the correct diagnosis. If they are seen in an adult, acute epididymitis is more likely to be the cause of the symptoms. If, however, there is a complete absence of signs and symptoms suggesting urinary or prostatic infection, torsion has probably taken place. This is the more likely if there is a history of previous attacks of severe pain and swelling lasting only an hour or so.

PROGNOSIS

Spontaneous untwisting often occurs, but unfortunately further attacks of torsion are only too common. If untwisting does not take place, the testicle will undoubtedly become gangrenous. How soon this will happen is unknown: forty-eight hours is the critical time usually mentioned, but no doubt it depends on the number of turns in the twist. If gangrene develops, the testicle will gradually shrink to a small painless fibrous knob no larger than a small marble. I have seen this in 2 cases in boys where reference to their notes showed that they had been previously treated for epididymitis. This process is usually called atrophy, but, as Roche (1928) stated, atrophy is a degenerative process in a living structure, and this is conversion of extravasated blood and the remains of the testicle into fibrous tissue.

If bilateral torsion takes place and gangrene follows on each side, the patient will manifestly be sterile. Whether he loses his libido or not does not seem to be known.

TREATMENT

The early case should always be operated on. If immediate surgery is not available, an attempt should be made to untwist the torsion. Nash (1893) successfully did this by twisting the right testicle to the right after turning it to the patient's left had aggravated the pain. Even if this manœuvre succeeds, the patient should be advised to have a subsequent operation to fix the testicle.

The testicle can be exposed through a scrotal incision and the tunica vaginalis opened. Roche (1928) recommended that the parietal layer of the tunica vaginalis should be preserved, but that one should reproduce the normal sessile type of testicle by incising the posterior layer and suturing the cut edges to the lateral margins of the testicle, so as to reproduce the "bare area." In cases 2, 8, and 10, where the testicle was obviously viable, I excised the parietal layer of the tunica vaginalis and sutured the tunica albuginea to the areolar tissue of the scrotum.

When at operation the testicle is gangrenous it is usually removed. This cuts short the patient's illness and relieves him of pain. I think, however, that if he has already had an orchidectomy on the other side, the torsion should be undone and the gangrenous testicle left in situ. The testicular remnant may preserve some of its interstitial cells and will at least have some psychological value.

The most difficult question to answer is whether or not one should explore the remaining (normal) testicle after a gangrenous one has been removed for torsion. This was done in Kennedy's (1948) first case, but no abnormality was found. If the remaining testicle has ever caused, or ever causes, symptoms suggesting torsion, it should be explored. The risk of operation must be negligible, and I think that, when one testicle has already been lost, that risk should be taken.

In the absence of such a history it is probably wiser to explain the position to the patient or his mother, and to emphasise the need for early medical advice at the first symptom.

Discussing this problem Kennedy (1948) cites the figures given by Riba and Schmidlapp (1946) as an argument against an exploratory operation—of 489 collected cases only 26 were bilateral.

SUMMARY

Twelve examples of torsion of the testicle or its appendix occurring in 11 patients are described.

Where the testis is fully descended, the condition is usually diagnosed as acute epididymo-orchitis with the result that gangrene often supervenes before operation is undertaken.

This differential diagnosis is discussed, and a plea is made for wider recognition of the true diagnosis.

Operation is advised in all cases if seen early enough.

I am greatly indebted to Mr. G. E. Neligan, Mr. Alan Perry, Professor Dix, Mr. Charles Donald, and Mr. G. C. Tresidder for permission to publish cases admitted under their care, and to Professor Dix for help in preparing this paper. Case 11 is published by permission of Dr. J. Harris, physician-superintendent of Claybury Mental Hospital, and Mr. E. C. B. Butler, of the London Hospital.

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"In the middle of the nineteenth century the whole orientation of Surgery was shifted by the work of Simpson on anæsthetics and Lister on the control of infection. Operations became more common, and surgeons, inspired by the possibilities of this new field, became technicians, so that surgical technique in the modern sense was born. Advances in Operative Surgery were made rapidly and no organ was exempt from the encroachments of the surgeon's knife. The surgeon moved his home to the operating theatre and the ward became his week-end cottage.... What of the future? Slowly but surely there is a drift back from the theatre to the ward. Surgeons are coming to realise that, in their 'gold rush' from the first field to the second, much had been left behind that was uncultivated. In nine cases out of ten one surgeon of experience will perform the operation as well as another and, if our results are to improve, it will come once more from a study of the processes of healing and repair. We appreciate that when the patient leaves the theatre our job is but half done and that the convalescence, the subsequent health, or even the chances of survival may be prejudiced by the kind of after-treatment which he will be given."—H. J. B. ATKINS. *After-Treatment.* London, 1952; p. xv.

MEGALOBLASTIC ANÆMIA OF PREGNANCY

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MEGALOBLASTIC anæmia of pregnancy (the so-called pernicious anæmia of pregnancy) is usually held to be rare. Davidson (1951) saw 42 cases at Edinburgh between 1940 and 1951; Thompson and Ungley (1951) at Newcastle had records of 46 cases seen in 17 years; and a recent estimate from New Orleans (Lund 1951) states that 1 case of megaloblastic anæmia occurs to every 100 of iron-deficiency anæmia.

In most of the published cases the patients had severe anæmia when first diagnosed, and the disease was more often first discovered in the puerperium than before labour; for instance, only 8 of Thompson and Ungley's 46 patients were diagnosed before labour. In our opinion, now that antenatal supervision is so much more common, and now that better diagnostic methods are available, many more patients could be diagnosed during pregnancy, and some undoubtedly are disguised as "refractory anæmias" in pregnancy that clear up after labour. The early diagnosis of megaloblastic anæmia of pregnancy is of much practical importance for the patient, since we have, in folic acid, a means of treating these patients effectively.

TREATMENT WITH FOLIC ACID

Soon after folic acid was discovered to be effective in the megaloblastic anæmia of sprue and in addisonian pernicious anæmia, it was applied to megaloblastic anæmia of pregnancy and good results were reported by Moore et al. (1945) and by Spies (1946). Subsequent results have confirmed these early reports: Davidson et al. (1948) reported 4 successfully treated cases; Thompson and Ungley (1951) had a poor response in only 1 out of 7 patients treated. When vitamin B_{12} was introduced it was soon found to have no effect on megaloblastic anæmia of pregnancy as it occurs in temperate climates; the original report by Day et al. (1949) has been confirmed by others since. Folic acid therefore remains the treatment of choice for the megaloblastic anæmia of pregnancy, and its use in properly diagnosed cases can at least ensure that the patient is in reasonable condition to face her labour.

We describe here 6 cases, 5 of which were found within a period of six months when a special effort was made to find them; 4 patients were diagnosed during pregnancy. The patients were all seen in the antenatal clinic or in the wards at St. Mary's Hospitals, Manchester, and all have been successfully treated with folic acid.

CASE-RECORDS

Case 1.—This patient, aged 25, was 24 weeks pregnant in her second pregnancy when first seen at the antenatal clinic in April, 1947. There was no history of anæmia in the family or during her previous confinement; there had been occasional attacks of diarrhœa during this pregnancy, lasting 2–3 days at a time. On July 12, 1947, she appeared pale, listless, and ill, and she was admitted to the ward for investigation of severe anæmia. A blood-count showed Hb 5·6 g. per 100 ml., red cells 1,900,000 per c.mm., colour-index 1·0, and white cells 2600 per c.mm. She had complained of painful ulcers in her mouth for several days; these were superficial symmetrical ulcers on the tongue, pharynx, epiglottis, and nasal septum, 0·5–1·0 cm. in diameter, with yellow sloughing bases and raised reddened margins. The Wassermann reaction was negative. There were no abnormal neurological signs. Sternal-marrow puncture revealed a predominantly megaloblastic marrow. Fractional gastric analysis showed a normal acid stomach content.

Treatment with folic acid 20 mg. daily by mouth was started. This was followed by a reticulocyte peak of 31% on July 20, and by July 24 a blood-count showed Hb 6·4 g. per 100 ml. and red cells 2,580,000 per c.mm. A sternal-marrow puncture was repeated, and this showed very few megaloblasts remaining.

Normal delivery of a living full-term child took place on Aug. 12. A blood-count on Aug. 21 showed Hb 10·4 g. per 100 ml., red cells 3,600,000 per c.mm., and colour-index 0·97.

Diet.—Careful inquiry revealed that the patient's diet had been full and adequate for pregnancy, and she had not been troubled by vomiting. After leaving hospital the patient was given desiccated stomach powder for two months. Thereafter she had no treatment. Seen on Jan. 4, 1952, she was in excellent health, with Hb 11·7 g. per 100 ml. and red cells 4,160,000 per c.mm.

Case 2.—This patient, aged 27, had had three previous normal confinements without anæmia. A month before term in her fourth pregnancy she was very pale, with a tinge of icterus, and a blood-count showed Hb 5·9 g. per 100 ml., red cells 3,581,000 per c.mm., colour-index 0·65, and white cells 9000 per c.mm. Her tongue, mouth, and throat had felt sore, and she had difficulty in swallowing. A course of intravenous iron injections was started, but the amount of hæmoglobin and the red-cell count remained stationary. A sternal-marrow puncture showed well-marked megaloblastic hyperplasia. A further blood-count showed Hb 6·3 g. per 100 ml., red cells 1,980,000 per c.mm., colour-index 1·13, and white cells 5000 per c.mm. A test-meal was abandoned because the patient could not retain the Ryle's tube.

Treatment was begun with folic acid 100 mg. in a saline intravenous drip, followed by 20 mg. by mouth daily. She began to feel much better.

Normal delivery took place on Nov. 24, 1951. A blood-count on Dec. 3 showed Hb 13 g. per 100 ml., red cells 3,840,000 per c.mm., colour-index 1·13, and white cells 6100 per c.mm.

Diet.—There had been a serious deficiency of meat and green vegetables, and the patient admitted that she did not spend much on food. Her appetite had been poor during pregnancy, partly owing to nausea and occasional vomiting.

Follow-up.—She was last seen on April 8, 1952, when a blood-count showed Hb 11·7 g. per 100 ml., red cells 4,120,000 per c.mm., colour-index 0·96, and white cells 6250 per c.mm. She had had no folic acid for four months.

Case 3.—This patient was a primigravida, aged 24, whose anæmia became apparent in the puerperium. She was delivered of twins on April 5, 1951, when she had a postpartum hæmorrhage of about 20 oz. She was transfused at the time with 2 pints of blood. Tachycardia and slight pyrexia followed, and she appeared still very anæmic.

On examination the spleen was just felt. A blood-count showed Hb 6·8 g. per 100 ml., red cells 2,180,000 per c.mm., and colour-index 1·09. A sternal puncture showed the red-cell series to be extremely active, with a very high proportion of pro-erythroblasts; some definite transitional megaloblasts were present. A fractional test-meal revealed a normal acid secretion.

Folic-acid therapy was started with 30 mg. intramuscularly for the first three days, and continued with 20 mg. daily by mouth thereafter. Subsequent blood-counts were:

May 7	Hb	11·5	g./100 ml.,	red cells	3,920,000/c.mm.,	c.i.	1·00
June 18	,,	13·0	,,	,,	4,420,000	,,	1·00
Nov. 5	,,	13·9	,,	,,	4,910,000	,,	0·96

Folic-acid therapy was discontinued on June 18, 1951. Inquiry revealed no personal or family history of anæmia.

The patient's diet had been notably deficient in meat and green vegetables; the bulk consisted of potatoes or other cooked root-vegetables, supplemented by cake, biscuits, or bread.

Case 4.—Normal full-term delivery took place on Oct. 11, 1951, in this 2-para aged 37. Because of extreme pallor 18 days after delivery a blood-count was done, which showed Hb 8·1 g. per 100 ml., red cells 2,590,000 per c.mm., colour-index 1·1, and white cells 9400 per c.mm. For 3 weeks before delivery she had felt rather weak and had noticed that her tongue was sore and "raw." Sternal-marrow puncture showed a hyperplastic megaloblastic picture. Fractional gastric analysis revealed achlorhydria.

Folic acid 20 mg. daily orally was given with the following results:

Nov. 9	Hb	10·1 g./100 ml.,	red cells	2,490,000/c.mm.,	c.i.	1·30
,, 16	,,	11·5 ,,	,,	3,000,000 ,,	,,	1·26
Dec. 7	,,	13·9 ,,	,,	3,670,000 ,,	,,	1·30
Jan. 25	,,	14·1 ,,	,,	4,650,000 ,,	,,	1·03

Inquiry revealed, once more, no history of anæmia or of dietary deficiency. Folic-acid treatment was stopped in February, 1952, and so far the patient has remained well.

Case 5.—A 2-para, aged 26, expected confinement on Dec. 2, 1951. On Nov. 19 she complained of sore tongue, gradual loss of weight, and dyspnœa on exertion.

On examination she was not very pale, but her tongue was red, smooth, and swollen. A blood-count showed Hb 11·6 g. per 100 ml., red cells 3,100,000 per c.mm., colour-index 1·22, white cells 5200 per c.mm. Sternal-marrow puncture showed a megaloblastic hyperplasia with many hæmocytoblasts and pro-erythroblasts. Fractional gastric analysis showed a normal acid content.

Folic-acid therapy was started with 30 mg. intramuscularly, and continued with 20 mg. by mouth daily thereafter. By Nov. 26, 1951, the tongue was no longer sore and red, though it was still smooth and glazed. A blood-count, however, showed no change.

Normal delivery took place on Nov. 29, and a blood-count on Jan. 17, 1952, showed Hb 14·2 g. per 100 ml., red cells 4,540,000 per c.mm., colour-index 1·06, and white cells 5450 per c.mm.

Diet.—There had been no previous history of anæmia before or during the previous pregnancies, and for 6–8 weeks before the start of folic-acid therapy the soreness of her tongue had prevented her from eating almost anything. A week after the start of treatment she could eat again. The diet itself revealed no gross deficiencies.

Case 6.—This patient, aged 29, was about 5 months pregnant in her seventh pregnancy when first seen at the antenatal clinic. There was a history of anæmia in her fifth pregnancy, treated with iron and "liver injections." There was some pallor evident at her first attendance, and a blood-count showed Hb 7·4 g. per 100 ml., red cells 3,912,500 per c.mm., colour-index 0·65, and white cells 15,600 per c.mm. She was given large doses of iron by mouth, under the care of her own doctor, but at the 34th week of pregnancy her hæmoglobin was still only 8·1 g. per 100 ml.; so she was admitted to the ward and given a transfusion of 2 pints of packed red cells; this increased the hæmoglobin to 10·2 g. per 100 ml. Two weeks later a blood-count showed Hb 8·6 g. per 100 ml., red cells 3,650,000 per c.mm., colour-index 0·8, and white cells 10,500 per c.mm. A sternal-marrow puncture showed well-marked hyperplasia with some transitional megaloblasts and large metamyelocytes. A mixed iron-deficiency and megaloblastic anæmia of pregnancy was diagnosed.

Treatment was begun with folic acid 20 mg. by mouth daily, together with oral iron as before. Fractional gastric analysis showed a normal stomach acid content, and on Nov. 26, 1951, a blood-count showed Hb 9 g. per 100 ml., red cells 3,900,000 per c.mm., colour-index 0·78, and white cells 7200 per c.mm.

Normal delivery took place on Dec. 3, but was complicated by a postpartum hæmorrhage of about 40 oz. On the 3rd puerperal day the Hb was only 8·7 g. per 100 ml., and on the 5th day the patient was given 1 pint of packed red cells, after which the hæmoglobin rose to 10·5 g. per 100 ml. On the 18th day after delivery she was discharged home, and continued with folic acid and iron by mouth.

Follow-up.—She was last seen on Jan. 7, 1952, when she had a much better colour and a blood-count showed Hb 12·5 g. per 100 ml., red cells 4,330,000 per c.mm., colour-index 0·98, and white cells 9450 per c.mm.

Diet.—Her diet appeared to have been quite adequate, and vomiting had not seriously interfered with this. She admitted to having had a sore tongue shortly before admission at the 34th week of pregnancy, without ulceration.

DISCUSSION

The average age of our patients was 29, and only 1 had had anæmia before, of unknown type, in pregnancy. 5 patients developed sore tongue with or without buccal ulcers; 5 had dyspnœa on exertion; 1 complained of dysphagia; vomiting in late pregnancy was slight in 2; and 2 had short bouts of diarrhœa. None showed any abnormality in the central nervous system.

Diagnosis in all our cases depended on examination of the sternal marrow. This procedure is essential in severe anæmia of pregnancy or of the puerperium, particularly in the patient who begins with an iron-deficiency anæmia but responds disappointingly even when intravenous iron is given. The bone-marrow picture is sometimes classically megaloblastic, but more often there are many pro-erythroblasts and normoblasts, and relatively few megaloblasts. In the early cases the picture shows "transitional" erythroblasts and typical large metamyelocytes (see Israëls 1951). Fractional gastric analysis is also important; 4 of our patients had free hydrochloric acid. The achlorhydric patients should be followed for at least twelve months after treatment has been stopped, in case they turn out to have addisonian pernicious anæmia; in practice this development is unusual, but case 4 in our series is a possible example. Ideally the achlorhydric patient should be given a course of vitamin B_{12} first, to see if she responds; but only too often time is too short, and the hæmoglobin level too low, to allow this experiment.

All our patients were treated with folic acid. This is usually given orally in a dose of 20 mg. daily; but, if time is short, it can be given intramuscularly (30 mg. daily for three days) or intravenously (100 mg. diluted in 250 ml. of saline solution given through the usual drip apparatus). Maintenance with a daily oral dose of 20 mg. of folic acid should be continued into the puerperium until the blood-count has been normal for a month; folic acid can then be withheld, but the blood-count should be checked again later.

Some of the patients treated with folic acid who have not had previous iron treatment later develop an iron-deficiency type of anæmia that will need oral iron as well as folic acid. If the woman is first seen very late in the pregnancy, or has severe blood-loss at labour, blood-transfusion may be needed to tide over the immediate emergency; but, of course, treatment with folic acid, and iron if needed, should be begun as soon as possible.

The prognosis, especially if the patient is seen and the condition diagnosed and treated well before labour, is excellent for both mother and child. For this reason we emphasise the importance of being on the alert for the early case of megaloblastic anæmia of pregnancy; and it should be remembered that the peripheral blood picture may be atypical, especially if the common iron-deficiency anæmia is present as well. Bone-marrow biopsy is essential to make the diagnosis certain.

SUMMARY

Six cases of megaloblastic anæmia of pregnancy which responded satisfactorily to folic-acid treatment are described.

The paramount importance of bone-marrow biopsy for correct diagnosis is emphasised.

The possibility that megaloblastic anæmia is present should always be considered when an anæmic pregnant patient does not respond as expected to iron.

Details of folic-acid treatment are given.

We are indebted to Dr. R. Newton and other members of the consultant staff at St. Mary's Hospitals, Manchester, for facilities for investigating patients under their care.

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THE LEFT AURICULAR PRESSURE PULSE IN NORMALS AND IN MITRAL VALVE DISEASE

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THE left auricular pressure has been directly recorded at operation in 37 patients, before and after valvulotomy, and in 14 patients with normal hearts during thoracotomy for various pulmonary diseases. The objects were to determine:

1. The form of the normal left auricular pressure pulse.
2. The form of the left auricular pressure pulse in mitral valve disease.
3. The changes in left auricular pressure following mitral valvulotomy.

We hoped to detect gross mitral incompetence unrecognised clinically, so as to spare such patients a needless digital exploration of the valve with its risk of systemic embolism. This object was not fully attained.

METHODS

Pressures were recorded through fine needles (21–23 s.w.g.) attached to cardiac catheter tubing * with acrylic cement.† The tubing bore was 1 mm., its length 1 metre. An electromanometer (Sanborn) and direct writer were used to record the pressure and electrocardiogram (lead I) simultaneously at a paper speed of 25 mm. per second. Some pressures, however, were recorded at 50 mm. per second. The level of the left auricle was taken as zero. Each recording was calibrated with a mercury manometer.

In the patients with mitral stenosis the needle was inserted into the intact left auricle with the pericardium open. The post-valvulotomy tracings were taken after the auricle had been sewn up. In the control series the pericardium was not opened, the needle being passed into the auricle through a pulmonary vein. In 3 patients a right auricular tracing was recorded simultaneously with the left. For some of the records a fine stylus was used, and these tracings have been darkened for reproduction.

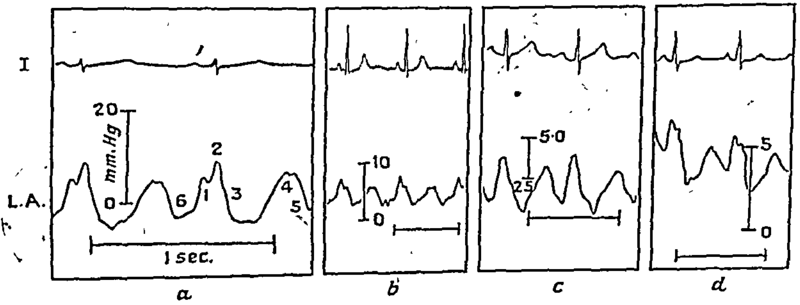

Fig. 1—Simultaneous lead I (E.C.G.) and left auricular pressure tracing in 4 patients with normal hearts. Time base = 1 sec. Pressures = mm. Hg.

The anæsthetic agents were thiopentone, curare, and a 50% oxygen/nitrous oxide mixture. Respiration was arrested during the recording of the pressures.

Mitral valvulotomy was performed digitally.

RESULTS

Left Auricular Pressure in the Normal Heart

The form of the left auricular pressure tracings were similar in the 14 patients. There were six main features, best illustrated by fig. 1*a*, which was recorded at a paper speed of 50 mm. per second:

(1) A wave, due to auricular systole, whose peak preceded the Q R S complex. Its amplitude, measured from the level at the end of diastole, varied in the 14 patients from 2 to 8 mm. Hg.

(2) A deflection beginning at the end of the Q R S complex—i.e., at the onset of ventricular systole. This was sometimes only just identified (fig. 1*b*) or absent (fig. 1*c*).

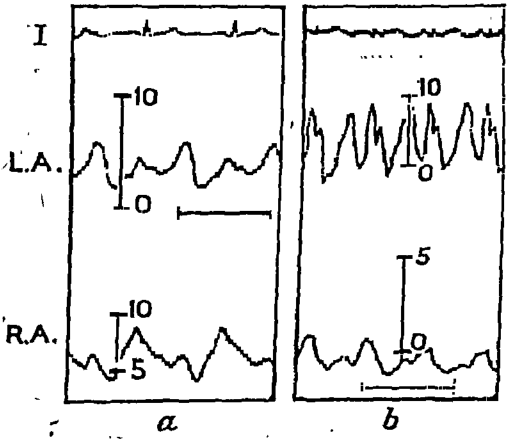

Fig. 2—Simultaneous lead I (E.C.G.) and left auricular and right auricular pressure tracings in 2 patients with normal hearts.

(3) A fall in pressure in early ventricular systole usually reaching to near the level at the end of diastole.

(4) A rise in pressure during late ventricular systole reaching a peak 0·04–0·12 sec. after the end of the T wave and measuring 1–9 mm. Hg above the pressure at the end of diastole.

(5) A steep fall in pressure at the opening of the mitral valve.

(6) A slight rise preceding auricular systole.

The left and right auricular pressure pulses recorded simultaneously (fig. 2*a* and *b*) were similar in form, although the amplitude of the late systolic wave in the left auricle was greater than in the right. The peaks of these waves were synchronous.

Left Auricular Pressure Pulse in Mitral Stenosis

No patient with clinical or operative evidence of mitral incompetence has been included.

With sinus rhythm.—This group comprised 19 patients. The form of these tracings, with some exceptions, resembled the normal (fig. 3*a*, *b*, and *c*), although the pressures were higher.

The pressure rise with auricular systole was surprisingly small, ranging from 1 mm. Hg (fig. 3*d*.) to 11 mm. Hg

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* Provided by W. H. Bailey, 2, Rathbone Street, W.1.

† 'Dentafil' (Dental Fillings Ltd., London, N.16).

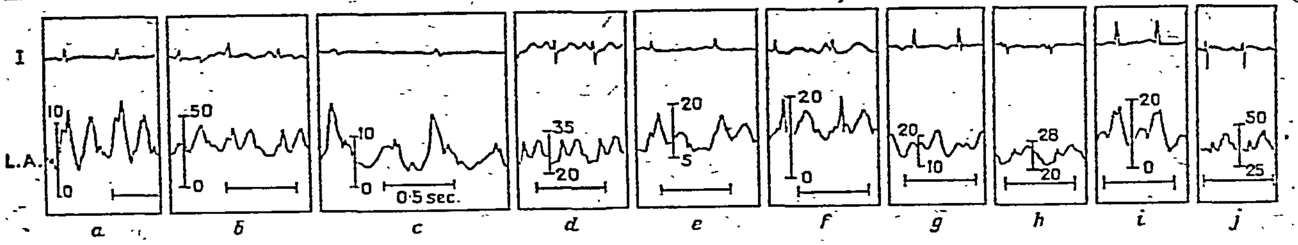

Fig. 3—Simultaneous lead I (E.C.G.) and left auricular pressure tracings in patients with mitral stenosis and sinus rhythm.

(fig. 3c) above the level at the end of diastole. It tended to be greatest when this level was low.

The pressure rise at the onset of ventricular contraction was usually greater than in the normal and began close to the peak of the auricular systolic wave (fig. 3e). Vibrations due probably to the first heart sound were sometimes also recorded at this time (fig. 3f).

The fall of pressure in early ventricular systole was as great as the normal in some patients (fig. 3a, b, c, f, and i) but slight or almost absent in 4 others—e.g., fig. 3g and h.

The pressure rise in late ventricular systole varied from 3 mm. Hg (fig. 3i) to 19 mm. Hg (fig. 3b) above the end diastolic level. The peak was closer to the end of the T wave (0·0–0·06 sec.) than in the normal.

With auricular fibrillation.—There were 18 patients in this group. The pressure in these patients rose sharply at the onset of ventricular contraction (figs. 4a–e and 5) and remained raised throughout. There was little or no drop in early systole except after a long preceding diastole (fig. 6a). In some tracings there was a considerable further rise in late systole—e.g., fig. 4e.

The pressure rise during ventricular systole tended to be greater when the end-diastolic pressure was high. Thus it was greater after a short preceding diastole than after a long one (fig. 6a) and greatly increased by tachycardia (fig. 6b).

The late systolic pressure peaks measured 3–16 mm. Hg above the preceding end-diastolic levels.

Left Auricular Pressure Pulse with Mitral Incompetence

Significant mitral incompetence was judged to be present at operation in 5 patients. Clinically an apical systolic murmur and considerable left auricular enlargement were also present. In 3 of these patients, with sinus rhythm, strong regurgitant jets were felt. The left auricular tracings (figs. 7a and b and 8) resembled those in patients with no evidence of mitral incompetence (compare with fig. 3j, f, and h respectively).

The auricular pressure rose sharply at the onset of ventricular contraction but then dropped in 2 patients to the end-diastolic level. The subsequent rise in late systole, measured from this level, was 25 mm. Hg in 1 patient (fig. 7a)—i.e., greater than the range seen in mitral stenosis alone—but only 8 mm. Hg in the other 2.

In the remaining 2 patients, who had auricular fibrillation, considerable mitral incompetence was considered to be present although no jet was felt. In each the orifice of the valve was about $1^1/_2$ times the diameter of the distal phalanx of the surgeon's index finger. The rigid calcified margins were felt to gape during ventricular contraction; no jet was felt, presumably because the mitral opening was relatively large. The left auricular tracings in these patients (fig. 7c and d) were similar to those obtained in mitral stenosis and auricular fibrillation. The pressure rise measured from the level at the end of the preceding diastole to the peak in late systole was 12 and 6 mm. Hg.

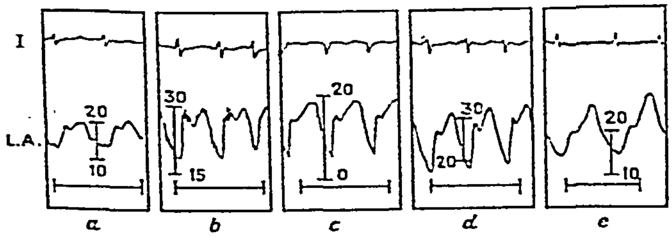

Fig. 4—Simultaneous lead I (E.C.G.) and left auricular pressure tracings in patients with mitral stenosis and auricular fibrillation.

Changes in Left Auricular Pressure Pulse After Valvulotomy

The changes in left auricular mean pressure after valvulotomy and the correlation between this and the clinical response will be published separately.

There were few significant changes in the form of the left auricular pressure pulse after operation, even in 3 patients in whom some mitral incompetence was produced. This was shown by a strong regurgitant jet and the development of a loud systolic murmur in the mitral area. In these patients, although the end-diastolic pressures in the auricle were lower after operation (fig. 9), the degree of pressure rise from the level at the end of diastole to the peak in late systole remained approximately the same, measuring 15, 8, and 7 mm. Hg compared with 14, 10, and 8 mm. Hg before operation.

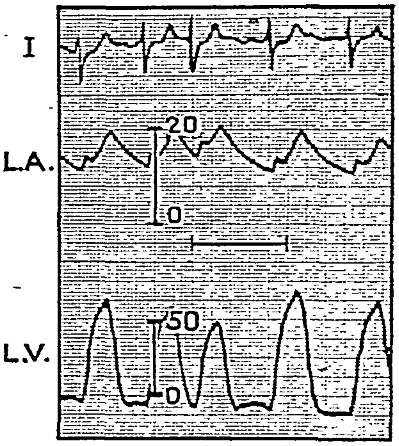

Fig. 5—Simultaneous lead I (E.C.G.) and left auricular and left ventricular pressure tracings in a patient with mitral stenosis and auricular fibrillation.

DISCUSSION

Hitherto only one left auricular pressure tracing in a normal human heart has been published (Munnell and Lam 1951), and this seems overdamped. However, tracings from the left auricle obtained by venous catheterisation in patients with atrial septal defects have been published by Cournand et al. (1947), Lagerlöf and Werkö (1949), and Calazel et al. (1951). In general the form of these curves is similar to our own.

The greater amplitude of the late systolic wave in the left auricle compared with the right has been shown to exist also in dogs by Opdyke et al. (1948). They attribute the difference to a lesser capacity and elasticity of the left auricle and pulmonary veins compared with the right auricle and systemic veins.

In the patients with mitral stenosis the pressure rise with auricular systole tended to be

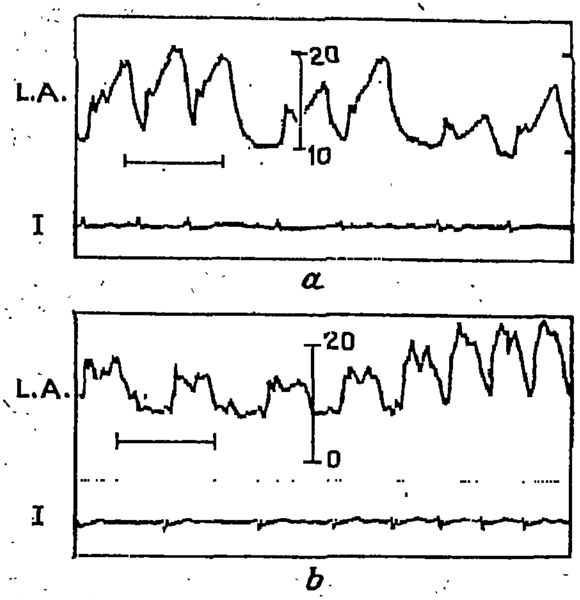

Fig. 6—Simultaneous left auricular pressure tracing and lead I (E.C.G.) in 2 patients with mitral stenosis and auricular fibrillation.

small, especially when the stenosis was severe, and the pressure at the end of diastole high. This pattern of response is familiar in relation to over-distension of the ventricular chambers (Wiggers 1952). The comparative weakness of auricular contraction may also be due to involvement of its myocardium in the rheumatic process, for Aschoff nodules were found in 30% of the auricular appendages amputated at operation (Pinniger 1952).

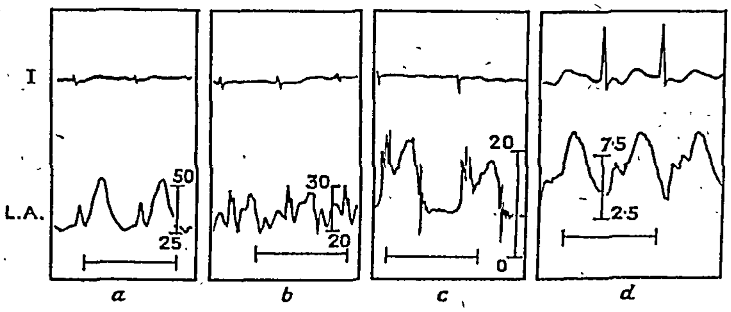

Fig. 7—Simultaneous lead I (E.C.G.) and left auricular tracing in 4 patients with mitral incompetence: *a*, *b*, sinus rhythm; *c*, *d*, auricular fibrillation.

The factors involved in the pressure changes in the auricle during ventricular systole in patients with mitral disease are complex, and detailed discussion must await the production of further data.

The pressure rise in the auricle with the onset of ventricular contraction may be due to inward bulging of the floor of the auricle and of the mitral valves. This was sometimes felt by the surgeon and is supported by observations on the movements of mitral calcification at fluoroscopy (Froment et al. 1950, Wynn 1952).

The variations in amplitude of the late systolic wave in the auricle is noteworthy. The factors which determine this may include the inflow from the pulmonary veins, mitral reflux, movements of the floor of the auricle, and the capacity and elasticity of the left auricle and pulmonary veins. The part played by mitral incompetence was difficult to evaluate because of the error inherent in the diagnosis of mitral reflux by palpation. Moreover, patients in whom mitral incompetence was thought on clinical grounds to be the predominant lesion were not submitted to operation. In only 2 of the 5 patients in whom mitral incompetence was found at operation was there no significant stenosis.

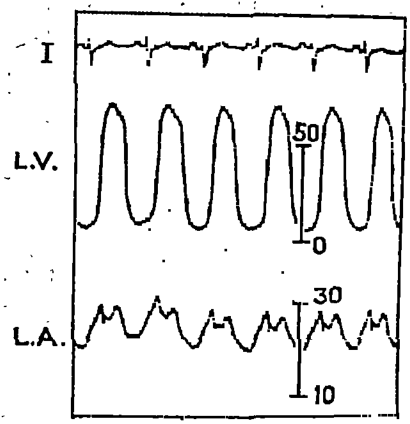

Fig. 8—Simultaneous lead I (E.C.G.) and left ventricular and left auricular pressure tracings in a patient with mitral stenosis and incompetence in sinus rhythm.

The experiments of Wiggers and Feil (1922) in dogs, which we have repeated and confirmed, suggest that mitral incompetence should increase the height of the late systolic wave. However, we have found at operation that the late systolic peak was as high in mitral stenosis as in 4 of the 5 patients with mitral incompetence and in the 3 patients in whom mitral incompetence was produced acutely by operation.

These observations are relevant to recent attempts to diagnose mitral incompetence from the prominence of the late systolic wave in "pulmonary capillary" tracings which are thought to reflect the pressure changes in the left auricle (Lagerhöf and Werkö 1949; Gorlin et al. 1952). These workers also consider that the absence of a fall in pressure in early ventricular systole in "pulmonary capillary" tracings is characteristic of mitral incompetence. However, in our left auricular tracings there was no pressure fall in early ventricular systole in 5 patients in sinus rhythm, of whom only 1 had evidence of mitral incompetence at operation. Moreover, this fall in pressure was slight or absent in all the patients with mitral stenosis and auricular fibrillation.

In the patients with auricular fibrillation the abrupt and sustained auricular pressure pulse with ventricular systole was striking. Its greater prominence when the end-diastolic pressure in the auricle was high, and the variations in its form and amplitude with the length of the preceding diastole (fig. 6*a*), underline the importance of the distension of the auricle at the onset of ventricular systole in determining the pressure changes within it. Thus with the decrease in distension at the end of a long diastole the sub-

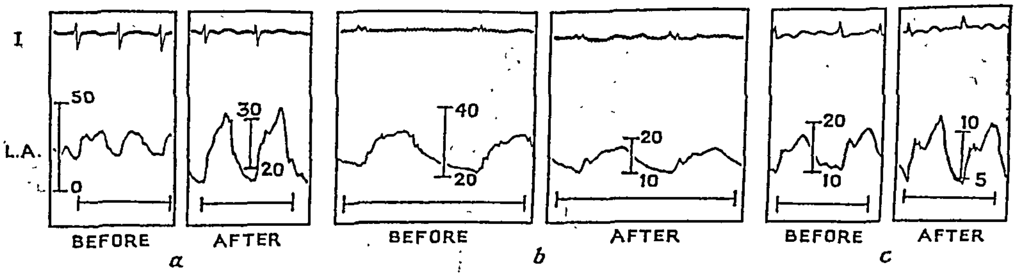

Fig. 9—Simultaneous lead I (E.C.G.) and left auricular pressure tracings before and after valvulotomy in 3 patients with mitral stenosis and auricular fibrillation who developed mitral incompetence after operation.

sequent rise with ventricular systole was smaller. If mitral reflex was the main factor causing this rise in pressure, this response would not be expected. The greater ventricular filling after a long diastole leads to a higher systolic pressure peak in the left ventricle (fig. 5) and hence a greater pressure differential between the left ventricle and left auricle. In these circumstances mitral reflux and the auricular pressure changes resultant from it should increase.

SUMMARY AND CONCLUSIONS

The left auricular pressure pulse has been studied at thoracotomy in patients without heart-disease and before and after mitral valvulotomy in patients with mitral valve disease.

In 14 normal persons the pressure rise with auricular systole was 2–8 mm. Hg, and the pressure rise in late ventricular systole 1–9 mm. Hg. The form of the pulse in the left auricle resembled that in the right, but the pressure rise in late systole was greater.

In mitral valve disease with sinus rhythm the form of the auricular pressure pulse usually resembled the normal, though the pressures were higher. The pressure rise with auricular systole above the level at the end of diastole was 1–11 mm. Hg and in late ventricular systole 3–19 mm. Hg.

In auricular fibrillation the auricular pressure rose abruptly with the onset of ventricular contraction. There was usually little fall in pressure in early systole and a variable further rise in late systole, but this was modified by the length of the preceding diastole.

The pressure peak in late systole was 2·5–16·0 mm. Hg above the previous end diastolic level.

In 8 patients with evidence of mitral incompetence, including 3 in whom this developed after valvulotomy, no significant difference in the form of the left auricular pressure pulse was found from those considered to have mitral stenosis alone. However, in 1 patient, in sinus rhythm, with preoperative mitral incompetence, the pressure rise in late systole was 25 mm. Hg.

In the presence of mitral stenosis, mitral regurgitation does not appear to produce any qualitative change in the form of the left auricular pressure tracing. Quantitative changes are difficult to assess because the major variable which determines them is the degree of distension of the auricle at the onset of ventricular contraction.

We are deeply grateful to Mr. N. R. Barrett and Mr. M. Meredith Brown for their patient coöperation in the operating-theatre. We should like to thank Dr. Evan Jones and Dr. A. C. Dornhorst for their helpful advice and criticism, Dr. James Sharkey for assistance in the early part of the investigation, Miss Z. Taylor for technical aid, and Mr. A. L. Wooding for reproduction of the tracings. The cost of the investigation was partly defrayed by a grant from the St. Thomas's Hospital Endowments Fund.

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FORMATION OF IMMUNE A ISO-ANTIBODIES

WITH SPECIAL REFERENCE TO HETEROGENETIC STIMULI *

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UNTIL comparatively recently little stress has been laid upon qualitative differences between immune and naturally occurring forms of anti-A. Previously it was considered that any strong anti-A serum would hæmolyse A cells if complement were present. Apparent discrepancies between the iso-agglutinin content of a serum and its hæmolytic effect were thought to be due to failure to standardise the amount of complement in the test (Wiener 1943). Nevertheless, as early as 1941 Wiener called attention to the change in the thermal optimum of anti-A agglutinins following incompatible transfusions and suggested that this might be a valuable sign of the formation of "immune antibody." This implied that qualitative differences existed between immune and naturally occurring forms.

The next qualitative difference to be demonstrated was that revealed by performing titrations in a medium of serum. Boorman, Dodd, and Morgan (1945) observed that, when anti-A sera were tested in doubling dilutions against A cells, their reactivity might be enhanced by diluting with serum rather than with saline solution. This effect was not observed when testing naturally occurring anti-A and was only observed when testing sera from people who had recently received an A stimulus.

Meanwhile an "incomplete" or "blocking" form of Rh antibody had been described (Race 1944, Wiener 1944), and it had been shown that this form of antibody was more heat-stable than the ordinary agglutinin. Boorman and Dodd (1946) demonstrated a similar form of antibody in two immune anti-A sera. They showed that by heating the serum to 75°C for twenty minutes its power of agglutinating cells suspended in saline solution was abolished, but that it would now "block" the reaction between A cells and naturally occurring anti-A. Moreover, A cells which were exposed to the heated serum and washed were agglutinated by an anti-globulin serum.

Witebsky (1948) described some further characteristics of immune anti-A sera. He showed that, if certain anti-A sera were treated with AB substance so that they would no longer agglutinate A cells suspended in saline solution, they would nevertheless agglutinate the same cells suspended in serum. Treatment of the sera with an appropriate dose of A substance was described as "partial neutralisation." Witebsky also showed that the same immune sera, unlike control sera, would fix complement in the presence of soluble A substance.

Ervin and Young (1950) and Ervin et al. (1950) studied hæmolytic transfusion reactions caused by the transfusion of group-O blood to group-A people. They found that in every case the donor's serum displayed the "immune" characteristics described by Witebsky. They extended Witebsky's observations by showing that partially neutralised immune anti-A sera would sensitise A cells to an anti-globulin serum. They also found that the sera of 12 out of 100 random group-O donors displayed "immune" characteristics.

The present paper describes the incidence of these "immune" forms of anti-A in a sample of the English

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[*] A short account of these findings was given to the International Congress of Clinical Pathology in July, 1951.

population. It also describes the development of these forms in people receiving various stimuli, and shows that injections of certain vaccines and animal sera often lead to the production of "immune" anti-A. Finally, attention is drawn to the probable clinical importance of these antibodies.

Methods

Titration in Saline Solution

Doubling dilutions of the test serum were made in saline solution in "agglutinin tubes" of 6 mm. diameter. The diluted serum in each tube was mixed with an equal volume of a 2% suspension of cells in saline solution (0·2 ml. of packed cells + 9·8 ml. saline). For anti-A titrations cells of subgroup A_1 were used. In some cases a direct dilution of 1/200 was made by adding 0·02 ml. serum to 4 ml. saline. One volume of this dilution was mixed with an equal volume of a 2% suspension of cells.

In all the cases the mixtures were examined for agglutination after two hours at room-temperature. The reciprocal of the highest dilution which produced clumps of 8–12 cells ("(+)" in the notation of Taylor et al. 1942) was recorded as the titre of the serum. The convention was adopted of ignoring the volume of cell suspension in calculating the final dilution of the serum.

Titration in Serum

The technique described for titrations in saline solution was followed, except that the test cells were suspended in group-AB serum and that AB serum was used instead of saline solution as the diluting medium.

Detection of Hæmolysins

Whenever possible, a fresh sample of serum was obtained for testing for hæmolysins. In these cases one volume of serum was mixed with a 5% suspension of cells in saline solution. After standing at 37°C for two hours the mixture was agitated and centrifuged, and the supernatant fluid was examined. The results were recorded as follows:

Complete hæmolysis	+ + +
50% hæmolysis ..	+ +
20% hæmolysis ..	+
Trace hæmolysis ..	tr.
No trace of pink colour	0

When the serum could not be tested on the day of taking, complement was added in the form of fresh human serum. For this purpose a single donor of group O was used whose serum contained weak anti-A and anti-B agglutinins and no anti-A or anti-B hæmolysin. Occasionally, fresh AB serum was used as a source of complement; and it was noted that if the AB serum was added to the anti-A serum before the addition of the test cells, hæmolysis might be inhibited, as originally observed by Moss (1910). This inhibition could be minimised by suspending the test cells in AB serum before adding them to the anti-A serum.

Indirect Anti-globulin Tests using "Partially-neutralised" Serum

Sera were tested as follows:

One volume of serum was added to each of three tubes. To tube 1 was added a half-volume of saliva from an A or B secretor; to tube 2 one volume of saliva; and to tube 3 two volumes of saliva. After half an hour at room-temperature one drop of a 50% suspension of test cells (A_1 or B) in saline solution was added to each tube. The mixtures were incubated at 37°C for two hours and examined for macroscopic agglutination. The unagglutinated mixtures were washed three times in saline solution, and the cells finally resuspended in 2 drops of saline solution. One drop of the suspension was mixed with one drop of anti-globulin serum on an opal tile, rocked gently over a source of light, and examined for the development of agglutination; a second drop of red-cell suspension was mixed with a drop of saline solution and examined similarly. The anti-globulin serum was used at the dilution which had previously been found to give the best reaction with Rh+ cells weakly sensitised with Rh antibody.

In exceptionally potent sera the agglutinin may not be neutralised by the addition of 2 volumes of saliva. It is not practicable to add relatively greater volumes of saliva, because the mixture then becomes so hypotonic that red cells are lysed. In such cases the agglutinin can conveniently be neutralised by the addition of purified group-specific substances (as prepared, for example, by Messrs. Sharp & Dohme, U.S.A.).

TABLE I—RELATION OF PREVIOUS HISTORY TO INCIDENCE OF α HÆMOLYSIN IN SERUM OF UNSELECTED GROUP-O DONORS

History	No. of donors	Hæmolysin present	Agglutination at dilution of 1/200
Injections during war service (1939–48)	27	10 (*37%*)	17 (*63%*)
Previous injection of anti-tetanus serum (only)	12	2 (*16%*)	5 (*42%*)
Previously pregnant	32	5 (*16%*)	17 (*53%*)
Remainder	54	5 (*9%*)	21 (*39%*)
Total	125	22 (*18%*)	60 (*48%*)

For the distribution of hæmolysins, $\chi^2 = 9{\cdot}71$ for 3 d.f.; $P < 0{\cdot}05$.

Choice of Group-A Donors

Donors of test cells were classified as A_1 or A_2 according to their reactions with an α_1 serum. Persons who reacted strongly with the α_1 serum were classed as A_1, and those who failed altogether to react were classed as A_2. Thus the use of "A intermediates" was avoided.

Clinical Material and Results

UNSELECTED GROUP-O DONORS

At two routine bleeding-sessions of the National Transfusion Service 125 consecutive group-O blood donors were questioned about past injections of various kinds, past transfusions, and past pregnancies. A sample of serum was obtained from each pilot tube for examination. From this survey several points of interest emerged.

Relation Between History of Prophylactic Injections and Characteristics of Anti-A

In table I the donors have been divided into four groups based on the answers given to various questions. Donors who had received injections during war service—presumably mostly T.A.B. vaccine and tetanus toxoid—had a significantly higher incidence of anti-A hæmolysin than others. They also appeared to have a higher incidence of high agglutinin titres, but this difference was not significant. Donors who gave no history of injections of vaccine or anti-tetanus serum ("remainder") had a significantly lower incidence of hæmolysin than those in the other groups.

The over-all incidence of anti-A hæmolysin in the 125 donors was 18%, defining a hæmolytic serum as one which gave a reaction of "+" or more; 48% of the donors had an agglutinin titre of 1 in 200 or more (the dilution of the serum being made in a single step).

Discrepancies Between Agglutinin Content and Immune Characteristics

Most of the sera with moderate or low agglutinin titres were non-hæmolytic; thus, among 72 sera with agglutinin titres below 200 all but 4 failed to hæmolyse A cells. However, sera with greater than average agglutinin titres were not necessarily hæmolytic; thus, of 53 sera

TABLE II—RELATION BETWEEN HÆMOLYTIC POWER AND AGGLUTINATING POWER OF ANTI-A IN BLOOD OF 125 GROUP-O DONORS SELECTED AT RANDOM

Agglutination* in direct dilution of 1/200	Total no. of subjects	Hæmolysis			
		None (0 or tr.)	Strong		
			+	+ +	+ + +
Nil	72	68	1	2	1
W	7	6	1	0	0
(+)	22	16	3	1	2
+	15	9	2	1	3
+ +	9	4	0	4	1
Total	125	103	7	8	7

*The degree of agglutination is recorded in the notation of Taylor et al. (1942).

with agglutinin titres of 200 or more only 18 hæmolysed A cells, and among the 9 sera with the highest agglutinin titres only 5 were hæmolytic (table II).

Sera containing potent agglutinins did not necessarily sensitise cells to an anti-globulin serum. Moreover, many sera containing agglutinins of less than average potency were capable of sensitising cells. In 19 cases (not among the 125 selected donors), with agglutinin titres of 8–128, 10 sensitised cells to an anti-globulin serum.

Most of the sera which would hæmolyse cells would also sensitise cells to an anti-globulin serum. Among the 125 donors there were 22 sera which were hæmolytic, and of these only 6 failed to give a clear-cut positive anti-globulin test.

Examples of discrepancies between the agglutinin content and the presence of immune characteristics are given in table III.

SUBJECTS RECEIVING INJECTIONS OF HORSE-SERUM

Blood was withdrawn from adults attending the casualty department of Hammersmith Hospital to receive a prophylactic injection of anti-tetanus serum. 12 persons reported again nine to thirteen days after the injection, and a second sample of blood was then withdrawn. Of these 12, 6 belonged to group O and 2 to group B; of these 8 only 1 had α hæmolysin before injection.

TABLE III—DISCREPANCIES BETWEEN PRESENCE OF POTENT ANTI-A AGGLUTININ AND "IMMUNE FORMS" OF ANTI-A

Group-O donors	Titre in saline solution	Indirect anti-globulin test	Hæmolysis
Case 98	64	+ + +	+ + +
Case 49	512	0	0
Case 26	64	(+)	+ +

After injection all 8 had α hæmolysin, though it was weak in 2 and only really strong (++ or +++) in 2 others. 7 out of 8 people showed a rise in anti-A agglutinin titre. 6 out of the 8 gave a stronger indirect anti-globulin test with A cells after injection. 3 of the responses are shown in table IV to illustrate: (1) a good specific response (Ba); (2) a poor response (We); and (3) response of both anti-A and anti-B (Co); anti-B hæmolysin also developed in one of the other 5 group-O subjects.

In the 4 group-A subjects receiving anti-tetanus serum no increases in anti-B agglutinin titre were observed. None of the 4 showed anti-B hæmolysin either before or after injection or gave a positive indirect anti-globulin test with B cells.

Tests of Anti-tetanus Serum in Vitro

The power of the anti-tetanus serum to inhibit anti-A and anti-B in vitro was tested. The serum inhibited anti-A to almost the same extent as saliva from an A secretor: one volume of a 1 in 32 dilution of the anti-tetanus serum added to an equal volume of a weak anti-A serum (titre 1 in 8) prevented the anti-A serum from agglutinating A cells. The effect on anti-B was much smaller: a 1 in 4 dilution of the anti-tetanus only very slightly reduced the titre of an anti-B serum serum.

TABLE IV—CHANGES IN ANTI-A IN 3 SUBJECTS (GROUP O) FOLLOWING AN INJECTION OF ANTI-TETANUS SERUM

Subject	—	Before anti-tetanus serum: Agglutinin titre: In saline	Before anti-tetanus serum: Agglutinin titre: In serum	Before anti-tetanus serum: Hæmolysis	Before anti-tetanus serum: Anti-globulin test	9–13 days later: Agglutinin titre: In saline	9–13 days later: Agglutinin titre: In serum	9–13 days later: Hæmolysis	9–13 days later: Anti-globulin test
Ba	α	8	8	0	0	512	2048	+	+ +
	β	4	4	0	0	8	4	0	0
We	α	128	128	0	0	512	512	+	+
	β	64	32	0	0	64	32	0	0
Co	α	128	256	0	+	1024	8192	+ + +	+ +
	β	32	16	0	0	128	128	+	+

TABLE V—ANTI-A RESPONSES IN 3 GROUP-O SUBJECTS RECEIVING T.A.B. VACCINE

Subject	Before injection: Hæmolysis	Before injection: Agglutinin titre (in saline solution)	Before injection: Anti-globulin test	18 days after injection: Hæmolysis	18 days after injection: Agglutinin titre (in saline solution)	18 days after injection: Anti-globulin test
La	tr.	256	+	+ +	256	+ +
Sc	0	256	0	+ +	4096	+
Fa	0	64	(+)	0	512	+ + +

The material used in the above tests was horse-serum which had been submitted to peptic digestion. Through the kindness of Dr. J. W. Trevan, F.R.S., director of the Wellcome Institute, it was possible to test untreated serum in parallel. It was found that untreated horse-serum agglutinated human red cells of all groups. However, after five absorptions with group-A red cells it would no longer agglutinate cells of that group, and thus its power to inhibit human anti-A serum could be tested; no inhibiting power was found.

SUBJECTS RECEIVING T.A.B. VACCINE

A sample of blood was withdrawn from 14 R.A.M.C. officers of group O who were about to receive their initial injections of T.A.B. (typhoid, paratyphoid A, paratyphoid B) vaccine; a further sample of blood was withdrawn eighteen days later.

4 of the 14 sera hæmolysed A cells before immunisation; 1 of these 4 showed a considerable increase in hæmolysin after immunisation. Of the 10 officers who had no hæmolysin at all initially, 6 developed a substantial amount after immunisation.

The results of the indirect anti-globulin test were not in close agreement. Some who developed strong hæmolysin gave only a moderately strong indirect anti-globulin test, and some who developed no hæmolysin developed a strongly positive anti-globulin test. 7 out of the 14 officers showed a significant rise in anti-A agglutinin titre (fourfold or more). On the whole, the development of hæmolysin was related to a rise in agglutinin titre, though again there were some discrepancies. Some examples are given in table V.

TABLE VI—RESPONSES OF BOTH ANTI-A AND ANTI-B IN 2 SUBJECTS AFTER INJECTION OF T.A.B. VACCINE

Subject	—	Before injection: Hæmolysin	Before injection: Agglutinin titre	After injection: Hæmolysin	After injection: Agglutinin titre
Wa	α	0	32	+ + +	1024
	β	0	8	+ + +	256
Yo	α	0	256	+ + +	2048
	β	0	128	+	1024

3 sera hæmolysed B cells before injection; 1 of these 3 showed an increased lytic power after injection. In 3 other cases the serum became lytic for B cells only after injection. In 7 of the 14 cases the anti-B agglutinin titre increased fourfold or more after the injection of T.A.B. vaccine.

Examples of cases in which there were good anti-A and anti-B responses in the same person are shown in table VI.

Tests of T.A.B. Vaccine in Vitro

The T.A.B. vaccine used throughout was a batch of alcoholised vaccine produced by the Army Vaccine Laboratory, Everleigh. The medium on which the organisms are grown is a tryptic digest of agar.

The vaccine was found to inhibit anti-A and anti-B *in vitro*, *but it also inhibited anti-M*, and it was concluded that the effect was non-specific. A sample of vaccine was centrifuged, and the supernatant fluid was reserved for testing. The deposit was then washed three times in saline solution. The supernatant fluid showed the same non-specific inhibiting effects as the whole vaccine, but the deposit was without effect.

Injection of Washed Deposit

1 group-B and 2 group-O persons were given two injections of the well-washed deposit from 0·5 ml. of the original vaccine; the injections were given at an interval of a week. Serum was withdrawn a week after the second injection and tested in parallel with a sample drawn before injection. The post-injection samples did not hæmolyse A cells, and showed no significant change in agglutinin titre; nor did they give a positive indirect anti-globulin test with A_1 cells.

SUBJECTS RECEIVING AB SUBSTANCE

4 male volunteers (2 group A and 2 group B) received injections of AB substance prepared by Messrs. Sharp & Dohme; the material is prepared from horse stomach and hog stomach. 0·2 ml. of the material, well diluted in saline solution, was injected intravenously. The group-B subjects received two injections at an interval of ten days; the group-A subjects received a single injection.

In the first group-B person the anti-A agglutinin titre in saline solution rose from 8 before injection to 256 ten days after the second injection; in serum the titre was 512; no hæmolysin developed. In the second group-B person the anti-A titre rose from 512 to 1024 in saline solution, and from 512 to 4096 in serum; the serum became hæmolytic for A cells after the second injection.

In the group-A subjects there were moderate increases in agglutinin titre with the development of a weak hæmolysin in one case.

SUBJECTS RECEIVING PURIFIED HUMAN A SUBSTANCE

2 male volunteers belonging to group O received two intramuscular injections, each of 1 mg. of purified human A substance prepared by Dr. W. T. J. Morgan from fluid from a pseudo-mucinous ovarian cyst. The injections were given at an interval of nineteen days in the first case and seven days in the second.

In both subjects there was a big increase in agglutinin titre (from 8 to 1024 and from 64 to 4096) and an α-hæmolysin developed, to a titre of 4 and 8 respectively. Both post-injection sera gave positive indirect anti-globulin tests with A_1 cells after partial neutralisation.

GROUP-O WOMEN RECENTLY DELIVERED OF GROUP-A INFANTS

Samples of serum were available from 8 group-O Rh-positive mothers, each of whom had given birth to at least one infant affected with hæmolytic disease of the newborn due to anti-A. In each case the mother's serum taken on the day of delivery hæmolysed group-A cells (complete lysis of a 5% suspension) and, after partial neutralisation, gave a positive indirect anti-globulin test with A cells. In 5 out of 8 cases the agglutinin titres in saline solution were well within the normal range; in the remaining 3 cases the titre was 1024–2048. These cases will be reported in detail elsewhere.

TABLE VII—DEMONSTRATION OF INCOMPLETE α

—	Composition of saliva-serum mixtures			A_1 cells		A_2 cells	
	Vols. of A saliva	Vols. of saline	Vols. of anti-A serum	Anti-globulin serum	Saline	Anti-globulin serum	Saline
i	8	0	4	+	0	0	0
ii	6	0	6	++	0	0	0
iii	4	2	6	++	0	tr.	0
iv	2	4	6	++	+	(+)	0
v	1	5	6	+++	++	++	0

Note that mixtures i and ii sensitise A_1 cells but not A_2 cells to the anti-globulin serum; the A_1 cells are not agglutinated in the sali [illegible] A_1 cells but not A_2 cells in s [illegible] mixture are agglutinated by

DEMONSTRATION OF INCOMPLETE α IN IMMUNE ANTI-A SERA

Witebsky (1948), describing his technique for demonstrating incomplete anti-A, stated that the antibody was essentially anti-A_1. This claim was based on the observation that, when the serum was treated with sufficient AB substance to abolish, or greatly diminish, the reaction with A_1 cells in saline solution, it would still react strongly with the same cells suspended in serum but would not react at all with A_2 cells.

We thought it might be possible to demonstrate an incomplete α, as opposed to an incomplete $α_1$, if an immune anti-A serum was "neutralised" only to the point where it would no longer react with A_2 cells suspended in saline solution. Under these conditions immune anti-A sera agglutinated A_2 cells suspended in serum and sensitised them to an anti-globulin serum (table VII).

Method.—The mixtures of A saliva and anti-A serum (table VII) were left for twenty minutes; then 6 drops of each mixture were added to 1 drop of a 50% suspension of A_1 cells in saline solution, and 6 drops were added to a similar suspension of A_2 cells. After two hours the red cells were washed and added to anti-globulin serum on an opal tile; a second drop of cell suspension was added to 1 drop of saline solution as a control. The degree of agglutination was recorded.

Discussion

INCIDENCE OF IMMUNE FORMS OF ANTI-A IN POPULATION

The present results show that group-O and group-B subjects respond variably to A stimuli. Some have a rise of iso-agglutinin titre only, whereas in others the serum develops hæmolytic properties with little rise in agglutinin content. The ability to sensitise A cells to an anti-globulin serum also develops to a variable extent. It is difficult to define the proportion of people in the population whose sera display "immune" characteristics, since sera may show one but not all of these characteristics. However, the properties may be considered singly.

The present finding that the sera of about 20% of group-O subjects hæmolyse A cells may be contrasted with Jonsson's (1936) finding that the sera of males contained iso-hæmolysin in only 3·5% of cases. On the other hand, it agrees fairly well with the original observation that about 25% of sera (of all groups) contain isohæmolysin (Moss 1910). The proportion of sera which hæmolyse test cells depends on (1) the technique of the test—for example, the strength of the cell suspension and the time for which the mixtures are incubated—and (2) the proportion of people in the population who have recently received an A stimulus—e.g., anti-tetanus serum. Again, the sera of women will be expected to contain iso-hæmolysins more often than those of men, owing to the stimulus of heterospecific pregnancies (Jonsson 1936).

Similar considerations apply to the ability of a serum to react with A cells after partial neutralisation with A substance. Ervin et al. (1950) found that 12 out of 100 random samples of group-O serum, after partial neutralisation, would agglutinate A_1 cells suspended in serum and give a positive indirect anti-globulin test with A_1 cells. The present findings show that these properties are influenced by a variety of stimuli, and thus the proportion of sera displaying such properties will be expected to vary widely.

STIMULATION BY HETEROSPECIFIC ANTIGENS

Davidsohn (1938) first observed that in people receiving injections of horse-serum, and particularly in those who developed serum-sickness, there might be a considerable increase in the anti-A and anti-B titres of the serum.

The anti-tetanus serum at present used in Britain is a peptic digest of horse-serum; since the pepsin is prepared from hog-stomach—a well-known source of A-like substance—it would be expected that the present anti-tetanus serum would be a more effective stimulus than untreated horse-serum.

The present observations show that most group-O people who receive an injection of the treated anti-tetanus serum can be expected to produce immune anti-A. In a case which has been reported elsewhere a serious hæmolytic transfusion reaction followed the transfusion of group-O blood to a group-A person, and it was shown that the cause of the potent anti-A in the donor's serum was almost certainly an injection of anti-tetanus serum received five weeks previously (Mollison 1951).

The ability of vaccines to stimulate anti-A may depend on the medium on which the bacteria are grown. Dausset and Vidal (1951) encountered some severe hæmolytic reactions in group-A people who had received group-O blood, and showed that in every case the group-O donor had recently received an injection of diphtheria toxoid which had been prepared from bacteria grown on a medium containing a digest of hog stomach. Moullec (1947) had previously shown that extract of hog stomach was the source of the A-like substance in the toxoid.

Stimulation of anti-A by T.A.B. vaccine has not been reported previously. Balgairies and Christiaens (1938) found no change in iso-agglutinin titre in 2 group-O persons and 1 group-B person after the injection of *vaccin anti-typho-paratyphique*. Nevertheless stimulation of anti-A by paratyphoid bacilli would not be surprising in view of the observation of Eisler (1931) that the injection of paratyphoid-B bacilli into rabbits produces a serum which specifically agglutinates human group-A red cells. To test the possibility that the injection of such bacilli can evoke the formation of immune anti-A in man, 3 people were injected with the well-washed deposit of T.A.B. vaccine. None showed any evidence of anti-A stimulation. Nevertheless further experience will be necessary before it can be concluded with certainty that paratyphoid bacilli do not stimulate anti-A in man.

The T.A.B. vaccine used in the present experiments was prepared from bacteria grown on a tryptic digest of agar. As mentioned, no clear evidence was obtained from inhibition tests of the presence of A-like substance in the medium. Nevertheless it remains probable that it is the medium which is responsible for stimulating anti-A when the vaccine is injected into man.

CLINICAL SIGNIFICANCE OF IMMUNE FORMS OF ANTI-A

Witebsky (1948), and Young and his co-workers (Ervin et al. 1950, Ervin and Young 1950) have drawn attention to the clinical significance of immune forms of anti-A. Witebsky described a case of hæmolytic disease of the newborn due to anti-A, and showed that the mother's serum contained powerful "immune" anti-A. Ervin and Young described hæmolytic reactions in group-A recipients transfused with blood whose plasma contained immune forms of anti-A. Observations briefly presented here show that immune forms of anti-A are regularly found in the blood of mothers of infants with hæmolytic disease of the newborn due to anti-A. Other (unpublished) observations support the contention that there is a close relationship between the immune characteristics of an anti-A serum and its ability to cause the destruction of A cells in vivo after transfusion.

The evidence suggests that it may be more valuable, from a clinical point of view, to know whether a serum has immune characteristics than to know whether it has a high agglutinin titre. Experience suggests that an anti-A serum which, diluted 1 in 4 in fresh serum, will not lyse an equal volume of a 5% suspension of A_1 cells after two hours' incubation at 37°C., will not cause appreciable destruction of red cells when transfused to a group-A recipient. Judged by this criterion more than 90% of group-O people are safe universal donors.

Since it is very troublesome to screen all group-O donors, it would be a wise precaution to refuse as donors all people who had received an injection of any vaccine or animal serum during the previous three months. Alternatively, bottles of blood obtained from such people might be marked to indicate that they should be given only to group-O recipients.

Summary

Among 125 group-O donors, taken at random, there were 22 (18%) whose sera hæmolysed A cells. Those donors who had received injections of bacterial vaccines during war service had a significantly higher incidence of α hæmolysin than the rest.

"Immune" forms of anti-A developed in the sera of most group-O people receiving one of the following stimuli: T.A.B. vaccine, anti-tetanus serum, injection of human A substance, and injection of animal AB-like substance. In the anti-tetanus serum the source of the A-like substance is in all probability the pepsin, derived from hog stomach, used for digesting the horse-serum. In the T.A.B. vaccine the source of A-like substance has not been identified but seems more likely to lie in the medium than in the bacteria.

Of the various "immune" characteristics of an anti-A serum, the ability to lyse A cells is the easiest to detect. It is suggested that the hæmolysin titre of a serum gives a good indication of its ability to destroy A cells in vivo.

We are very grateful to Dr. J. D. James, director of the North London Blood Supply Depot, for arranging for us to test and question a large number of blood donors; to Dr. Dorothy M. Parkin for the supply of blood samples from patients receiving anti-tetanus serum; to Brigadier A. Sachs, director of pathology, the War Office, for permitting us to obtain blood samples from Army personnel; to R.A.M.C. officers for volunteering to provide blood samples; and to Dr. I. D. P. Wootton for collecting the samples.

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THE ASSESSMENT OF GROWTH IN DISEASE

THE USE OF WETZEL'S GRID ILLUSTRATED BY RHEUMATIC FEVER

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When children arrive at hospital having lost flesh, it is difficult to assess their subsequent weight changes during illness. The commonly used comparison of a patient's serial weights with standard monthly increments according to age and sex, which may be made by deriving an equation from mean values obtained by observation of the appropriate groups of normal children, is fallacious (Bransby and Gelling 1946, Friend and Bransby 1947); for children grow in spurts, and their increments in height and weight are variable in magnitude and time relations, as well as from one child to another. One is concerned, too, with the return of an individual to his or her optimal weight and not to an average. What is required is a method of utilising the weight changes on recovery so that each patient provides his own standard of normality, and the point in the illness when return to normal growth is achieved should be indicated as early as possible. Use of an index which includes a factor for age is undesirable because this involves comparing an individual's growth with that of the sample of the universe on which the index is based—e.g., Tuxford index, and red graph.

Two methods meet the requirements set out above. One method is to take the final weight on discharge from hospital as representing the optimal weight and to use it retrospectively. At best this is presumptive and is no use to the clinician at the bedside; but it may be of help when weight changes are being studied in a series of cases.

The other method is to use the "grid for evaluating physical fitness" described by Wetzel (1941, 1944). This grid is in two parts. The first is independent of age, consisting of weight plotted against height. Across this is a ladder-like scale running diagonally from the origin to the top right-hand corner of the graph. Each rung of the ladder represents an arbitrary value which Wetzel called an "iso-developmental level." Knowledge of an individual's height and weight can thus be used to determine this value, which can then be plotted against age on the second part of the grid. The first part of the grid gives a graph depending only on the individual's own growth, whereas the second relates this to that of the group of children upon whom was based the calculation of the percentiles drawn on it. Wetzel reported that normal children developed in such a way that the graph of their weight plotted on the first chart follows a straight line parallel to one running from the origin towards the top right-hand corner of the graph. The course of the individual's graph remains along the channel which is appropriate to his or her physique.

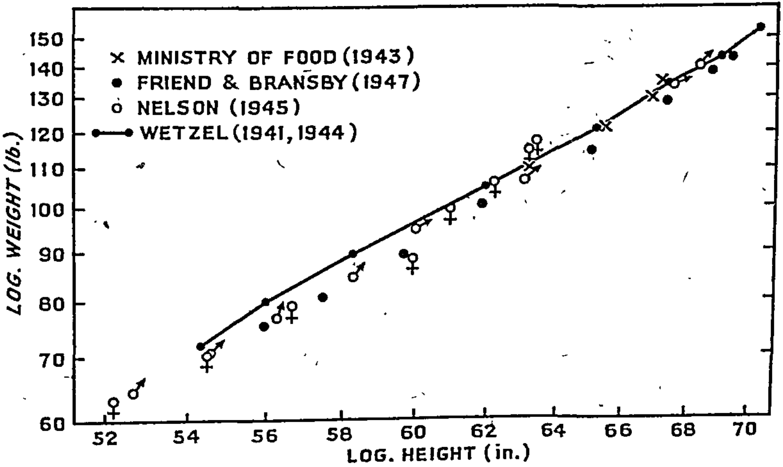

Fig. 1—Comparison of middle-channel values of Wetzel's grid with data from other sources on a double logarithmic scale.

To test whether Wetzel's observation that log-weight/log-height of growth was a straight line is applicable to British children, data from Friend and Bransby (1947), the Ministry of Food (1943), and Nelson (1945) were plotted against the values from the middle channel of Wetzel's grid. The mean height and mean weight for each group per year of age from the three sources mentioned above were used. The results are given in fig. 1 and show the good agreement obtained.

Until the age where the rate of height increase slackens and finally stops, the course of weight plotted against height on a double logarithmic scale is confirmed as being in a straight line. Girls' growth ceases to follow a straight line at about the age of 15, whereas that of boys follows it until the age of 18 or even more.

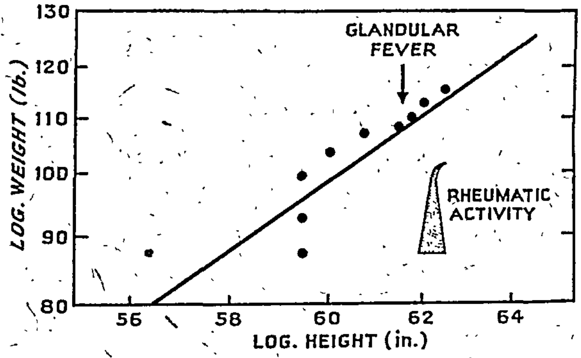

Fig. 2—Plotting points represent serial monthly observations from below upwards. Shaded wedge represents rheumatic activity great at first where base is wide and tapering off later. Line represents middle channel of Wetzel's grid.

The utility of Wetzel's principle was confirmed in a study of the criteria of rheumatic activity (Forbes 1952) when the period of observation was over four months. An example is given in fig. 2.

If reliable data are available from the period before the illness to indicate the patient's "physique channel," the graph could be used for a shorter period of observation. When the graph of the patient's growth ceased to be nearly vertical and turned obliquely into the channel appropriate to his physique, recovery from the illness was usually found by other tests and subsequent experience to be complete. Some children who had become over-fat in bed lost weight a little without apparent ill effect when physical activity was resumed.

Once the lost weight is regained the child may enter or remain in a period of "no growth." This is illustrated in fig. 3, where for four months there was no appreciable increase in growth without anything being untoward. Such a failure to gain weight would be interpreted by the standard monthly increments method as being abnormal.

It must, however, be pointed out, lest too much reliance be placed on the use of Wetzel's grid, that in rheumatic fever a steady gain in weight, not due to congestive heart-failure, is occasionally observed when rheumatic activity is continuing. In rheumatic fever many factors affect the patient's weight, among which may be the following:

(1) In the early stages the increase in body-fluids found to take place in rheumatic fever by Bradley (1938), Reid et al. (1950), and Cochran (1951), may mask the wasting, with the result that, when the patient recovers, reduction in both processes may lead to a lack of change in weight.

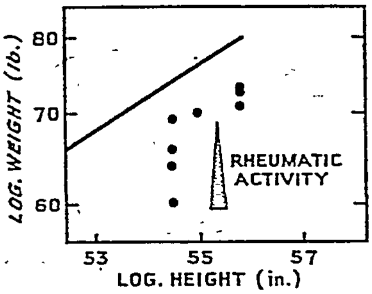

Fig. 3—Symbols as in fig. 2. Note four-month period of no growth though child was well.

(2) In spite of continuing rheumatic activity the placing of a rheumatic child at rest in bed may be sufficient to stop a loss of weight which would have occurred had the child remained ambulant.

(3) A child may be ill fed at home but, when placed on a good diet in hospital, may gain weight in spite of rheumatic activity.

SUMMARY

The problems of assessing weight changes in disease are discussed.

The underlying principle and advantages of Wetzel's "grid" as a solution are set out and illustrated by reference to rheumatic fever.

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CHRONIC ULCERATION OF THE LEG TREATED WITH AMNION AND CHLORAMPHENICOL IN PROPYLENE GLYCOL

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WHEN chronic ulcers of the leg were treated by covering them with a layer of amnion (Troensegaard-Hansen 1950, 1951), healing was sometimes delayed by bacterial infection. It is well known that *Pseudomonas æruginosa* may become established in chronic leg ulcers and is particularly difficult to eradicate.

PRELIMINARY TESTS

A 2% 'Phenoxetol' cream was used in the original treatment of ulcers with amnion, and acetic acid and sodium propionate have also been used in the past against pseudomonas infections. The inhibitory action of these compounds was tested as follows:

Cups 8 mm. in diameter were cut from nutrient agar plates. Three pseudomonas strains from chronic ulcers were spread on the plates, and the various preparations were placed in the cups. The results, using three different bases for the medium, are shown in the table. Inhibition depends largely on the ability of the drug to diffuse into the medium.

Trials of terramycin were not satisfactory.

A powder containing 1 part of terramycin in 200 parts of prepared starch (Boots K2S5) was applied to 6 chronic ulcers before covering them with amnion. The powder caked in the wound, and the antibiotic did not seem to penetrate the tissues; much pus formed and the membrane was displaced.

The use of chloramphenicol in propylene glycol was suggested by Dr. J. D. Gray, who had been using a solution containing 15 g. in 100 ml. in chronic otorrhœa (Lewis and Gray 1951). Propylene glycol has proved a satisfactory vehicle; it is non-toxic, miscible with water, and hygroscopic, and it can penetrate denuded surfaces.

Using the cup-plate technique ten organisms that were found resistant to 0·25% chloramphenicol in water were tested against 2·5% chloramphenicol in propylene glycol; there was a large zone of inhibition in each case. The organisms included *Ps. æruginosa*, two strains of *Staphylococcus aureus*, *Bacterium coli*, *Proteus vulgaris*, and two strains of streptococcus (non-hæmolytic and fæcal). Propylene glycol alone gave no inhibition.

RESULTS OF TREATMENT

The treatment previously described (Troensegaard-Hansen 1950) was used up to and including the scraping of the ulcer under general anæsthesia. A solution of 2·5% chloramphenicol in propylene glycol was then sprayed on the wound once daily. Most wounds were free from infection within 7 days. Amnion was then applied and covered with tulle gras, cotton-wool, and a light bandage. The patient stayed in bed, and dressings were left in place for six weeks if possible.

10 patients who had had ulceration of the legs for at least two years were treated in this way; 5 had associated varicose veins, and 4 had been unsuccessfully treated with phenoxetol and amnion. 7 of these ulcers healed in six weeks and 1 in three weeks; they have now remained healed for from six to eight months.

The 9th patient was a lady of 80; her ulcer healed in six weeks but recurred five months later.

The 10th patient had a chronic ulcer with eczema and swelling of the leg and foot. Local penicillin had previously produced a rash on the leg, but there was no other history of allergy or sensitivity, or of fungus infection. After two days' spraying with chloramphenicol in propylene glycol an urticarial rash appeared on the arms, the backs of hands, and the cheeks, but there was no local reaction. Treatment was stopped and saline dressings applied. On the eighth day she had an asthmatic attack; the acute phase subsided in twenty-four hours but her chest was not completely clear for a month. The ulcer remained clean, and amnion was applied after two weeks' treatment. The ulcer healed in six weeks, and the swelling and eczema of the leg also subsided, but a mild scaly eczema of the hands and forearms persisted.

One of these patients had a similar ulcer on the other leg which was treated with chloramphenicol in propylene glycol, but no amnion. At six weeks this ulcer was clean but unhealed; amnion was applied and the ulcer healed after a further six weeks.

INHIBITION OF *Pseudomonas æruginosa* BY PHENOXETOL, ACETIC ACID, AND SODIUM PROPIONATE IN DIFFERENT BASES

Reagent	Base		
	Ung. alcoh. lan.	Water	Ung. emulsif.
2% phenoxetol	−	+	+ + +
1% glacial acetic acid ..	−	+	+ +
10% sodium propionate ..	−	+	+ +
2% phenoxetol and 1% glacial acetic acid ..	−	+	+ + +
2% phenoxetol and 10% sodium propionate ..	−	+	+ + +

Equal effects were shown on three strains of *Ps. æruginosa*.
− = no inhibition.
+ = slight zone of inhibition at 8 hours, when growth was first obvious, but no inhibition at 20 hours.
+ + = slight zone persisting at 20 hours.
+ + + = moderate zone persisting at 20 hours.

A patient who was not treated with amnion had a band of ulceration, 6 in. wide, round the leg. Spraying with chloramphenicol in propylene glycol every other day has reduced it to 2½ × 1 in.

DISCUSSION

All the organisms isolated from these ulcers were sensitive to chloramphenicol in propylene glycol, as shown by a definite zone of inhibition in the cup test.

The possibility of local or generalised allergy can best be assessed by further trial of the method. Intradermal tests which we performed on our patient who had urticaria and asthma did not suggest that chloramphenicol was the sensitising agent. Pure propylene glycol produced a marked weal, but no surrounding erythema. A healthy adult control reacted similarly to the same amount intradermally. The weal was probably the result of absorption by the hygroscopic propylene glycol. In the 10th case it may be that the infection was overcome so rapidly that there was a sudden release of bacterial products. The patient may have been sensitive to the bacterial protein or to something else produced by the action of the antibiotic. If cultures were kept of organisms isolated from an ulcer, it would be possible to check this hypothesis by injecting a killed bacterial suspension, should an allergic reaction occur.

Despite the one reaction in this small series, chloramphenicol in propylene glycol seems to be a very useful adjunct to treatment with amnion.

We are grateful to Dr. J. Stanley White and Dr. Robert Hodgkinson of the department of clinical investigation of Messrs. Parke, Davis for supplies of chloramphenicol in propylene glycol.

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SECRETION OF A SALT-RETAINING HORMONE BY THE MAMMALIAN ADRENAL CORTEX

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In recent years the division of adrenal cortical steroid hormones into glucocorticoids and "mineralocorticoids" (Selye 1950) has been seriously questioned by some authors (Verzar 1952), and Conn, Louis, and Fajans (1951) have gone so far as to suggest that all the actions of adrenocorticotropic hormone (A.C.T.H.) in humans could be accounted for if the human adrenal be supposed to secrete 17-hydroxycorticosterone (Compound F) alone. Thus the three most active known glucocorticoids, cortisone, Compound F, and Compound B, all produce sodium retention in man (Sprague et al. 1950, Conn, Fajans et al. 1951, Conn, Louis, and Fajans 1951), and cortisone does so in dogs (Roberts and Pitts 1952). Similarly all the active cortical hormones have been found to have some effect in depressing the urinary Na^{24}/K^{42} ratio of adrenalectomised rats (Simpson and Tait 1952). Since chemical estimations of the corticoids in adrenal venous blood have shown Compound F and Compound B (corticosterone) to be by far the major secretory products of the adrenal cortex of many mammalian species (Nelson et al. 1950, Hechter et al. 1951, Bush 1951) it has appeared to some (see Sayers 1950) unnecessary to postulate the secretion of a specific "mineralocorticoid" or "salt-retaining hormone" by the mammalian adrenal cortex.

However Selye's comprehensive theory of the existence of "diseases of adaptation" (Selye 1950) depends at least in part on the postulate that the adrenal cortex secretes a mineralocorticoid distinct from and antagonistic in action to the glucocorticoids. Furthermore the glucocorticoid "cortisone" is not fully effective in controlling Addison's disease (Conn, Fajans, et al. 1951, Forsham 1951), nor is it as effective as whole adrenal extract in correcting various deficiencies of adrenalectomised animals (Ingle et al. 1952).

Many objections to the theory of mineralocorticoid secretion by the adrenal were made on the grounds that the actual secretion of desoxycorticosterone (deoxycortone) had not been demonstrated and that this substance was possibly only an artefact in adrenal gland extracts (Dobriner 1952). At the time no other potent mineralocorticoid was known.

The whole question became more complex when it was discovered (Grundy, Simpson, and Tait 1952) that by far the greater part of the "salt-retaining activity" of whole-beef adrenal extract was contained in a hitherto unknown substance of high potency, which could only be separated from "cortisone" by prolonged chromatography. We wish to present evidence in this communication that a similar or identical substance is actually secreted into the blood-stream by the adrenal of the dog and the monkey. It thus appears to be an active hormone of physiological significance and not only a component of gland extracts or simply an artefact.

METHODS

Monkey.—The isolated left adrenal of a 6·35 kg. rhesus monkey was perfused with blood by a technique similar to that of Vogt (1951) and the effluent blood collected in an ice-cooled flask. The blood was extracted at the end of the experiment with ethyl acetate and the extract purified and concentrated by washing quickly with cold N/5 Na$_2$CO$_3$, water, distillation, and partition between petrol and 70% ethanol. The final extract was divided into several parts and fractionated by paper chromatography (Bush 1952). The content of α,β-unsaturated ketonic steroids was determined by their fluorescence reaction with NaOH in two fractions of the extract and the position of "cortisone" on the chromatogram was marked with a pencil. The remaining fractions were run on the same chromatogram but not treated with NaOH. The region of the chromatogram containing the cortisone from these fractions was eluted with ethanol, and the ethanol eluate was evaporated and assayed (table I) by the method of Simpson and Tait (1952).

Dog.—Blood from the left adrenal vein of a 21·5 kg. bitch was collected in vivo under pentobarbitone anæsthesia and after evisceration (Vogt 1943). The splanchic nerves were intact. The blood was extracted and was fractionated by chromatography.

The whole of a chromatogram run in the system toluene : methanol : water (100 : 75 : 25 by volume) was divided into regions and assayed in parallel by the sodium/potassium ratio assay and the fluorescence reaction with NaOH.

A measured portion of the cortisone fraction of the blood extract was acetylated and chromatographed with the benzene : formamide system of Burton et al. (1951).

RESULTS

The results of the two types of assay when applied to these extracts of adrenal blood are given in table I. It is seen that the "cortisone spot" on the chromatogram of the monkey's adrenal blood extract contained 1–2 μg. of cortisone, which would be equivalent to 0·2 μg. deoxycortone in the mineral ratio bioassay used. However, the biological activity of this spot when assayed in the adrenalectomised mouse was equivalent to that of 15 μg. deoxycortone and could not be accounted for by the small amount of cortisone present in the extract.

A more complete study was made of the extract of dog adrenal venous blood. In this experiment the whole

TABLE I—RESULTS OF BIOASSAY OF "E FRACTION" OF 45 MIN. PERFUSATE OF ISOLATED MONKEY ADRENAL GLAND

Substance injected	Dose per rat	No. of animals	Na^{24}/K^{42} urinary ratio
10 % alcohol ..	0·1 ml.	13	3·527 ± 0·357*
E fraction of perfusate	1/30th of total in 0·1 ml. 10 % alcohol	8	2·868 ± 0·387
E fraction of perfusate	1/15th of total in 0·1 ml. 10 % alcohol	8	2·280 ± 0·110
Adrenal extract ..	0·01 ml. in 0·1 ml. 10 % alcohol	8	2·010 ± 0·169
	0·02 ml. in 0·1 ml. 10 % alcohol	7	1·451 ± 0·130

Adrenal extract employed was equivalent to 140 µg. deoxycortone.

$$* \text{S.E.} = \sqrt{\frac{d^2}{n(n-1)}}$$

chromatogram was divided into regions and each assayed for mineral activity. Table II shows that no activity was found in the region occupied by compounds more polar than Compound F, and that the activity in the regions occupied by Compound F and Compound B could be completely accounted for by the amounts of these substances determined chemically. Again, however, the activity of the cortisone region was equivalent to 56 µg. deoxycortone whereas only 15 µg. of cortisone was determined chemically. This amount of cortisone alone would have an activity equivalent to 1 µg. deoxycortone only. No other region of the chromatogram was found to possess salt-retaining activity.

The region of the chromatogram containing cortisone was acetylated and the product chromatographed. The chromatogram was eluted in three parts: (*a*) from the origin to cortisone acetate; (*b*) from and including cortisone acetate to the position of Reichstein's S acetate, which was run parallel with the extract; and (*c*) from Reichstein's S acetate to the front. Appreciable activity after hydrolysis was found in fraction (*c*) which does not include cortisone acetate. This corresponds with the behaviour of the acetyl derivative of the potent mineralocorticoid found in the adrenal extract 'Eucortone' (Grundy, Simpson, and Tait, 1952, Grundy, Simpson, Tait, and Woodford 1952).

DISCUSSION

The above evidence suggests that both the isolated perfused adrenal, and the adrenal in vivo, of two mammalian species can secrete a highly potent mineralocorticoid similar to if not identical with that previously found in adrenal gland extracts. The great activity of this substance would explain why it has not been detected previously by the chemical methods used for examining adrenal venous blood. Table II shows that even when the secretion-rate of the two principal glucocorticoids was high (in the dog) this substance accounted for more than half the total salt-retaining activity of the total adrenal secretion. Whether this relation holds at low secretion-rates or in other conditions remains to be seen.

TABLE II—MINERAL ACTIVITY OF FRACTIONATED DOG ADRENAL PERFUSATE

Fraction number	Region of chromatogram	Amount of known corticosteroids in region	Expected mineral activity from known steroids in region	Actual mineral activity found in region
1	From and including origin to 17-hydroxycorticosterone (Compound F)	0	0 µg. deoxycortone	0 µg. deoxycortone
2	From and including Compound F to cortisone	225 µg. F	20 µg. deoxycortone	20 µg. deoxycortone
3	Cortisone region	15 µg. E	1 µg. deoxycortone	56 µg. deoxycortone
4	Corticosterone region	65 µg. B	10 µg. deoxycortone	15 µg. deoxycortone * 0 µg. deoxycortone
5	Deoxycortone region	0 µg. deoxycortone	0 µg. deoxycortone	0 µg. deoxycortone *

* Fractions 4 and 5 were tested in a different assay from fractions 1, 2, and 3. The cortisone area was found to have comparatively high activity in both assays.

These quantities represent a quarter of total 18 minutes adrenal perfusate. Deoxycortone acetate was used as a standard.

There is no similar evidence that an unknown very active glucocorticoid is secreted by the mammalian adrenal. The secretion-rate of Compound F and/or Compound B is sufficient to account for the results of Vogt using the Selye-Schenker assay, and of Brownell using the liver-glycogen deposition assay (Bush 1951). If, as in table II, we assign these two sorts of biological activity to the compounds secreted by the adrenal in the dog experiment, it is clear that this so far unidentified substance is a biologically significant secretory product of the adrenal cortex and can be reasonably described as a mineralocorticoid. It should be emphasised that if this substance is secreted by the human adrenal, significant changes in the rate of its urinary excretion could not be discovered by any of the usual analytical methods. For instance, Davis (1952) has suggested, mainly as a result of histochemical examination of adrenal glands, that there is adrenal dysfunction in essential hypertension. Hertzel et al. (1952) from a study of glucocorticoids and reducing steroids in the urine of such patients, have found no evidence for this. Our findings indicate that no conclusions can be drawn from these latter estimations, for the active mineralocorticoid such as is secreted by the adrenal gland of monkey and dog would not have been detected. In particular the "benzene : water partition" technique (Talbot et al. 1945) would achieve no separation of this compound from the glucocorticoids found in urinary extracts.

The excessive secretion of salt-active corticosteroids has been suggested as a factor in the ætiology of a wide variety of human diseases (Selye 1950), including rheumatoid arthritis and essential hypertension, and more recently and specifically as a possible cause of toxæmia of pregnancy (Masson et al. 1952). These theories have been questioned on the grounds that deoxycortone, the only known highly salt-active steroid, has not been found to be secreted in physiologically significant amounts by the mammalian adrenal gland (Sayers 1950, Rosenberg et al. 1952). Our findings suggest that the ætiology of such diseases must be reconsidered on the basis that it is probable that a mineralocorticoid is secreted by the mammalian adrenal gland.

SUMMARY

Extracts of adrenal venous blood from a monkey and a dog have been shown to contain a substance very active in its effect on the urinary Na^{24}/K^{42} ratio of adrenalectomised rats. The effect is similar to that previously obtained with extracts of adrenal gland.

Evidence is presented that this substance is secreted in biologically significant amounts and can be reasonably described as a mineralocorticoid.

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Reviews of Books

Foetal and Neonatal Pathology

J. EDGAR MORISON, M.D., B.SC., reader in pathology, Queen's University, Belfast; pathologist, Royal Victoria Hospital, Belfast. London: Butterworth. 1952. Pp. 366. 50*s.*

THIS book, which gives a résumé of present knowledge of fœtal and neonatal pathology together with copious references, is on the whole a well-balanced review of a remarkably wide field. Though it is not easy reading, pædiatricians and pathologists will value it as a work of reference. Whether it will appeal equally to the general practitioner, who is specially mentioned on the dust-cover, is more doubtful, but Dr. Morison has certainly succeeded in what he describes as "an attempt to provide a basis for the study of disease in the fœtus and newborn infant."

The book is divided into three sections—disturbances of prenatal life, adaptation to extra-uterine existence, and infections in fœtal and neonatal life. The description of defence mechanisms in the fœtus and newborn infant might perhaps have been given more than ten pages in view of its outstanding importance, and the subject of immunity (which does not appear in the index) treated with less breathless haste. On the other hand, many of the sections are outstandingly good, though Dr. Morison has been careful not to let his personal interests upset the balance of the whole. There remains much that is still obscure or speculative in neonatal pathology, and this book should stimulate further investigation. The diagrams are well chosen and clear, but the reproduction of some of the photomicrographs might be improved.

Clinical Use of Fluid and Electrolyte

JOHN H. BLAND, M.D., assistant professor of medicine, University of Vermont College of Medicine. Philadelphia and London: W. B. Saunders. 1952. Pp. 259. 32*s.* 6*d.*

Companionship of Water and Electrolytes in the Organisation of Body Fluids

Lane Medical Lectures. JAMES L. GAMBLE, M.D. California: Stanford University Press. London: Oxford University Press. 1951. Pp. 90. 20*s.*

IT is only since the war that the development of flame photometry has made possible the rapid and easy determination of inorganic ions in body-fluids. The complete biochemical picture now obtainable has increased interest in disturbances of electrolyte balance. There can be no doubt of the importance of the subject when we observe the recovery of anuric patients or watch easy postoperative recovery from abdominal operation instead of the continued and excessive vomiting which often imperilled life.

Dr. Bland's book is a lengthy and complete discourse on the whole subject, ranging from the use of mercurial diuretics and low-salt diets in heart-failure to problems of fluid-balance in pædiatrics and geriatrics. The book is well documented, but it shows signs of haste in preparation. Fig. 7, for instance, is repeated in fig. 47.

In his Lane lectures Dr. Gamble describes fully dehydration and parenteral-fluid therapy and gives special attention to the problems arising in infancy. But even the greatest authority may have a blind spot, and his description of the respiratory adjustment to acidosis is confusing.

Leptospirosen

Klinik und Epidemiologie von Weilscher Krankheit, Feld-, Ernte- und Sumpffieber, Schweinehüterkrankheit, Canicolafieber, Reisfeldfieber, und andern Leptospireninfektionen bei Mensch und Tier. OTTO GSELL, director of the medical clinic, Canton Hospital, St. Gallen. With an appendix on Bacteriological and Serological Methods by E. WIESMANN, director of the Canton Bacteriological Institute, St. Gallen. Berne: Huber. 1952. Pp. 323. Sw. Fr. 28.

Dr. Gsell is an acknowledged authority on the clinical and epidemiological aspects of leptospirosis. His own observations in Switzerland on the so-called benign forms have added notably to our knowledge of these diseases, and his example and enthusiasm have stimulated many other workers to carry out investigations. Here he gives us a well-documented review, with a bibliography of leptospirosis in general, and develops and explains the conclusions he has drawn from his own experience.

The physician, he thinks, should look on all leptospiral infections as fundamentally the same. It is then possible to divide them broadly into two clinical groups—the benign (non-icteric) and the icteric (often malignant) forms. In the icteric group the prognosis depends, not on the degree of liver damage, but on the extent of the accompanying nephritis, intoxication, and circulatory involvement. Though certain species (e.g., *Leptospira pomona* and *L. grippotyphosa*) usually produce a comparatively mild illness, they can on occasion give rise to very severe disease. In his clinical description Gsell therefore focuses attention primarily on the symptoms which are common to all forms: the sudden onset, high fever often biphasic in type, myalgia, meningismus, renal involvement, reduced blood-pressure, injected conjunctivæ, and rashes. Depending on the severity of the attack, and the organs or tissues chiefly affected, the symptoms may be predominantly renal, hepatic, meningeal, typhoid, or purely febrile. As there is no specific treatment, management depends on the clinical condition of the patient, and not on the species of leptospire producing the disease.

For the epidemiologist such a broad division is insufficient. In general, each species of leptospire has its own characteristic carrier-host, and the differing habits of the animals greatly influence the mode of transmission to man. Thus very different measures would be required to prevent transmission from sewer-rats, field-mice, pigs, and dogs; and the occupational, seasonal, age, and sex incidences of the various forms of leptospirosis are also influenced by the type of carrier animal. In the extensive section on epidemiology Gsell therefore deals with each of the more important species separately, and this practical approach has much to commend it.

In an appendix on the bacteriological and serological methods used in the investigation of leptospirosis, Dr. Wiesmann gives full details of techniques and comments usefully on the interpretation of serological reactions.

Diseases of the Nervous System (7th ed. Edinburgh: E. & S. Livingstone. 1952. Pp. 365. 24*s.*).—This is the seventh edition of Dr. F. M. R. Walshe's book to appear since 1940, which shows how popular it has been with the medical student and general practitioner for whom it has been written. Its girth has increased since the first edition, but its scope has not changed and it remains an unrivalled account of the best approach to a neurological case and description of the more common neurological disorders. The production of the book is good, and considering the number of excellent illustrations of pathological specimens and X-ray pictures, the price is remarkably low by today's standards.

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THE LANCET

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Charges for Pay-beds

If the new tables of hospital costs[1] are used for calculating the charges made for pay-beds, these charges will rise yet further. In one of the London specialist hospitals the private patient is already asked to pay £27 8*s*. a week, and such figures may soon be the rule rather than the exception. Many people who have been willing to take a private bed will find that they can no longer afford to do so.

By paying his doctors and by paying the hospital, the patient in the private bed gains certain privileges which he may value highly. First, if he is given a room of his own, he has privacy, which he may like for its own sake or because it enables him (if he is not too ill) to see more visitors, attend to his affairs, or even conduct his business by telephone and correspondence. Secondly, being admitted privately under the care of a particular member of the hospital staff, he can be reasonably sure that he will be treated by the doctor of his choice and not handed over to an assistant. Thirdly, by making these private arrangements, he may hope to be admitted and treated at a time that suits him—probably much sooner (if he wishes) than some other patient who is put on the non-urgent waiting-list of cases for the ordinary wards. The idealist may object to anyone being able to buy these privileges: privacy and early treatment may be as much desired, he will say, by the worn and nervous young mother from Seven Dials as by the woman with unbreakable social engagements in Belgrave Square; and in a National Health Service the criterion should be need not money. The answer to this, however, is that these paying patients are *not* being treated under the N.H.S. and are making no claim on it, since they pay for everything they get—and indeed something in addition. This answer would become less valid if (as has been proposed by the British Medical Association's Amending Acts Committee[2]) pay-beds were partly paid for out of N.H.S. funds; for it would then appear that, within the service, money would buy additional and substantial privileges denied to those who could not afford them. As things have stood since 1948, and should continue to stand, no privileges can be bought within the service (except the amenity bed, for which a relatively small charge has been made); and people who want privileges and are prepared to pay for them are treated under separate arrangements though not necessarily in a separate building. Egalitarians may say that it will be better for the community when everybody goes to the same schools, and occupies the same hospital beds, but we have not yet reached so egalitarian a society that people with money can be prevented from purchasing the services they want, when they harm no-one else by doing so. Before the N.H.S. Act was introduced, the well-to-do patient (and even the not so well-to-do) could purchase the advantages of a private bed from most of our big hospitals, and it would have been wrong for the service to deprive him of the right to do this. As the amenities of the public wards improve, fewer and fewer people will wish to pay for privacy, which (because it may breed boredom and depression) is quite often against their real interests. But it would again be wrong to hasten this development by imposing penal conditions on those who do not change their attitude as fast as the social reformer would like. Reform would be a far more popular process if it never removed anything good until it had provided something better.

Our opinion, then, is that hospitals should continue to offer private beds to people who want to be treated privately; that they should charge the patient the full cost of maintaining a private bed; and that the N.H.S. should neither penalise the private patient, nor try to make a profit out of him, by charging him more than the true cost. Under the present system he has to pay what is supposed to be the average weekly cost of a public bed in the hospital, plus 25% to cover the extra labour of attending to him individually in a small ward, the larger space he occupies, and any additional amenities he may enjoy. Now that the basic cost of the public bed has become so high, this 25% is far from being a negligible figure and ought to be reconsidered: logically perhaps the additional charge to paying patients should be the same as the charge made when a public patient transfers to an amenity bed—a charge which has lately been raised to the uncomfortably high figure of 12*s*. a day. More important, however, is an equitable revision of the method of calculating the true cost of a private patient; for the way in which this is now done is far from satisfactory. The most conspicuous fallacy is one to which we have already drawn attention.[1] A substantial but very variable proportion of the income of many hospitals is spent on their outpatient departments, and, now that some of these have become major centres of consultation and investigation, this proportion is often underestimated by the arbitrary decision that the cost of each outpatient attendance is to be reckoned as a fifth of the cost of one inpatient day. Whenever this is in fact an underestimate of the cost of outpatients, the returns will show the expenditure on inpatients as higher than it really is. Thus there is good reason to think that the cost of beds as stated in the report lately issued, which is likely to be used by hospitals in deciding their pay-bed charges, usually includes a subsidy to the outpatient departments; and it is unfair that private patients, who are outside the service, should be expected to share in subsidising departments which hardly any of them have ever used. Another question that needs further thought is whether the charge made for a private bed should be based on the weekly cost of all the public beds in the hospital or only on the cost of the occupied beds. Calculation of the cost of a hospital bed is a complex piece of accountancy, and a wide range of figures can be produced. A fair interpretation of the Act would permit a substantial reduction of some of the present charges, which would not only be just to the paying patient but also be sound economics for the N.H.S.

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[1] National Health Service: Hospital Costing Returns, year ended March 31, 1951. H.M. Stationery Office, 1952. See *Lancet*, 1952, i, 1213, 1255.

[2] *Brit. med. J.* 1951, ii, suppl. p. 141; see *Lancet*, 1951, ii, 710, 731.

If an effort were made to ascertain the actual cost of private patients at each hospital, there would be less risk of the charges becoming prohibitive. It should be borne in mind that if the beds become too expensive, and are not fully used, the N.H.S. will lose financially.

Treatment of Bacterial Meningitis

PÆDIATRICS offers no greater satisfaction than the successful treatment of a child with bacterial meningitis. Early and precise diagnosis followed by planned and vigorous treatment lead directly to an earned reward: the sight of a child rescued from death or idiocy and restored to lasting health.

The spectacular multiplication of chemotherapeutic agents in this field has tended dangerously to obscure the essentials of treatment. We have already urged[1] that in hæmophilus meningitis early diagnosis, intensive chemotherapy, and the thorough treatment of complications are the triune foundation of success. Dr. HATTIE ALEXANDER, in her admirable contribution to the fifth volume of Advances in Pediatrics,[2] now asserts that these three principles are equally important in all types of meningitis. She shows that, in general, the older drugs have not yet been surpassed by the new antibiotics. Sulphadiazine for meningococcal meningitis, penicillin for pneumococcal meningitis, and streptomycin for tuberculous meningitis, remain the weapons of first choice. Improved results have sprung, in Dr. ALEXANDER's words, from "optimal therapy rather than minimal therapy," and she cites the work of DOWLING and his colleagues[3] as an example. These workers, with a generous boldness native to their country, recommend 12 million units of intramuscular penicillin a day as the basic dose for an infant with pneumococcal meningitis. This may be excessive; but those who have seen the results of partial treatment will agree that there is no place for niggling dosage: there is certainly no economy in saving on drugs if the outcome is prolonged illness with a risk of mental defect. Even with this huge dosage, it may be noted, penicillin must still be given by the intrathecal route. ALEXANDER found that therapeutic levels[3] of penicillin in the cerebrospinal fluid (C.S.F.) were not attained for 8–12 hours, although the meninges were acutely inflamed and 1 million units was being given every 2 hours. Dr. ALEXANDER recommends that an adjuvant chemotherapeutic drug should be administered routinely in each form of meningitis both as a secondary attack against the invader and to prevent the emergence of drug-fast strains. Most workers in this country endorse such a practice. The number and the splendour of the new antibiotics may, however, tempt the unwary into a blind polypharmacy, with results possibly disastrous to the patient and certainly valueless in the trial of the new agents. There is still no indication for giving more than two drugs in any form of meningitis.

In the treatment of complications there have been three recent advances. Firstly, the Waterhouse-Friderichsen syndrome has been treated with cortisone with apparent success,[4,5] and Dr. ALEXANDER confirms its value. The number of treated cases is, however, small, and the antemortem diagnosis of bilateral adrenal hæmorrhage is notoriously difficult. Meanwhile, doctors treating meningococcal infections will do well at first to chart the blood-pressure every fifteen minutes.[6] They may thus catch a case of adrenal failure in the early stages, and they will certainly obtain useful evidence of the pressures to be expected in septicæmic children without adrenal damage. Secondly, subdural effusions of fluid have begun to be a relatively common complication of purulent meningitis,[7] especially in centres where the intrathecal route of medication is avoided; and in some patients aspiration of the fluid has been found to relieve persistent fever or focal neurological signs. Finally it has been established that convulsions complicating purulent meningitis are both ominous signs and dangerous per se[8]; routine prophylaxis with anticonvulsants and vigorous treatment of emergent seizures are integral parts of successful treatment.

None of the newer remedies has yet proved more valuable than streptomycin in the treatment of tuberculous meningitis, though some early results recorded by Dr. SWEETNAM and Dr. MURPHY in our last issue[9] supported the hope that isoniazid is going to be useful in these acute illnesses. A recent advance has been, paradoxically, a brilliant reversion to KOCH's treatment with tuberculin. The intrathecal injection of the purified protein derivative (P.P.D.) has resulted in dramatic cures of children apparently moribund.[10] This method of treatment, and indeed the treatment of tuberculous meningitis by any method, is not for the tyro: the pitfalls are many, and the best results can be won only by a team working in a special centre. Delayed diagnosis remains the first cause of failure. P.P.D. was, of course, introduced by SMITH and VOLLUM primarily as a research tool; and their elegant experiments have already thrown fresh light both on the nature of tuberculous sensitivity and on the intimate nature of bacterial inflammation.[11] Their work, which sprang from the contemplation of unexplained spikes on the graphs of C.S.F. changes in affected children, is a pleasing example of clinical research repaying some of its debt to the basic sciences.

Dr. ALEXANDER's review makes it plain that, although many pockets of resistance remain, the broad sweep of conquest over bacterial meningitis is within sight of completion. Yet, for the physician, the battle begins afresh each time a child presents with a stiff neck. Failure to diagnose with speed and to treat with vigour carries unchanged penalties; and "a victory is twice itself when the achiever brings home full numbers."

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[1] *Lancet*, 1952, i, 1003.

[2] Advances in Pediatrics. Volume 5. Edited by S. Z. Levine Chicago: Year Book Publishers. 1952. Pp. 273. $7.

[3] Dowling, H. F., Sweet, L. K., Robinson, J. A., Zellars, W. W., Hirsh, H. L. *Amer. J. med. Sci.* 1949, 217, 149.

[4] Nelson, J., Goldstein, N. *J. Amer. med. Ass.* 1951, 146, 1193.

[5] Breen, G. E., Emond, R. T. D., Walley, R. V. *Lancet*, 1952, i, 1141.

[6] Banks, H. S. *Ibid*, p. 1305.

[7] Everley Jones, H. *Ibid*, 1952, i, 891.

[8] Ounsted, C. *Ibid*, 1951, i, 1245.

[9] Sweetnam, W. P., Murphy, E. F., July 26, 1952, p. 160.

[10] Smith, H. V., Vollum, R. L. *Ibid*, 1950, ii, 275.

[11] Swithinbank, J., Smith, H. V., Vollum, R. L. To be published.

Œsophageal Hiatus Hernia

HERNIATION of part of the stomach through the œsophageal hiatus of the diaphragm is a fruitful source of errors in diagnosis. Though this disorder is being detected increasingly often,[1] it is still commonly overlooked; HARRINGTON[2] found in his series an average of three previous erroneous diagnoses—the commonest being gall-bladder disease, peptic ulceration, carcinoma or stricture of the œsophagus, heart-disease, anæmia, hyperacidity, and intestinal obstruction. On the other hand, it is no less easy to fall prey to the opposite danger "and repair a hernia for gall-bladder trouble."[3]

In most cases hiatus hernia is probably due, not to developmental error, but to factors operating in adult life—notably laxity of the tissues at the hiatus with advancing age and increased intra-abdominal pressure from such causes as pregnancy, obesity, tumours, coughing, and belching. HARRINGTON[4] examined the œsophageal opening in 500 consecutive abdominal operations and found that in 33% more than one finger could be inserted between the diaphragm and the œsophageal ring. VON BERGMANN[5] emphasised that the longitudinal fibres at the lower end of the œsophagus were continuous with those of the stomach; and he suggested that herniation might be due to a vasovagal reflex from the upper abdominal viscera. GILBERT and his associates[6] confirmed that in dogs stimulation of the vagus, directly or reflexly from the abdominal viscera, caused shortening of the œsophagus and pulling up of the stomach—an effect that was abolished by atropine. They found, too, that more than half of their patients had some possible source of such a reflex. Congenital short œsophagus with a thoracic stomach is rare; but herniation may sometimes be caused by secondary shortening from inflammation and subsequent cicatricial contraction.

The two main forms of hiatus hernia are the œsophagogastric and the para-œsophageal—termed by ALLISON[7] the sliding and rolling types. In the first type the stomach slides through the hiatus with the œsophagus leading, and the incompetent sphincter allows regurgitation of acid gastric juice. In the rolling type the sphincter is normal and there is no regurgitation. The two types may be present together. The hernia may present only intermittently and may disappear when the patient stands; and likewise symptoms may be constant, intermittent, or completely absent. The condition is usually found in middle-aged overweight women of nervous disposition who commonly have some other abnormality—for example, of the stomach or gall-bladder. HURST[8] remarked on the influence of fatigue and nervous factors in precipitating symptoms. These symptoms have been well described by NICHOLSON[3] in an account of 62 cases. With the sliding type they may consist of belching, fullness after meals, and epigastric discomfort; and if the disorder is complicated by reflux œsophagitis there will be intense burning pain behind the lower end of the sternum, often coming on in the middle of the night and radiating to the back, the arm, the ears, the palate, and vaguely to the neck. With the para-œsophageal hernia, on the other hand, œsophagitis does not occur; and the symptoms consist in flatulence, "wind around the heart," "asthma," anæmia, and attacks of severe upper abdominal pain and of vomiting with remissions. There may be slight dysphagia, and a gastric ulcer may develop near the cardia. Dyspnœa and cough may result from a large hernia in the posterior mediastinum.

VON BERGMANN[5] first pointed out the similarity of the pain of hiatus hernia to that of angina pectoris; and possibly reflexes from the hernia may cause true angina from coronary insufficiency, for GILBERT and his colleagues[9] showed experimentally that distension of the stomach resulted in decreased blood-flow through the coronary circulation. VAN DELLEN,[10] moreover, found typical electrocardiographic evidence of coronary insufficiency in records taken while herniation was present, whereas while the hernia was absent the electrocardiogram was normal. On the other hand, anginal pain may be initiated by distension of the herniated part of the stomach or œsophagus since the nerve pathways are the same. NUZUM[11] found that the prevalence of hiatus hernia in otherwise normal people had been variously estimated at figures ranging from 0·13 to 8·9%. Of 100 patients with angina pectoris whom he studied 25 had a hiatus hernia; whereas of a control group of 957 patients subjected for various reasons to radiographic examination of the gastro-intestinal tract only 12% had such a hernia. The lesson seems to be that cases of angina pectoris, especially with unusual symptoms, should be investigated for a hiatus hernia. Both in such cases and in others where atypical upper abdominal symptoms suggest the possibility of a hernia, the radiologist should be asked to make a special examination for it.

Treatment in the first place should always be medical; for medical treatment, together with reassurance as to the absence of heart-disease, often suffices to relieve symptoms. When œsophagitis is present the régime should be similar to that for peptic ulceration. Late meals should be avoided, and the patient should be advised to sleep propped up in bed or with the head of the bed raised on a block, and, as far as possible, to avoid bending. Œsophagoscopy is necessary if there is dysphagia or suspected ulceration, in order to place the diagnosis beyond doubt. CLERF and his colleagues[12] have found that many patients are relieved by dilatation of the œsophagus when this is narrowed, or by the application of silver nitrate when ulceration is present. Many years ago SAUERBRUCH[13] reported good results from interruption of the left phrenic nerve. This method has since been followed by many surgeons; and PICKHARDT and his colleagues[14] are convinced that in older patients it is the most satisfactory treatment. If a stricture or severe ulceration has developed, resection of the affected portion may be necessary. Usually, however, *reduction of the hernia and repair of the defect is the* surgical treatment of choice; and this should preferably be carried out by the transthoracic approach.

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[1] Avery Jones, F. *Proc. R. Soc. Med.* 1952, 45, 277.
[2] Harrington, S. W. *Ann. Surg.* 1945, 122, 546.
[3] Nicholson, F. *Ibid*, 1952, 136, 174.
[4] Harrington, S. W. *Amer. J. Surg.* 1940, 50, 881.
[5] von Bergmann, G. *Dtsch. med. Wschr.* 1932, 58, 605.
[6] Gilbert, N. C., Dey, F. L., Rall, J. E. *J. Amer. med. Ass.* 1946, 132, 132.
[7] Allison, P. R. *Surg. Gynec. Obstet.* 1951, 92, 419.
[8] Hurst, A. F. *Guy's Hosp. Rep.* 1934, 84. 43.
[9] Gilbert, N. C., Le Roy, G. V., Fenn, G. K. *Amer. Heart J.* 1940, 20, 519.
[10] Van Dellen, T. R. Cited by Gilbert et al., footnote 9.
[11] Nuzum, F. R. *J. Amer. med. Ass.* 1952, 148, 1174.
[12] Clerf, L. H., Shallow, T. A., Putney, F. J., Fry, K. E. *Ibid*, 1950, 143, 169.
[13] Sauerbruch, F. Chirurgie der Brustorgane. Berlin, 1925; vol. 2, p. 693.
[14] Pickhardt, O. C., Rafsky, H. A., Ghiselin, F. H. *J. Amer. med. Ass.* 1950, 142, 310.

Annotations

THE RIGHT PLACE FOR THE CHILD

GROWING up, like navigation, is always a difficult art. All agree that a child usually masters it best when living in his own home surrounded by his own family; but if he is deprived of this favourable situation, then, the experts say, he will do better in the home of congenial foster-parents than in an institution, however benignly conceived. By an extraordinary suspension of the well-known laws of cussedness, it so happens that in this case the best is also the cheapest. The Select Committee on Estimates, who have just reported on child care,[1] find that the estimated expenditure by local authorities in England and Wales for children in their care for 1952–53, is £1 8*s*. 10*d*. weekly for a boarded-out child, £2 9*s*. 2*d*. for a child in a voluntary home, and £5 5*s*. 1*d*. for a child in a local-authority home. In Scotland the cost of boarding out is a little lower, and the cost of maintaining a child in a voluntary or local authority home a little higher. It might reasonably be supposed that in these hard times boarding out would be widely preferred to institutional care for children; but in fact the committee found great variety of practice up and down the island. Thus in Cheshire 59% of the children in care are boarded out, in Staffordshire 49%, in Hampshire 33%, and in Bradford 23%; the lowest figure was 18% and the highest 77%. Scotland has boarded out 59% of children since 1950, but there is as wide a variation between different Scottish local authorities as between authorities in England and Wales. It is worth noting, however, that Glasgow, with nearly 3000 children in care, manages to board out 70%.

These divergences of practice reflect differences of opinion on the proportion of children in care who are fit for boarding out. Some think that only about half are suitable; others, by taking thought, have raised the percentage greatly in a matter of a few years. Thus Bournemouth, where only 21·6% were boarded out in February, 1949, was boarding out 82·1% by March, 1952. The Home Office believes that it should be feasible to board out between half and two-thirds of the children in care in England and Wales.

Of course there will always be some children who, because of physical or mental disability, need the constant care of trained staff. Apart from these there are children who have been neglected or ill-treated who perhaps need building up in the friendly unemotional atmosphere of a children's home or residential nursery before they are fit for the rough and tumble of ordinary home life. Then a child who has been sent back from a foster-home for one reason or another (or perhaps because a foster-parent has fallen ill) may need more training in social behaviour, or some reassurance to restore his shaken confidence, before he is tried again. Difficult and maladjusted children may be unacceptable to, or unmanageable by, the usual types of foster-parents; and it is also sometimes difficult to find foster-parents for coloured children. The committee rightly object to a Home Office statement that 'institutionalised' children "would find too difficult the uprooting from a large community and adjustment to ordinary family life." What, indeed, can be said for an upbringing that unfits one for ordinary manners and customs? It is a different matter, however, when the good house-mother in a residential home proves unwilling to part from a child with whom she has made a successful parent-child relationship—a situation on which the committee might have commented more fully. Some of these homes are small, and run on the family pattern, taking some dozen children of both sexes ranging in age from 2 or 3 to 12 or 15. The house-mother is often married, her husband, like other fathers, going out to work daily; and the children go to the local school and join in the local activities. With so much family life going on, both the child and the house-mother may wonder what he has to gain by going into a foster-home. Finally there is the thorny question of opposition from the real parents; and if there is a chance that the child may return home before long, their objections must be taken into account. Parents sometimes object to foster homes because they fear alienation of the child's love, and sometimes because they honestly think the child would be better cared for in an institution. The London County Council have found that boarding out against the wishes of parents so often ends in trouble for the child (because of his divided loyalties) and annoyance for the foster-parent that they no longer board children out without the parents' consent. A troublesome parent may make a foster-parent withdraw from the panel, and this, the council say, influences the recruitment of new foster-parents in the neighbourhood. On the other hand, very little has been done so far to advertise the need for foster-parents, and if unsuccesful boarding out acts as adverse propaganda, successful boarding out has the opposite effect. Glasgow, for example, has records of boarding out going back for 170 years, and the tradition is maintained and spread by the foster-parents themselves. London, which did not start boarding out seriously until 1949, had 18·2% of its children in foster-homes by the end of that year, and had only raised the proportion to 24·4% by the end of 1951.

The committee feel that the need for foster-homes should have much wider publicity. They recommend that the Home Office should renew their instructions to local authorities to regard boarding out, with due safeguards, as "the primary objective." Regular returns should be made to the Home Office, and to each children's committee, giving the name of every child not boarded out, and the reason why. They also think more thought should be given to training unsuitable children so that they may become fit for boarding out; and it might be arranged for authorities with difficult areas to board out some of their children in the areas of authorities more fortunately placed. Certainly there must be a vast undiscovered pool of willing foster-parents in the country who have never offered their services because the idea has never been presented to them. A few clever posters might well have an astonishing response.

ERYTHROMYCIN: ANOTHER ANTIBIOTIC

THE antibiotics in current use can be roughly divided into those whose action is relatively specific and those with a broad spectrum of activity. Of the broad-spectrum antibiotics, the three most effective are aureomycin, chloromycetin, and terramycin; but a versatile newcomer now threatens their supremacy. McGuire and his colleagues[1] isolated this substance in crystalline form from a strain of *Streptomyces erythreus* (Waksman) in a soil sample collected in the Philippine Archipelago; it has been named erythromycin, with the trade name of 'Ilotycin' (Lilly). It was significantly active against pathogenic gram-positive organisms and some of the more important gram-negative ones, such as the neisseria, hæmophilus, and brucella groups; it also had some activity against *M. tuberculosis* and other mycobacteria, against rickettsia, viruses of the lymphogranuloma and mouse meningopneumonitis type, *Entamœba histolytica, Trichomonas vaginalis*, and threadworms in mice. Staphylococci resistant to other antibiotics were susceptible.

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[1] Sixth Report from the Select Committee on Estimates. London: H.M. Stationery Office. 1952. Pp. 161. 7*s*.

[1] McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M., Smith, J. W. *Antibiot. & Chemother.* 1952, 2, 281.

Erythromycin is a basic compound that readily forms salts with acids; it is soluble in water to the extent of 2 mg./ml., and is extremely soluble in alcohol. The empirical formula is $C_{34-35}H_{60-65}NO_{11-12}$. Its toxicity is very low—mice tolerated single doses as high as 2000 mg./kg. by mouth, and there were no deaths after subcutaneous doses up to 1000 mg./kg., the LD_{50} by subcutaneous injection being about 1800 mg./kg.; no toxic signs were found in mice receiving 1400 mg./kg. by mouth or 700 mg./kg. subcutaneously or intraperitoneally daily for a fortnight. In dogs no signs of toxicity were found after they had taken 0·5 g. twice daily by mouth for a fortnight. Erythromycin could readily be detected in the blood, urine, fæces, and cerebrospinal fluid of the dogs; the method of assay was an adaptation of Rammelkamp's procedure, using group-A streptococci. The blood-level reached its peak about an hour after an oral dose, and the drug could be detected in the blood for about 8 hours. It must be wholly distinct from "actinorubin," a toxic and far less active substance derived from an actinomyces resembling *erythreus*; and should not be confused with erythrin, an antibacterial substance obtained from red cells.

Preliminary clinical trials are described as "encouraging." By mouth, erythromycin was effective against streptococcal and pneumococcal infections and virus pneumonia.

COLD IN KOREA

IT has been calculated that cold-injury casualties among the American troops in Europe during the winter of 1944–45 were equivalent to the loss of the effective fighting strength of 12 infantry divisions for fifty days. Accurate or not, this calculation illustrates the importance of cold for modern armies.

A report by Orr and Fainer [1] on cold injuries in Korea during the winter of 1950–51, as well as providing useful clinical data, contains much ecological information. Over 4000, or more than half, of the cold casualties evacuated from Korea were admitted to a special cold-injury unit in Japan. In addition to those evacuated primarily for frost-bite, there must have been many wounded men whose injuries were substantially aggravated by frost-bite, but who would not be listed as suffering from cold injury. Some 16% of the casualties so classified were unusual in that they had none of the clinical features regarded as typical of frost-bite, and no history of the feet becoming very cold or numb. Instead there was a gradual onset of stinging and burning of the feet, which showed hyperhidrosis with erythema and maceration of the skin on the soles. Physical irritation from trauma and chemical irritation from long-continued contact with sweat in impermeable footwear were regarded as contributing to this syndrome. A simple classification of frost-bite into four grades of severity was adopted. The first degree showed erythema, swelling, and desquamation; the second, vesiculation; the third, damage to the entire thickness of the skin; and the fourth, damage to the entire foot, making amputation necessary. Few or no vesicles were seen in the most severe grade, but large thin-walled bullæ were commonly present just proximal to the zone of worst damage, and their position gave an indication of how extensive an amputation would ultimately be needed.

The report contains a great deal about environmental circumstances; while, in general, little of it is new, the quantitative aspects are valuable. The duration of exposure in 90% of cases was less than twelve hours; the incidence was highest, as might be expected, among troops actually engaged with the enemy; and the rifleman was affected more often than the N.C.O. or the officer. Not only do winter battle conditions preclude the use of artificial sources of heat, but they involve short bursts of activity with profuse perspiration and prolonged immobilisation in the closest possible contact with frozen ground.

Great interest centres around treatment and especially prophylaxis. Here Orr and Fainer come to the melancholy but inevitable conclusion that in winter climates, such as that of Korea, a considerable incidence of frost-bite must be accepted during combat. But the number of casualties can be reduced in various ways, such as the exclusion of highly susceptible men. Negroes are more susceptible than fair-skinned people, and peripheral vascular disease, previous cold injury, and a high cold-hæmagglutinin titre also seem to make things worse. Thorough and prolonged low-temperature combat training is of undoubted value. Improvements in protective clothing are certainly possible: for instance, severe frost-bite rarely attacked those who wore leather mittens or gloves with woollen inner gloves. Dryness is very important, but it was found that where external moisture was excluded by impermeable gloves or boots, endogenous moisture from perspiration became troublesome. However, this difficulty might be overcome by some of the new fabrics or plastics which permit the escape of water vapour while preventing the entrance of liquid water.[2]

In discussing the immediate treatment, Orr and Fainer emphasise the removal of clothing, and the warming of the frost-bitten area by exposure to a room-temperature of 70°–78°F or by putting the patient's hand in his axilla. Brisk rubbing is better avoided, for it may cause trauma. The authors refer to data indicating that rapid rewarming in baths at 98°–103°F is advisable; but even if this is so it would be impracticable in the field. Chilling, rather than heating, of the injured part certainly seems to result in greater tissue loss,[3] and general body warmth is important.

The consideration of this aspect of military surgery cannot fail to arouse a certain thankfulness in those who fought the late war in desert or jungle rather than on steppe or tundra.

TREATMENT OF LARGE ANEURYSMS

FROM the day that it is discovered, an aortic aneurysm troubles the patient either with pain or with the threat of sudden disaster. Most victims die of the disease; for treatment still falls short of what is needed. In John Hunter's time popliteal aneurysms were common enough to attract much surgical attention; and his method of ligation above the first collateral vessel is still one of the basic principles of vascular surgery. But with the aorta the problem is to apply compression without causing rupture. Halsted ligated the aorta experimentally with metal bands, which had less tendency to cut through the wall than a silk ligature, and Blakemore [4] has employed a similar method in abdominal aneurysm.

Arterial grafting might seem the ideal way of dealing with an aneurysm. In the limbs this may prove to be so, but the aorta has only two places at which a sufficient length can be mobilised—below the renal arteries, and between the left subclavian artery and the diaphragm. Lam and Aram,[5] Brock,[6] and Dubost et al.[7] have described successes with this kind of reconstruction. In most cases, however, the lesion is in a stretch of aorta which bears several large and vital branches; and here

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1. Orr, K. D., Fainer, D. C. *Medicine*, 1952, 31, 177.
2. Bull, J. P., Squire, J. R., Topley, E. *Lancet*, 1948, ii, 213.
3. Davis, L., Scarff, J. E., Rogers, N., Dickinson, M. *Surg. Gynec. Obstet.* 1943, 77, 561.
4. Blakemore, A. H. *Ann. Surg.* 1951, 133, 447.
5. Lam, C. R., Aram, H. H. *Ibid*, 134, 743.
6. Brock, R. C. Lettsomian Lecture, Medical Society of London, Feb. 17, 1952.
7. Dubost, C., Allary, M., Oeconomos, N. *Arch. Mal. Cœur*, 1951, 44, 848.

the problem is to reinforce the sac. More than seventy years have passed since Morrant Baker enlisted relays of dressers to maintain digital compression of a femoral aneurysm for days on end—apparently with good result. Since then other and less simple procedures have been followed, of which wiring and external strengthening are the most popular. A saccular aneurysm is suitable for the insertion of one or more Colt's umbrellas; the surprisingly large amount of wire which they contain is specially treated to collect thrombus. Patients often gain much relief of pressure pain, and embolic complications are less common than would be supposed. Another method is to introduce one long piece of steel wire through a lumbar-puncture or similar needle. Linton and Hardy[8] have described their experience of this; fusiform aneurysms which would otherwise be inoperable can be filled with 300 feet or more of wire. External application of fascia or foreign material met with little success until the discovery of the fibrosing properties of some forms of 'Polythene' 'Cellophane.'[9] Poppe and Oliviera[10] produced periaortic fibrosis by wrapping the aneurysm with a particular sample of the polymer, which was later shown by Yeager and Cowley[11] to contain small quantities of dicetyl phosphate as the active principle. This substance is sometimes added to the pure solvent cast polythene as a plasticiser. Berman and his associates[12] have shown that in rats injection of this compound into the perivascular tissues will cause intense fibrosis but no toxic effects in strengths several times greater than the 0·9% in olive oil which is the recommended therapeutic dilution. They also describe the results of using periaortic injections of dicetyl phosphate in the treatment of patients with aneurysm of the aorta. In no case could reduction in the size of the sac be shown; but a thick layer of fibrous tissue can be relied on to form and probably to limit the further expansion of the aneurysm. Symptoms were relieved in most of the patients who were followed up, but rupture has been seen. Injection of dicetyl phosphate may prove most useful in combination with other methods; it is particularly convenient in treating obscure or dangerously thin portions of the sac. Bearing in mind the limitations of scar tissue as a surgical material, this substance may become a useful member of the selected team of drugs which the surgeon likes to keep in the theatre.

ULCERATIVE COLITIS AND PREGNANCY

THE incidence of ulcerative colitis is greatest during the child-bearing years; and its presence may give rise to some difficulties in the management of married women who are, or wish to become, pregnant. Pregnancy has a very variable effect on the course of the disease, but it may precipitate both first attacks and relapses. Wittkower[13] found that of 40 patients with ulcerative colitis, 3 first had symptoms of it during pregnancy; and Sullivan[14] reported that in 2 out of 15 cases which he analysed the onset of diarrhœa was related to pregnancy. Feder,[15] Bargen et al.,[16] and Buzzard et al.[17] noted that pregnancy was one cause of relapses in their cases. The difficulty in predicting the effect of a pregnancy on any given case has been shown by Kleckner et al.,[18] who found that of 19 patients with ulcerative colitis who had been pregnant at least once, 5 improved in the course of pregnancy, 4 became worse, and 4 were unaffected; but 3 of the cases which improved relapsed in the postpartum period, while 2 of those which relapsed during pregnancy improved after delivery. In the remaining 6 of the 19 patients the disease first began during pregnancy, particularly the first three months.

Patterson and Eytinge,[19] of Boston, have recently reported on 16 patients with ulcerative colitis associated with pregnancy and have divided them into three groups.

> The first group comprised 8 patients who became pregnant while the disease was active (though in no case was the course fulminating). Of these patients 4 thought that their colitis was improved by pregnancy, 3 thought that the disease was aggravated both during and after pregnancy, and the remaining patient was unaffected. In 2 cases the disease became much more severe; 1 of these patients died while being prepared for ileostomy, and the other is likely to undergo an ileostomy. The colitis had no obvious effect on the pregnancy. In a total of 18 pregnancies there was 1 spontaneous abortion and 1 fœtal death, but both these mishaps were thought to be unrelated to the disease.
>
> In the second group were 3 patients who became pregnant while their colitis was in remission. Of these, 2 thought that pregnancy had no effect on their condition, while 1 believed that her symptoms were aggravated. (Tumen and Cohn[20] have also described 3 cases in which the patients went uneventfully through pregnancy during a remission of the disease.)
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> The third group consisted of 5 patients who developed ulcerative colitis during pregnancy. All 5 were acutely ill, and the entire colon was involved. 1 patient died in the sixth month following a miscarriage, and another required ileostomy as a life-saving measure. (Tumen and Cohn likewise observed 3 cases of colitis beginning during pregnancy, in all of which the disease was extremely severe and required ileostomy, followed in 1 by colectomy.)

From the small amount of evidence it appears that during a remission of ulcerative colitis there is a good chance that a patient may be unaffected by pregnancy. In considering whether a patient in remission should be permitted to undertake a pregnancy, the factors to be taken into account include the duration of the remission (it would seem unwise to allow pregnancy in a patient who has been in remission for less than a year) and the frequency and severity of previous attacks. In addition, remembering the important part which psychological factors may play in the course of ulcerative colitis, it is important, as Patterson and Eytinge point out, to discover whether the patient really does want to become a mother or whether she is inquiring at the instigation of her husband or to be assured that she cannot have children. Where pregnancy is genuinely desired, to deny it may itself lead to a relapse. In a patient in remission who is already pregnant, the pregnancy may often be allowed to continue; but termination may have to be considered in certain cases, particularly where it seems that the patient could not bear the extra strain imposed by an addition to the family. When the disease is clearly active, pregnancy is better avoided; but Patterson and Eytinge have shown that in these circumstances the disease need not necessarily become worse; so in some cases, especially when the pregnancy is much desired and the disease mild, it may justifiably be allowed to continue.

Mr. O'DONEL BROWNE, master of the Rotunda Hospital, died in Dublin on July 24.

Mr. A. A. GEMMELL has been elected president of the Royal College of Obstetricians and Gynæcologists in succession to Dame Hilda Lloyd. He will take office in October.

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INTERNATIONAL CONGRESS OF DERMATOLOGY

THE tenth International Congress of Dermatology was held in London from July 21 to 26, under the presidency of Sir ARCHIBALD GRAY. The attendance was well over a thousand, drawn from 45 countries including the U.S.S.R. The scientific meetings were held at Bedford College, and simultaneous translation into English, French, German, and Spanish was available for the larger meetings.

Addressing a great audience at the congress dinner held at Grosvenor House on July 24, Sir HENRY DALE, O.M., F.R.S., proposed The Future of Dermatology. The founders of the specialty had, he said, pursued industriously the task of classification, and nothing in science was more imposing than dermatological nomenclature. The discovery of the itch-mite was the first recognition of an external organism as the cause of a disease, and dermatologists were cultivating fungi long before the days of Lister. Study of the skin, because it afforded such easy access, had played a large part in revealing the rôle of spirochætes, protozoa, and other organisms in causing disease; and in Professor Hoffmann the congress was able to salute in person the co-discoverer, with Schaudinn, in 1905, of the *Spirochæta pallida*. Dermatologists had been early in the field of morbid histology, and they were helping to write the still unpublished chapters in pathological physiology. Anaphylactic and allergic reactions—representing a perversion of reactions of immunity—formed a basis of their present discussions; and having taken his share in demonstrating the significance of the liberation of histamine, Sir Henry felt some grandfatherly pride in the antihistaminics latterly developed in France. He could safely prophesy (1) that dermatologists would continue to make discoveries of first-class importance, and (2) that there would remain a large number of conditions which they could do no more than identify and palliate.

As the first of five visitors to reply to the toast, Prof. L. M. PAUTRIER (France) spoke of the way in which the study of diseases as they affect the skin has thrown light on their general pathology: among others he instanced tuberculosis and sarcoidosis, and he expressed pleasure at recent evidence of the foresight of colleagues who had applied themselves to research on collagen tissue. Prof. E. HOFFMANN (Germany), in recalling old and famous names, exhorted the young to make the most of their opportunities. Dr. D. M. PILLSBURY (U.S.A.) thought that at times the useful basic knowledge about the skin lagged behind knowledge about other organs whose movements and secretions appealed more to investigators; but in this respect times were changing. He expressed the thanks of those present to their British hosts for overcoming all difficulties and re-creating this international conference: medical problems transcended nationalism, and advance would be easy if men could but grasp the hand of colleagues throughout the world. Two further responses came from Prof. FRANCO FLARER (Italy), who had been delighted by the spirit of freedom in the congress discussions, and the fraternal feeling, and from Prof. GAY PRIETO (Spain).

Prof. H. HAXTHAUSEN (Denmark) proposed the toast of The Ladies' Committee, without whose distractions, he said, "many of us would have collapsed under the heavy burden of scientific discussion." To which Lady GRAY most modestly replied.

The programme included the demonstration of cases on two afternoons, a most creditable selection of disorders being assembled at the Queen Alexandra Hospital, Millbank. A number of films were shown, and throughout the week there was a display of photographs, wax models, microscopical preparations, and books of historical interest. On July 25 the Royal College of Physicians held an evening reception at which members of the congress were welcomed by Sir Russell Brain, the president, and Lady Brain.

Eczema

Since there is still no general agreement on the concept of what constitutes eczema Dr. J. C. BELISARIO (Sydney) suggested that the term be limited to a morphological entity comprising erythema, minute papules, vesicles, pits, and crusts. He outlined the known facts and theories on the pathogenesis of eczema and laid stress on the beneficial effect of an increased oxygen supply in inflammatory skin eruptions.

Dr. D. M. PILLSBURY (Philadelphia) indicated the magnitude of the problem of eczema by stating that more American troops were evacuated from the Pacific theatre on account of skin disease than because of wounds. At least half of the skin sick had some form of eczema. Even in temperate climates, sweat retention played an important part in the aggravation of eczema, notably in atopic dermatitis. The origin of nummular eczema remains obscure.

Prof. G. MIESCHER (Zürich) wondered how far one was justified in regarding all eczema as allergic. The only type in which we had satisfactory evidence of allergy was contact dermatitis of sensitisation. Here the histological appearances were uniformly similar whatever the allergen: there was epidermal spongiosis with an infiltrate of lymphocytes. In dermatitis due to primary irritants one saw foci of pyknotic epidermal cells.

Dr. R. T. BRAIN (London) found skin-testing of very little value in the elucidation of the cause of infantile eczema. Histamine did not appear to play a direct part in the production of eczema. A great deal could be achieved in infants with adequate sedation: control by adrenocorticotropic hormone (A.C.T.H.) or cortisone was often incomplete.

Prof. J. GATÉ (Caluire, Rhône) felt that results of treatment had shown that psychological factors contributed to the pathogenesis of eczema but that they did not explain everything. He had been unable to show the congenital transmission of eczema in experimental animals, and doubted whether circulating antibodies existed in them.

Prof. G. HAGERMAN (Lund) advanced a theory to explain how lymphocytes transmitted epidermal hypersensitivity: according to Andrew and Andrew, lymphocytes were transformed into epidermal cells. At Lund, lymphocytes were being injected intraperitoneally after vital staining and their fate studied in excised skin.

Several contributors emphasised the importance of physicochemical factors in the production of exogenous dermatitis. Dr. D. ANDERSON (London) said that the pH of the skin in normal adults was between 4 and 6: in the axillæ it might be as high as pH7. In alkali dermatitis readings up to pH12 were obtained. In these cases there appeared to be a deficient buffering capacity of the skin, as had been demonstrated by Prof. W. BURCKHARDT (Zürich) by his alkali neutralisation and alkali resistance tests. The buffering properties of the epidermis were attributable to the amphoteric properties of keratin, the diffusion of carbon dioxide, and the amino-acids of the skin secretions (Dr. D. J. H. VERMEER, Holland) and skin cells (Dr. H. SPIER, Munich). Increased alkalinity of the skin made it more susceptible to sensitisation, and according to Dr. M. SULZBERGER (New York) the pH might rise through undercleanliness, through overzealous use of detergents, and by infection. It was therefore a surprise that a victim of alkali dermatitis ever got better.

Dr. D. S. MITCHELL (Canada) described cases of wool dermatitis in Servicemen. One case of atopic dermatitis had been cured by using cotton and synthetic substitutes for woollen clothing: this patient's intradermal test with wool had been negative. Dr. J. H. TWISTON DAVIES (Chester) said he had seen no such cases since the end of the war, and that he felt there must be an endocrine factor in these patients, who were hypogonadal and had similar facies.

Sensitisation to chrome salts was found by Prof. H. Jaeger (Lausanne) to underlie many cases of cement dermatitis. Some cases of occupational eczema in pottery workers had been traced to sensitisation to cobalt (Dr. V. Pirilä, Helsinki). Polymorphic light sensitivity in cases of lymphogranuloma inguinale was described by Dr. C. E. Sonck (Helsinki). In his cases, no sulphonamides had been given. To their use Dr. D. Bloom (New York) ascribed three cases of bullosis mechanica toxica.

A.C.T.H. and Cortisone

Dr. L. A. Brunsting (Rochester, Minn.) said that the manner in which A.C.T.H. and cortisone acted in skin diseases was not yet known. It was certain that they did not alter the fundamental disease processes. He felt that their use was hardly justifiable in cases of chronic discoid lupus erythematosus. They could control the acute form of the disease, but remission depended upon continued administration. The milder cases of the acute form did not need cortisone but did well with rest in bed and blood-transfusions. The hormones do not abolish the "L.E. cell" phenomenon: indeed on necropsy, treated cases showed all the typical histological changes. An economical and effective way of giving cortisone was by intravenous drip using 500 ml. of 5% dextrose solution in 8–12 hours: in this way 10–20 mg. of cortisone was as effective as 100 mg. intramuscularly.

Dr. L. P. Ereaux (Montreal) found the hormones of use in the relief but not cure of pemphigus vulgaris. They were of less use in pemphigus vegetans, and cases of pemphigus foliaceus might be changed into rampant acute pemphigus. In spite of antibiotics, severe but masked infection remained a risk.

Dr. M. Sulzberger (New York) was more optimistic than other speakers. He thought that possibly pemphigus might be a self-limited disease if one could keep the patient alive long enough. He described the effect of the hormones on the allergic disorders as "morbidostatic": they did not inhibit the formation of antibody or its union with antigen. In some way they buffered the body against the effects of the reaction. Although the fundamental processes were unchanged, this was not entirely to the bad, since they did not alter the chances of a natural remission. The local application of cortisone was quite ineffective, even on denuded surfaces. The local use of Compound F, however, appeared promising.

According to Dr. D. Bloom (New York) the mouth lesions of pemphigus required much higher doses of the hormones than the skin—doses so high that side-effects are inevitable. Dr. B. A. Newman (California), unlike Dr. Sulzberger, had found it impossible to reduce the maintenance dose of the hormones in cases of atopic dermatitis: he also found topical cortisone specific for necrobiosis lipoidica and successful in chronic discoid lupus erythematosus.

Dr. R. Aron-Brunetière (Paris) found implants of 25–50 mg. of cortisone effective in Besnier's prurigo, dermatitis herpetiformis, and psoriasis. Dr. F. W. Jacobson (West Indies) described a case of generalised psoriasis which cleared up on traditional treatment only after cortisone was discontinued. Dr. C. Grupper (Paris) said that the pigmentation resulting from treatment with these hormones might be more ugly than the original dermatosis: it could be avoided by giving large doses of vitamin C and methionine during the treatment.

Tuberculosis of the Skin

The treatment of skin tuberculosis with calciferol was described independently by Dr. G. B. Dowling (London) and Dr. J. Charpy (Marseilles) during the war. Unfortunately the latter was unable to attend the congress and his paper was read by a deputy.

Dr. P. Marcussen (Copenhagen) indicated that there was a high rate of relapse in cases of lupus vulgaris treated with calciferol and that some of the old figures for Finsen light therapy were much better.

Dr. E. A. Sainz de Ajá (Madrid) said that despite the discovery of streptomycin, thiosemicarbazone, *p*-aminosalicylic acid, &c., there was still no drug which was to tuberculosis what arsphenamine was to syphilis. There was still a place for physical procedures—curettage, grafting, and cautery. Calciferol was of most use in lupus vulgaris. Thiosemicarbazones were of success in fistulised bone lesions, scrofuloderma, and Bazin's disease.

Preliminary treatment of cases of lupus vulgaris with P.A.S. and streptomycin permitted a shorter course of treatment with vitamin D_2, in the experience of Prof. M. L. O. Craps (Liége). Diamino-diphenyl-sulphone alone was ineffective in tuberculosis cutis (Dr. A. K. Banerjee, Calcutta). The action of calciferol on virulent and attenuated strains of tubercle bacilli had been studied by Dr. G. Wetherley-Mein (London). No inhibition of cultures had been observed after the addition of calciferol, the serum of calciferol-treated patients, or calcium. The healing of experimental wounds in guineapigs was not retarded by calciferol.

Lupus Erythematosus

Dr. Stephen Gold (London) regarded lupus erythematosus as a sensitivity reaction to various infections and drugs. In the chronic discoid form, the process was inhibited by the normally functioning pituitary-adrenal system. Where the latter was disturbed, the normal immune mechanism no longer operated and the disease became systemic. In the systemic form there was evidence of gamma-globulinæmia and antibody formation on an unusual scale resulting in cold agglutination, and a positive Coombs test and Wassermann reaction. Occasionally it was impossible to transfuse such patients, because of numerous abnormal antibodies. The L.E. cell phenomenon was not a constant finding. It was due to an immunologically distinct fraction of the gamma-globulin.

Dr. T. Inderbitzin (Zürich) described the artificial induction of the L.E. cell, using polymolecular anticoagulants—'Liquoid' (Roche), which is a sodium polyethanolsulphonate, and the sodium salts of polyvinyl alcohol sulphuric esters. He suggested that since these substances have physicochemical properties similar to heparin and hence chondroitin-sulphuric acid, the production of L.E. cells in acute lupus erythematosus may be due to the release of abnormal heparinoids from foci of collagen degeneration.

Psychiatry in Dermatology

Dr. Twiston Davies felt that a useful approach to the problem of psychiatric help for the skin patient was afforded by a scheme which he had operated for eighteen months. The psychiatrist sat in on almost all outpatient interviews, and was then able to select those cases which he felt could be helped by psychiatric means.

Dr. Ida Macalpine (London) had made a study of patients with facial dermatoses of various kinds. She had found no personality types in regular association with the skin diseases. In most there was a masked depression which had anteceded the rash. In cases of dermatitis of the lids there was evidence of suppressed grief. All showed paranoid concern with their appearance which was not found in cases of organic disease, such as lupus, in which the disfigurement was much greater. Improper handling of such cases might free them of their skin disorder but precipitate a thoroughgoing depression. Dr. Hugh Gordon (London) described the successful application of hypnosis to the treatment of itching dermatoses. Of his series of 102 cases, 51 were cured and 26 improved; 13 were still under treatment and there had been 10 failures.

Dr. J. Duverne (France) made a plea for objectivity in psychiatric investigation of skin cases. Dr. E. Hachez

(Westphalia) denied that this was possible, since "psychosomatics" was a point of view and nothing could be verified by amassing statistics. Dr. SULZBERGER said that he felt there was great likelihood of abuse of the psychosomatic approach: most non-dermatologists had greater difficulty with skin cases than any other, and to be able to attribute all and sundry lesions to "nerves" would obviate the necessity of precise dermatological diagnosis.

Dr. F. F. HELLIER (Leeds) felt that more could be achieved by dermatologists without psychiatric assistance if they were prepared to devote time to a sympathetic hearing of the patient's case with its social ramifications and economic burden.

Various Investigations

Dr. J. S. PEGUM (London) described estimations of the loss of protein by scaling and exudation in exfoliative dermatitis, psoriasis, and pemphigus. In some instances the serum-proteins were pathologically low, and the critical amount of loss appeared to be about 7 g. per square metre of skin per day. However, since psoriasis cases could lose as much and more without depression of the serum-proteins, it seemed likely that loss from the surface was not the sole cause of hypoproteinæmia.

Dr. T. B. FITZPATRICK (Rochester, Minn.) reported preliminary results of work which suggests that pigmented nævi contained an inhibited tyrosinase system, whereas malignant melanomata, whether pigmented or not, had an active tyrosinase system. This could be the basis of a test for malignancy.

Dr. C. J. WHITE (Chicago) reported histological findings in diseases of the nails. He described the occurrence of cocci in the nailplate suggesting that a bacterial onychitis must exist.

Special Articles

INGENUITY IN WHITECHAPEL

SOME recent developments in equipment at the London Hospital deserve to be generally known.

AN OXYGEN TENT

Work in cerebral, cardiac, and thoracic surgery has grown so much that oxygen tents are nowadays needed in quite large numbers: for patients prefer them, it seems, to B.L.B. masks, which are not comfortably tolerated after an hour or two. At the London there are often as many as a dozen oxygen tents in use at a time; and these, with their accessory cooling-chambers mounted on large metal stands, are costly to buy (£180–£237) and relatively expensive to hire. In any case it has been almost impossible to buy them at all lately, supplies are so scarce.

Fortunately the plastic canopies in which the patients are enclosed can easily be made, and Mr. R. W. Davis, instrument supervisor to the hospital, has found no particular difficulty in designing a home-made cooling-chamber and stand. In the original model, entry and exit ports were fitted to a 5-gallon drum, and this, with an escape pipe in the bottom, to allow water to run off, made an efficient cooler when filled with broken ice. The drum was lagged with an insulating jacket, and —with a bucket under it to take the water draining off the ice—was mounted on a wheeled metal stand. A right-angled arm, attached to the stand, carried the tent, which was fitted, by a collar, to the exit port of the drum, and slung to the arm by means of three metal bars like coat-hangers. The oxygen cylinder, of course, was connected to the entrance port. The upper part of the tent was made of transparent plastic, so that the patient could see and be seen.

This apparatus has proved to be thoroughly successful. Even the smallest nurse, when she wishes to put the whole apparatus away, can unhook the hangers, fold up her tent, like an Arab, and silently wheel off the stand. Moreover, the whole thing packs up against the wall in a very small space; even the carrying arm can be taken out of its slot, reversed, and put back, so that the long bar slips out of sight and only a short bar is visible.

The drum holds 20 lb. of ice, which needs renewing every 4–6 hours. Oxygen is run in at 10 litres per min. for the first 20 min. and after that at 6 litres per min. Tests made on volunteers showed that oxygen concentration reached 40% in 20 min. and 50% in 1 hour. The carbon dioxide level did not rise above 1·7% even after 4 hours of running with the canopy closed, and temperature and humidity remained constant during use. These results were almost identical with those obtained from the use of a standard oxygen tent.

Some 8 of these "London Hospital Pattern" tents have been in use in the hospital for the past year, with entirely satisfactory results, and they are now on the market at £50 apiece. The makers are Hospital Appliances Ltd., 18, Manor Road North, Hinchley Wood, Surrey.

STERILISING SYRINGES

Another good invention is a metal syringe-container for use in the hospital central sterilisation service. Before the war syringes were sterilised in the wards —as they still are in many hospitals. After the war they were centrally sterilised, parcelled up in grease-proof paper. This was quite satisfactory, but the packing took time, there were many breakages, and it was not always easy to get enough of the paper.

Mr. Davis has now devised cylindrical metal containers, made in four sizes, to carry syringes of different capacity. Any known make of syringe of the type which can be sterilised assembled will fit these containers. (At the London they use glass syringes with metal nozzles, the metal and glass being welded without the use of cement.) The flange at the base of the syringe rests on a circular constriction near the open end of the container; and the metal cylinder is narrower below this constriction, so that the syringe fits snugly down inside it with its needle pointing towards but, not reaching, the end of the tube. Part of the container above the constriction is cut away, so that the syringe can be slipped in without damage to the needle.

The cap which closes the container has a circular perforation in its side: when this lies opposite the place where the tube is cut away, steam can enter through it during autoclaving. After sterilisation the container is closed by turning the cap so that the hole no longer lies opposite the open part. It can then be dated with an ordinary date stamp and sealed with a strip of 'Sellotape.' A piece of non-absorbent wool in the cap acts as a filter for dust and protects the syringe against mechanical damage: even when the container is thrown violently on the floor, the syringe generally remains intact. Breakages, which with the old paper pack amounted to 1 in 160 syringes sterilised, have now fallen to 1 in 550. Moreover much time and space have been saved: at the London they sterilise 3000 containers a week, and one man using a 6 ft. bench for packing can pack, sterilise, date, and seal 60 containers in an hour.

The containers cost 3s. each (which is less than must be paid for a heat-proof glass container of the same size) and they last more or less for ever. Tests have proved that their contents remain sterile after autoclaving or hot-air sterilisation. The point of the needle cannot be damaged whether the nozzle is of the central or the eccentric type; and if the needle is firmly fitted in the first place it does not come off. In the wards, of course, it is a great convenience to be able to use the syringe straight away without having to assemble it.

The containers, like the oxygen tents, are made by Hospital Appliances Ltd.

RADIO-OPAQUE SWABS

The London Hospital has recently taken to using, as a routine, swabs with a thread which is opaque to X rays woven into them. In any uncertainty about the swab-count, the patient is now radiographed at once, and any question of a swab being retained is settled out of hand. Several brands of these swabs are on the market, but some are said to be unsatisfactory, because, though they are opaque to X rays outside the body, they do not throw a detectable shadow through the tissues of the patient. 'Ray-Tek' swabs, the brand used at the London, are made in England by the American firm, Messrs. Johnson & Johnson of Slough. Only one criticism is offered against them—that they are made only in small sizes. Large swabs, measuring 9 × 6 and 10 × 9 in. are now in use in operating-theatres, and it is not so difficult as might be supposed to pack one of these into the abdomen and overlook it. Devices for preventing such accidents are never foolproof. It is easy enough to clip a Spencer Wells forceps on to each swab as it is put in position; but it is natural, and equally easy, in case of sudden hæmorrhage, to seize the nearest forceps to control it, and let the released swab take its chance. A system which ensures that, in case of a miscount, no swabs will be left in the patient, is a safeguard on which every surgeon (not to mention every patient) should be able to depend. A general demand for these swabs seems likely, and manufacturers might well turn their attention to providing them in the large sizes now so commonly used, as well as in smaller sizes.

SILENT CURTAIN RUNNERS

To be roused from sleep by the abrupt clash of curtain runners can be quite an alarming experience, even for those who are perfectly well. Every bed at the London, now, can be enclosed in a cubicle of curtains, to the great comfort and satisfaction of patients. But when these are drawn, the familiar rattle is absent. The little wheels travelling along the grooved bar, with which we are all familiar, have been replaced by strips of metal, covered in strong woven cotton, and bent to grip the bar at each side. These slide as readily as wheels, but with a gentle and soothing susurrus, hardly to be heard. They are made by Messrs. Cope & Timmins, 91 and 93, Paul Street, Finsbury, London, E.C.2.

The Wider World

IN EASTERN NEPAL

MICHAEL WARD

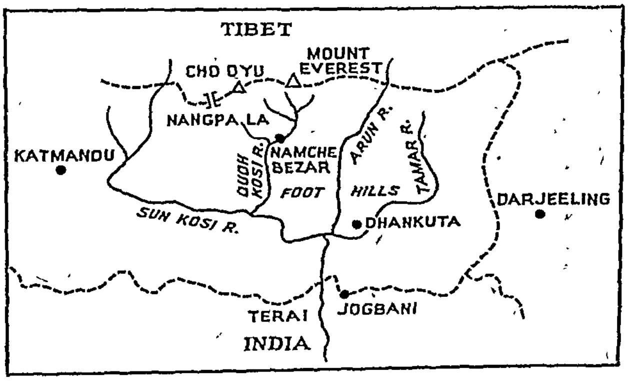
M.B. Camb.

WHEN the 1951 expedition explored Mount Everest from the south, few doctors had been through Eastern Nepal. I knew of an American doctor who had travelled in this area but of no others. I had no microscope or other aid to diagnosis, except a stethoscope; and to talk to the local inhabitants I needed one and sometimes two interpreters.

We started on the edge of the *terai*—the jungle-covered plain—at a town called Jogbani (see sketch map). A good many people here were pock-marked, and cholera epidemics broke out fairly regularly. *Aul* or malignant tertian malaria was prevalent in the *terai*, especially in the monsoon season. The number of cases usually began to decrease by the end of September. Chronic diarrhœa —presumably a chronic dysentery—was endemic, but no-one took any notice of it. I saw a few people with scars in the groin—possibly the result of lymphogranuloma inguinale.

Our party then spent three weeks in the foothills, at heights varying from 1500 to 8000 feet. Sanitation in the villages was non-existent: the streams which supplied drinking-water were invariably used as lavatories as well; and villages could be smelt long before they were seen. The houses abounded with insects of different kinds; and our sleeping-bags often became infested with insects from those in which we stayed. D.D.T. was very useful but we did not have enough of it.

Dhankuta, the main village of the area, had cholera and smallpox, but its height of 5000 feet meant that there was little if any malaria. We crossed the River Arun, at 1500 feet, soon after leaving Dhankuta. The Arun valley has a bad name for malaria. We travelled along its banks for two or three days, and saw a few people with "fever." We came across many leeches, especially on the paths near the villages, and the animals belonging to the villagers were covered with them. The natives picked them off with their fingers—they seemed to have no other way of dealing with them—but when we did this we developed sores which did not heal until the monsoon stopped.



We passed a village which had been attacked by a "plague." People were dying after four or five days' illness with a high fever. There were no swellings on their bodies, no eruption or rash, and no diarrhœa. In this area similar epidemics broke out from year to year in the monsoon period in one or other of neighbouring villages, separated from each other by deep gorges. I thought the disease might be typhus, but, as all my information was second-hand from different interpreters, it was difficult to tell. Near this village our party lost their way along one of the paths, which were very bad, and inadvertently walked through a hornets' nest. A few porters were stung 4 or 5 times; within fifteen minutes they began shivering violently and sweating. I had no thermometer immediately handy, but their pulse-rates were between 120 and 130. Within six hours they had recovered, though they all thought they were going to die.

We arrived at Namche Bezar (12,000 feet) in the third week of September at the end of the monsoon. I saw several people with gonorrhœa; in some cases the infection was several weeks old. They said they had contracted it in Tibet, a few miles away over the Nangpala pass (19,000 feet), but I think it was also present in Namche Bezar. During the exploration of the southern approaches to Everest we returned to Namche Bezar several times. Once a member of the party ate some local honey, and lost consciousness for about ten minutes. Apparently Nepalese honey is poisonous in October and November because the bees then feed on rhododendrons.

I heard of another epidemic in the valley of the Dudh Kosi, 2000 feet below Namche Bezar. It started after the monsoon, and attacked the villages along the river. Abdominal pain and nose-bleeding were common symptoms. This may have been one of the acute epidemic hæmorrhagic fevers, akin to the one which has been encountered in Korea.[1]

Blepharitis, chronic conjunctivitis, and cataracts were fairly common, especially in the Namche Bezar region.

Our party suffered less from sore throats and respiratory infections than those who approached the mountain from the north. The moister atmosphere was probably responsible; we had less dust and wind to contend with than in Tibet, and previous expeditions had not had the advantage of antibiotics. All of us, including the Sherpa porters, took proguanil ('Paludrine') while we were in the malarial areas, and for three or four weeks after we had left them. None of the party suffered from malaria; the risk was not great because we crossed the *terai* rapidly in a lorry, and we were not in the worst areas for long.

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[1] *Lancet*, 1952, i, 757. Mayer, C. F. *Ibid*, p. 975.

Medicine and the Law

The Straffen Case

IN October, 1951, John Thomas Straffen, charged at Taunton assizes with the murder of a child, was found unfit to plead and was ordered to be detained "until His Majesty's pleasure be known"—the direction of indefinite duration usual with persons sent to Broadmoor. On July 25, 1952, Straffen, charged at Winchester assizes with the murder of another child, having pleaded "not guilty," was found "guilty" and was sentenced to death. As his counsel observed in his final address to the jury, the medical evidence offered by the prosecution and by the defence was unusually harmonious. The witnesses substantially agreed that he knew, when he killed the child, that he was doing wrong; the difference between them was that the Crown witnesses said he knew perfectly well, while the defence witnesses said he knew, but only within the limits of his limited intelligence. The defence was in the difficulty, not infrequent in such cases, of contending firstly that Straffen was not the man who killed the child, and, simultaneously or alternately, that, though he might have killed her, he was not responsible for his actions. It is hard to assert the first plea convincingly if the main battle develops on the second.

The Solicitor-General, who prosecuted, obtained the leave of the court to offer evidence of the similar killing of two other little girls attributed to Straffen. This course, prejudicial to his chances of acquittal, was permitted as in the interests of justice because, although helping to establish the identity of the killer, it was capable of proving the design or criminal intent in circumstances of remarkable similarity. As usual, the jury had to be warned that they were trying Straffen upon the charge of one killing only. Normally the law is particularly careful to exclude evidence of previous similar offences by an accused person; a jury must not be asked to conclude that, because he has previously committed similar crimes, it is probable that he has committed the crime with which he is charged, although juries would really be more than human if they managed to keep out of their minds such an element of strong probability as would certainly influence them in the ordinary affairs of life.

A police officer's evidence of Straffen's history, elicited more fully in cross-examination by Straffen's counsel, was as follows.

> Born in 1930, he went with his mother to India (where his father was a serving soldier) at the age of 2. Brought back to Bath in 1938 with his family, he attended school up to the age of 10, when he was certified as a mental defective under the Education Act. In 1939 he was charged at the Bath juvenile court with larceny of a purse from a little girl and was placed on probation for two years. Seven months later he came before the Bath magistrates for breach of the terms of probation, was certified as a mental defective, and was sent to a home for defectives. From an institution of this kind (to which he had been transferred) he was discharged in 1946, having reached the age of 16. Returning to Bath, he worked as an errand-boy.
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> Next year he was arrested on a charge of housebreaking. When tried at Bath quarter sessions, he asked for one other charge of housebreaking and 11 charges of larceny to be taken into account. The police then informed the court that Straffen had wrung the necks of five fowls, leaving their carcases in the fowlhouse, had assaulted a 13-year-old girl, and had said—though no proof was forthcoming—that he had committed several sexual offences. He was certified a mental defective for the second time and removed to an institution for mental defectives from which he twice escaped. He was granted a licence in April, 1951, and went back to his parents in Bath, working in a market garden.
>
> Brenda Goddard, aged 6, was murdered in Bath by strangulation in the following July. Five days after Straffen had been seen by the police, Cicely Batstone, aged 9, was similarly murdered. Tried at Taunton assizes in October, he was (as already stated) found unfit to plead, the only witness being Dr. P. W. J. Parkes, medical officer at Bristol prison. Straffen escaped from Broadmoor on April 29 last. Linda Bowyer, aged 5, was similarly murdered later on that day, not far away.

Dr. C. R. Gibson, the Bath police surgeon, gave evidence of the manner of death of Brenda Goddard and Cicely Batstone. Dr. R. D. Teare, the pathologist who examined the body of Linda Bowyer, indicated the similarities discoverable in all three cases. There was no sexual interference or other injury than strangulation in any of them. Of the medical witnesses for the defence Dr. A. Leitch said he had first seen Straffen in 1947 when in the prison service at Bristol. Straffen was a feeble-minded mental defective with little or no moral sense. Dr. Leitch thought he felt no more emotion in killing these girls than a normal person would feel in killing a fly. He showed no regret or remorse, but rather took pleasure and pride in speaking of his delinquent actions; his mental age was 9½ years. He saw him again in Bristol in 1951; an encephalograph indicated abnormal functioning of the brain. Straffen was unable to foresee the real nature and consequence of his acts: he told the witness that he killed Cicely Batstone to annoy the police, and that it was a sensible thing to do and easier than stealing; after the crime he slept soundly. He had seen Straffen at Wandsworth prison in the present month; the mental condition showed only slight changes; he had become more familiar in a glib way with court procedure, but his intelligence and reasoning power were no better; he was rightly certified as a mental defective; his condition was incurable. He knew the nature and quality of his acts, but only within the narrow limits of his own defective low intelligence; from the medical point of view he was not insane. Mr. Justice Cassels put some significant questions to the witness:

> Q. Do you think he has a desire to kill?—A. His desire to kill seems to me to spread from his desire to pay back the police because of his hatred of them.
>
> Q. Had he the intelligence not to select a policeman to strangle but a defenceless girl?—A. Evidently, my lord.
>
> Q. You say he knew the nature and quality of his act within the limitations of his intelligence and he knew he was squeezing a human throat; did he know he was squeezing a little girl's throat?—A. Yes.

Dr. Parkes, recalling that at Taunton in October he had told the court that Straffen was unfit to plead, said he was now fit to plead; the accused had profited by his experiences. Dr. R. S. Williams said Straffen came under his personal care at Broadmoor from last November till his escape; he was a feeble-minded person; he knew the nature and quality of the act of killing Linda Bowyer but not as a normal person.

Although it may have been doubtful how far this medical testimony would affect the verdict, the Solicitor-General obtained leave to call rebutting evidence. Dr. J. C. Matheson, principal medical officer at Brixton prison, said that Straffen gave him a clear account of his movements after his escape from Broadmoor; he needed little prompting and was able to trace his route on a map. He was feeble-minded and certifiable as such, but not insane; he knew that, if one killed a person, one should be punished; he was simple and childish in conversation. Dr. J. H. Murdoch, principal medical officer at Wandsworth prison, said Straffen showed no signs of insanity while there. He would put him in a higher category than feeble-minded; he was rational in conversation, well behaved, clean, and tidy; Straffen said he had played contract bridge in Broadmoor; he knew how many cards and suits there were in a pack. He was sane. "Sane although he has been in Broadmoor?" asked counsel for the defence. "Yes," replied the witness, "there are quite a number of sane people in Broadmoor." Dr. T. A. H. Munro, physician in psychological medicine at Guy's Hospital, said that Straffen was feeble-minded, "of a high-grade type, coming at the top end of the scale"; he was unstable.

These expressions of opinion will be important if, as is usual with all convictions of murder, the verdict is to be examined in the Court of Criminal Appeal. The Rules in McNaughten's case appear to be inapplicable. The facts may stir the public conscience, but the public may show less interest in forensic disquisitions than in the problem of what to do with persons who have Straffen's history.

Public Health

Poliomyelitis

POLIOMYELITIS notifications in the week ended July 19 were (previous week in parentheses): paralytic, 104 (78); non-paralytic, 59 (41); total, 163 (119).

A comparison between this year and the preceding five years is as follows:

Year	*Total cases up to and including 29th week*	*Cases in 29th week*
1947	805	193
1948	791	45
1949	847	99
1950	1920	261
1951	1161	134
1952	1176	163

Up to and including the week ended July 19 the overall notification-rate for England and Wales was 2·68 per 100,000 population.

The districts which have notified 10 or more cases up to July 19, with incidence per 100,000 population, are:

District or borough	*Total cases*	*Incidence*
Gateshead	61	55·2
Felling	21	83·3
Liverpool	23	2·9
Woolwich	17	11·3
Newcastle upon Tyne	32	11·0
Birmingham	41	3·7
Leeds	36	7·2
Manchester	23	3·3
Whickham	13	61·0
Ealing	10	5·3
Harrow	13	5·9
Blyth (Suffolk)	12	46·1
Coventry	10	3·8
Malvern	10	51·0
Sheffield	13	2·5
Cardiff	14	5·7
Yeovil	18	102·0

The increase in weekly notifications is maintained, and the disease is becoming increasingly distributed throughout England and Wales.

Statistics for the Second Quarter

The Registrar-General[1] announces the following provisional figures for England and Wales in the quarter ended June 30 this year (corresponding figures for the same quarter last year in parentheses): birth-rate 16·0 (16·6) per 1000 population; stillbirth-rate 22·4 (22·5) per 1000 total live and still births; death-rate 10·6 (11·1) per 1000 population; and infant mortality 25·1 (28·7) per 1000 related live births.

In England Now

A Running Commentary by Peripatetic Correspondents

WHAT is the quaintest oddity on permanent view in the streets of London? I have been abroad over-long and perhaps the competition has already been held. If not, I would confidently enter No. 429, The Strand. In Muirhead Little's history of the British Medical Association up to 1932 is described the installation of the Epstein statues on the outside of the old B.M.A. building, showing "physiological and pathological changes in the human form." The author describes a "stunt" by an evening paper castigating the "outrages upon decency and good taste." He continues: "the statues have since been allowed to rest in peace, scarcely noticed by the passer-by, in their elevated position." I ask you, *have* they? After a diet of mutilated Dissolution statues in provincial cathedrals and abbeys—even the painful climbers up Jacob's 40-feet stone ladder on the west front of Bath Abbey were beheaded—I returned to London and went to enjoy those Epstein statues. But it looks as though some mighty-muscled mason has rioted in an orgy of weird operative surgery—amputation, decerebration, thoracoplasty, mastectomy, infanticide, and steatopygectomy. Eighteen dejected remnants keep their vigil high up there, and proclaim that London's outraged philistines are more easily pacified than London's atmosphere and weather.

* * *

Our new neighbours have just moved in, and their first care was to erect an H above their chimney. Thanks to the B.B.C. report on television this has saved us an immense amount of trouble. Thumbing our copy of the report we deduced at once that we are not likely to be asked to act as half of a bridge four or as "sitters-in," that our neighbours have not read any good books lately, and that their income is less than £650. Most comforting of all, we find that their educational level is lower than our own. *We* have a radiogram.

* * *

A scientific friend of ours had occasion recently to attend a meeting in one of the brisk industrial cities of the North, and was offered accommodation in a women's hostel. Ever anxious to see how the other half lives, our friend accepted; and it is a tribute to his scientific spirit that he persevered even on finding that the female denizens were still in residence.

He was a trifle mystified to find in his room a notice saying "No furniture is to be removed from this room without permission of the warden," but it came to him that the midnight-feast tradition of his own schooldays might be represented among the female sex by midnight furniture-removing parties. The hormones, you know. He was, however, fascinated to find similar notices on the top of the bookcase and on the back of the wardrobe. The room was dark and damp, and surrounded on all sides by a stand of sturdy rhubarb. However, the high holiday spirits common to all whose expenses have been paid carried him through until bedtime, when he first took adequate stock of the sleeping apparatus provided.

Our friend is a large man, and like so many large men nowadays (and for that matter small women too) he suffers from a Disc. The bed had been designed for an achondroplasic some four feet in length, and a large iron bar had been placed at either end to prevent the achondroplasic from pushing her feet or her head beyond the allotted span. It was now too late to make representations, and there was nothing for it but to sleep on the floor. The bedding came off reluctantly, exposing a by now familiar notice on the bedstead.

Our friend spent an uneasy night. The stairs re-echoed to the sound of girlish laughter until after midnight, and in a room across the rhubarb a furniture-removing party was in progress. He was able to stem the torrents of light and sound flowing through the fanlight with a blanket, and, flushed with success, attempted a similar operation on the window, a pane of which promptly fell out with a thunderous crash into the rhubarb. Our friend waited timorously for the Head Girl, but no-one took any notice; clearly windows did not come under the furniture-removing ban.

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[1] Registrar-General's Return for the Week ended July 19. H.M. Stationery Office. Pp. 20. 1s.

At two the owls took over, rooting mournfully about in the rhubarb outside the space where the window had been. Our friend is something of an ornithologist, and recognised every known British species as well as a number of South American families. The floor was hard, and so were the osteophytes in his lumbar spine. Moreover, there were several pieces of scrap metal in his pillow, and at half past four he gave it up and concentrated on his Simenon.

There were no mirrors in the bathroom—so much for feminine vanity—and our friend shaved guiltily by his reflection in the door-knob, not daring to remove the mirror from his room without first approaching the warden. After breakfast he left as hurriedly as possible, having first signed himself in on the visitors' book as a male guest of the Head Girl on the previous evening and carefully omitted to sign himself out again.

* * *

Holland is still one of the most charming countries in Europe, and Dutch hospitality is as warm as ever; but I do wish they did not keep such a virulent brand of mosquitoes. Perhaps it was the admirably hot spell of weather which was produced for the International Diabetic Conference the other week, or perhaps I am becoming "allergic" to the little brutes, but I have never been so effectively bitten night after night. The next time I go I shall certainly not forget to take an ample supply of dimethylphthallate; or perhaps the Dutch authorities will remedy the situation by supplying all hotels with quantities of D.D.T. It is an interesting commentary on the progress which has been achieved in public health that one should have been more worried by mosquitoes in Western Europe than in Malaya—but such at least has been my experience.

* * *

> "In discussing the results of treatment we must bear in mind that all, or almost all, the reported cases have been of one type, viz., patients suffering from very advanced disease, in whom other methods had proved incapable of arresting the morbid process, and in whom the mortality would most likely have been at least 90 per cent. Many cases have been too recently published for us to be able to judge what their ultimate fate may be, but undoubtedly the initial results have been full of promise. Certainly well over one hundred cases have, however, been recorded . . . and in these there would seem to have been a permanent arrest of the disease in at least 60 per cent. In many of the more recent cases immense improvement has already ensued, and patients who a few months back seemed almost moribund now appear to be on the high road to recovery."

Isoniazid? No, Mr. Hubert Chitty on the "Artificial Production of Pneumothorax in Phthisis by Injection of Nitrogen" in the *Bristol Medico-Chirurgical Journal* for 1912.

* * *

It is useless (they said) to go down to the River until we get some rain. The River is so low (they said) as to be almost stagnant. If you fish it in its present condition (they said), you will be wasting your time. Fortified by all this good advice I went down to the River. It was a lovely evening, hot and thundery, and the River was exactly as they said it would be, a thin trickle, glassy still, and clear as gin. A few fingerlings were rising at something so small as to be invisible and the midges were active. Conscientiously I fished up the whole length of Top Meadow. One or two tiny trout played leapfrog over my cast but did not take hold of my fly. This year's brood of mallard flew over my head within easy gunshot, and a dipper, flying straight and purposefully, passed to and fro. My spaniel swam lazily across the River several times, crossing just in front of my line, which did not improve my chances, and by 9.15 P.M. I had accomplished nothing. I went down once more to the bottom of the water and fished up Head Run. About twenty yards from the top I caught a fat dace which fought surprisingly well. This was better than nothing. Two casts later I was smartly taken by a peal, which came out of the water half a dozen times. Handling him roughly I dragged him downstream, and, having no net, chased him out on to a patch of shingle. He was a pretty little fish of rather more than a pound and in excellent condition. It was nice to feel that, despite what they said, I had not wasted my time.

Letters to the Editor

HOSPITAL BEDS FOR MENTAL DEFECTIVES

SIR,—It is refreshing to see that an increasing interest is being taken in this problem, though even now the whole truth has yet to be stated. The figures given in Parliament by the Minister of Health, and quoted in your issue of July 19, still fail to give a complete picture of the appalling state of affairs. It is generally accepted that 2 per 1000 of the population—i.e., 100,420 people—need hospital care by reason of their mental defectiveness. If only 48,742 patients are occupying beds, as given in the Minister's figures, then there should be 51,678 on the waiting-list, not a mere 8070. The fact is that waiting-lists have long since ceased to have any meaning because ascertainment, having become futile, has often been neglected. If waiting-lists were complete and the present admission-rate remained unchanged, it seems that a patient ascertained today would have to wait some 15 years for a vacancy. Unless these facts are faced, the magnitude of the problem will not be realised and it will only be met by half-measures.

If the national conscience is not stirred by the thought of more than 50,000 inarticulate persons in need of care and treatment, and of the distress caused to their relatives, then we have indeed reached a sorry plight.

Morpeth, Northumberland. C. GUY MILLMAN.

THE McNAUGHTEN RULES AGAIN

SIR,—The recent discussion of the McNaughten Rules in your columns raises once again the question as to wherein their inadequacy lies.

Dr. Haas and Mr. Ellison (June 21) argue the absurdity of the Rules, reasoning from presuppositions implied in their crucial points which bear on the questions designed for the jury. "In order," they conclude, "to determine whether a man is insane, so as not to be responsible in law for his acts, one assumes that he is a reasonable man."

Part of this conclusion is certainly valid in a sense which will emerge later. In its entirety, however, it would seem rather to obscure the issue, which is precisely that the McNaughten Rules are not primarily designed to determine whether a man or woman is insane—i.e., suffering from a psychosis. If they were so designed no judge would presume to rule, unaided, whether an issue of insanity should go to the jury. He would leave the diagnosis of psychosis to an expert, preferably to an independent panel of experts. But we know that, even when established, psychosis per se does not exempt an accused person from criminal responsibility.

This is what many psychiatrists feel to be the inadequacy of the legal practice. "Insanity" has, after many centuries, at last acquired its due status as a natural illness—not the only one, one should remember, that may be killing to others—and the psychiatrist, to paraphrase John Haslam,[1] objects to his patient receiving his cure at the gallows.

The whole vexed problem might perhaps be brought a step nearer solution if attention were given to the attitude of the authors of the legal doctrine towards insanity. Mr. Justice McCardie is quoted[2] as having said that insanity was one thing from the medical point of view and another from the viewpoint of criminal law. How does the criminal law view insanity?

The relevant legal thinking is given in the reply of the judges to the fourth of the questions put to them at the historic session of the House of Lords. The question reads: "If a person under an insane delusion as to existing facts commits an offence in consequence thereof, is he thereby

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1. Medical Jurisprudence. London, 1817; p. 4.
2. See Henderson, D. K., Gillespie, R. D. Textbook of Psychiatry. London, 1947; p. 694.

excused ?" The judges replied[3] that a great deal depended on the nature of the delusion. If, under the influence of his delusion, the accused had supposed another man to be in the act of attempting to take his life, and he killed that man, as he supposed in self-defence, he would be exempt from punishment. If his delusion was that the deceased had inflicted a serious injury to his character and fortune, and he killed him in revenge for such supposed injury, he would be liable to punishment.

It will be noted that although the *question* refers to "an insane delusion as to existing facts," the *answer* transposes facts belonging to the plane of mental pathology to the plane of objective reality with the result that the psychotic act is regarded as if it had arisen in an objectively real setting.

In this sense one has to agree with Dr. Haas and Mr. Ellison. The psychotic *is* being treated as if he were "a reasonable man"—that is to say, any man of sound mind who, as in the examples cited, has met with a real threat to his life or with a real injury of a lesser kind and has acted either within the law or by breaking it. Thus criminal law views insanity by looking, as it were, the other way, *by denying it*. In so doing it mirrors an age-long attitude of society towards mental illness.

In the very circumstance of this denial of insanity and in the consequent dealing with the psychotic on a basis of equality with the mentally healthy may perhaps be sought the psychological source of the contentment with which the judiciary appears to regard the McNaughten Rules. The lawyer may, in a vague manner, feel proud of the advance which lies in the fact that the psychotic is treated on a level with his mentally healthy brethren and not worse—as, an outlaw for centuries, he used to be treated.

In writings from periods of transition one meets with a curious co-existence and conglomeration of new insights and outworn attitudes. The McNaughten Rules are in this category. As such they inherently fail to do justice to modern demands.

West Park Hospital,
Epsom.

J. ZELMANOWITS.

FLUORIDATION OF WATER-SUPPLIES

SIR,—The U.S. Select Committee on Chemicals in Food issued their findings on fluoridation of water-supplies on July 10. They warned against precipitate action in the use of what is still a relatively new means of reducing dental decay, and recommended caution in adding fluorides to drinking-water. They pointed out that there are a number of "unanswered questions" and that a conservative attitude is warranted. They urged that all the facts about fluoridation be made public in communities where its use is under consideration, and that the people in each community be given the opportunity to decide whether they wish to take what is at this time still "the calculated risk" inherent in fluoridation programmes. They chided the fluoride supporters who say, that the use of fluorides is comparable to the long accepted practice of adding chlorine to drinking-water, for chlorine is added to destroy harmful bacteria while fluoridation causes "a physiological change in the body."

Lieut.-Colonel E. F. W. Mackenzie, in his recent paper,[4] claims to have given the pros and cons, and he makes out a strong case for fluoridation. He omits to state however that, where water containing 1 part per million of fluorides is in use, as many as 10% of the children may have varying degrees of "mottled teeth." He does not mention that, where cryolite has been used on fruit crops, an apple can contain as much as 1 mg. of fluorine (the approximate amount in four glasses of water containing 1 p.p.m. of fluorine). He states that the use of high-fluorine waters for irrigation did not increase the fluorine content of vegetables, but contrary evidence was given before the committee by Mr. H. V. Smith, associate agricultural chemist of Arizona University.

The basic ethical objection to compulsory mass medication is reinforced by the committee's adverse findings. Would it not be a good idea to explore more fully other methods of adding fluorine to the diet of those who need and want it ? In 1950 Prof. W. A. Albrecht, of the University of Missouri, wrote an important paper on the Pattern of Caries in relation to the Pattern of Soil Fertility in the U.S.A., in which he suggested that "the soil fertility pattern, not in terms of higher yields but of quality output, deserves more consideration in looking at the health condition of the teeth."

WINIFRED M. SYKES
Vice-chairman,
British Housewives' League.

2, Stepney Green,
London, E.1.

LIVER EXTRACT FOR HERPETIC PAIN

SIR,—Professor Dunlop is reported in your issue of July 19 to have said at the Dublin meeting of the British Medical Association that the injection of liver extract is of no value for the relief of pain in herpes.

In the last year I have treated 4 such cases.

In 3 of them the pain disappeared in twenty-four hours, never to return. In the 4th the pain, which was agonising and involved the area supplied by the left brachial plexus, disappeared, but was succeeded by intense itching. In each case 'Campolon' 2 ml. was injected intramuscularly, and it seemed to me that the change of infliction in the last case might be due to an insufficient amount of some constituent in the liver extract.

I therefore quite empirically gave an injection of vitamin B_{12} ('Cytamen' 2 ml.) and the itching vanished overnight. When I last saw the patient a week ago he had been free from symptoms, except slight numbness, for a month.

Being a clinician and not a chemist I cannot explain things of this nature, but I shall continue to use liver extract until and unless I am convinced that my experience is entirely fortuitous. There are times in general medicine when the aphorism of Pascal, that the heart has its reasons which the brain cannot understand, seems evident; and as the relief of pain without the unnecessary use of narcotics is in all our hearts I hope that this simple procedure will be given an extended trial.

London, W.1.

CHRISTOPHER HOWARD.

PROVISION FOR THE MENTALLY DEFECTIVE

SIR,—The differences between Dr. Rose and me are, I think, more apparent than real, and have arisen from the necessity for brevity in writing. To reply point by point :

1. The fact that intelligence is distributed amongst the population in a continuous curve is generally accepted, and I did not think it necessary to refer to it.

2. That the justification for making distinctions between different groups is an administrative one is also agreed, but the distinctions are supported by laws and regulations which are for the specific purpose of providing the most suitable environment for the individual concerned. It follows that there will be, at the merging of the groups, borderline cases, and the decision how they can best be placed may prove difficult and require a period of observation.

3. Dr. Rose feels shocked at the expression "stigma of mental defect" and says it does not exist except in the minds of the ignorant and prejudiced. He admits, however, that it does actually exist, and to call those parents who feel it "ignorant and prejudiced" may be true but does not really solve anything. One still has to endeavour to get the parents' confidence and fullest coöperation. That the stigma ought not to exist is true, but the same would apply to that sometimes attached to many other mental and physical conditions.

4. To suggest that we are perpetuating ignorant prejudices by assuring some anxious parents of educationally subnormal children, in reply to their queries, that the special

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[3] *Ibid*, p. 692.
[4] *Lancet*, 1952, i, 961.

schools are not for mental defectives, is very strange indeed. We are merely telling the truth and it is a truth that needs telling as it is not sufficiently widely known.

5. As Dr. Rose is concerned that we are not helping to educate public opinion in an enlightened attitude towards mental deficiency, I can reassure him. My letter did not deal with this, but on meeting children who are ineducable and telling their parents that they will require to be notified under the Education Act, 1944, Section 57/3, some parents may show, in addition to intense disappointment, personal shame and hurt pride. It surely goes without saying that we do all that we can to help them to develop a healthier attitude to their problems.

Sheffield. M. C. TAYLOR
School Medical Officer.

PERIODIC DISORDERS OF CHILDREN

SIR,—In your issue of July 12, Dr. Howells rightly welcomes Dr. White Franklin's article (June 28) on periodic disorders of children. We agree with Dr. Howells when he implies a greater place for psychiatric help in managing these than did Dr. White Franklin; but we disagree with Dr. Howells's statements (1) that "explanation is futile," and (2) that "it is clear that the . . . psychiatrist should . . . apply the psychotherapy."

Simple exploration and psychotherapy (including explanation) by a family doctor or a pædiatrician does, in some cases, bring about a cure and not merely symptomatic improvement. Perhaps the pædiatrician will try to treat some unsuitable cases and thus delay their arrival at a psychiatrist's clinic, but it would be impracticable for a pædiatrician to send to the psychiatrist all the children he sees with symptoms of emotional origin; already at many psychiatric clinics the interval before a patient's treatment starts is months or years. Is the general practitioner or pædiatrician to refrain from treatment?

Part of the function of a *consultant* (perhaps he may be contrasted with a *specialist*) is to teach the doctor who sends or brings cases to him. It seems to us important for the family doctor and pædiatrician to learn which are the most suitable cases to be referred to the psychiatrist. On occasion it is reasonable for a pædiatrician to get help in *diagnosis* from the child-guidance clinic and then himself, for a time at any rate, do psychotherapy.

Child[illegible] CHRISTOPHER HAFFNER
Chi[illegible]
Guy's [illegible] RONALD MAC KEITH.

SIR,—The problem of the child so emotionally disturbed as to need a visit to the doctor is one of practical concern to the assistant medical officer working in the local-authority service, the general practitioner, and the pædiatrician.

The recognition of a psychiatric disorder is important, but Dr. Howells is being unrealistic when he suggests that "the child psychiatrist, or, better, family psychiatrist, should explore the psychopathology and apply the psychotherapy." The frequency of the condition, which some have put as high as 50% of all children's illness, and the disturbing effect on the child, the home, and the school necessitate action more immediate than is possible with the very long waiting-lists of the child-guidance clinics. Confronted by these disturbed children in clinics, surgeries, and outpatient departments, a sympathetic attitude combined with the will to treat can go a long way in helping parents in the understanding of the emotional needs of their child. It is encouraging to see parents becoming aware, so often for the first time, of what has been wrong and the almost immediate effect this has on both parent and child. This understanding differs fundamentally from "the explanation—the mere instruction—the mechanical change of technique" which Dr. Howells puts as the only alternative to full-blown psychotherapy.

In answer to the needs of the patient we must do what we can, and in the process of so doing acquire more skill, experience, and judgment. It is time, however, that psychiatrists made some efforts to bring their special knowledge to doctors working with children in order that they may be better equipped in their work in this field.

London, N.W.3. DAVID MORRIS.

CAR-DRIVERS WITH DEFECTIVE VISION

SIR,—The statement (July 19) of the Faculty of Ophthalmologists on the danger of visual disabilities in people driving motor vehicles is of great interest to members of this association, emphasising as it does the weakness in the present system of issuing driving licences.

This association thinks that the fact that a candidate for a driving test wears spectacles should be recorded on the driving licence. This would ensure that, in the event of such a driver being involved in an accident, it would be possible to check whether or not he, or she, was wearing spectacles at the time, or, in other words, was properly equipped to be in charge of a vehicle.

One of our members has reported that in the past year he has handled two cases in which elderly people, after being involved in accidents, were convicted of dangerous driving and had their licences suspended until they passed a driving test. In *both* cases, the instructor detected signs of defective vision immediately. On his advice they consulted ophthalmologists who advised them both to give up driving. Fortunately, in these cases this advice was taken.

We know of another candidate who failed the test because of defective vision. After the test she admitted to her instructor that she knew that she had bad eyesight, but said that she did not like to wear spectacles. She did, however, get spectacles, entered for the test a month later, passed (with spectacles), and has not worn them since.

J. S. GRANT ROBERTSON
Hon. Press Officer,
London, N.W.3. The Motor Schools Association.

HALLUX VALGUS

SIR,—While welcoming the authoritative survey by Dr. Hardy and Mr. Clapham (June 14), I am not entirely happy about the radiographic technique employed in collecting the data.

With the technique used, the distortion produced will tend to show a metatarsus varus, by virtue of the divergence of the cone of X rays centred, as it was, between the two feet. Furthermore, owing to the lateral direction of the projection of each foot, as the angle between the first metatarsal and the plane of the film increases, so an increase in the apparent degree of hallux valgus will be seen in the radiograph. Moreover, as the centre of the cone of rays was not directed through the apex of the angle formed by the first and second metatarsals, the angle of the first interspace would be apparently narrowed; and as the dihedral angle between the plane of the first and second metatarsals and the plane of the film increases, so the angle between these two bones in the radiograph will apparently decrease.

The type, then, with the higher longitudinal arch will tend to show in the radiograph, taken under these conditions, a greater degree of apparent hallux valgus together with a narrowing of the first interspace. Is this not significant in view of the findings of the survey?

Having spent some thirteen years in radiography before turning my attention to the foot, I remain unconvinced that radiography affords a suitable medium for measuring angles in such a multi-planed structure as the skeleton of the foot.

I am aware of the almost insurmountable difficulties involved in a mass examination of school-children's feet; but I feel that a more reliable assessment could be made by direct measurement, particularly with regard to the degree of varus or valgus of the metatarsus as a whole, which is of fundamental importance if the design of footwear for the growing child is to be improved.

Royal Northern Hospital,
London, N.7. JESSE W. J. TURVEY.

MEGALOBLASTIC ANÆMIA

SIR,—The article by Dr. Foy and his associates in your issue of June 21 contains much of great interest to those concerned with the problems of nutritional anæmias and vitamin deficiency states, especially the observation that there is an optimum dosage level above and below which no response can be obtained, and the relation of this observation to an effect on the intestinal microflora.

I have been keenly interested in this subject since 1939 when I first saw the anæmia of pregnancy so common in Assam. It appeared to me that this anæmia was not a specific disease, but only a manifestation in pregnancy of a disease or process which also affected men and non-pregnant women.

The identity of the condition was suggested not only by the clinical and laboratory findings but by the history given of a state, preceding or following pregnancy, indistinguishable from the clinical state of women in whom pregnancy had played no part, and of men suffering from anæmia and hypoproteinæmia with or without œdema and ascites, in whom there was neither renal disease nor vitamin deficiencies. Pregnancy made the treatment of women with this condition difficult, or unsuccessful, not because of a specific toxic factor due to the presence of the fœtus (the then generally accepted hypothesis) but because the inexorable demands of the growing fœtus for hæmopoietic substances and proteins finally exhausted the maternal reserves; and these reserves could not be replenished because of the primary "debilitating" process.

The common factor, the *disease*, presented itself as a long-continued mild diarrhœa, occasionally initiated by acute dysentery, which presented the peculiar feature that it was aggravated by protein foods. Many such patients deliberately avoided milk, meat, fish, and eggs, because it made the diarrhœa worse, the stools became more offensive, and they themselves felt more ill.

The end-result was hypoproteinæmia and anæmia of greater or less severity, with all the usual complications of œdema, ascites, and, in the long run, liver failure.

Arising from these observations and the basic assumption, it was argued that a disturbed microflora made essential amino-acids inutile, by conversion into other forms, or produced metabolites which were toxic, or, thirdly, competed successfully with the patient for essential amino-acids already in short supply in the diet. It was thought that the first two possibilities were the likeliest to be important.

An elementary attempt to establish the point was made by estimating daily the ratio of ferrous/ferric iron in the stool, with and without the addition of iron to the diet, it being considered that "putrefaction"—reduction—was the likeliest chemical process by which the amino-acids were rendered inutile. These results were rather inconclusive; for, whether the estimation was made with or without added oral iron, some healthy patients showed a ratio as high as that usually seen with the anæmic patients. It was decided that although the results were suggestive there were too many variables involved to make the estimation significant without a great deal more information which was not available.

Some patients were then treated with sulphapyridine (circa 1941–42); and it may be noted that the first severely ill patient with anæmia of pregnancy presenting in mid-pregnancy to go to term with a rising blood-count was one treated with sulphapyridine. These results were not obtained with sulphaguanidine, mappenide, or the later insoluble sulphonamides. Dr. Foy's findings with penicillin suggest the reason for the failure of the later sulphonamides to reproduce the effects with the less "efficient" sulphapyridine—namely, that they were indiscriminately lethal to both useful symbiotic organisms and the "deviationists."

Some of our patients from the plains were accustomed to use edible clays—alkaline bentonites—and a trial was made with a local acid clay to see if the pH of the bowel contents could be lowered and "putrefaction" checked. This produced no significant results.

It was found, incidentally, that patients with mild diarrhœa, or dysentery, treated with phthalylsulphathiazole or succinylsulphathiazole were apt to continue with abnormal stools unless they were also given vitamin-B complex with the idea of encouraging the growth of a normal flora.

In the main, although the hill people live on a diet consisting chiefly of rice or maize and very deficient in all proteins, fats, and vegetables, and although the children invariably show signs of vitamin-A deficiency and mild rickets, vitamin-B complex deficiencies rarely appear unless they develop dysentry or diarrhœa or are treated with sulphonamides for intercurrent infections. When deficiencies do appear, riboflavine deficiency is usually the first to be manifest. I have wondered whether this normal absence of B-group deficiencies is related to poor cooking—not merely that inadequate cooking destroys loss of the vitamin content of the food, but because uncooked starch is a better medium to permit refection.

Now that there is so much evidence to relate the state of the bowel microflora to anæmia, vitamin deficiencies, and possibly protein synthesis, and there is possibly a hint as to the characters of the organisms antagonistic to the establishment of a profitable symbiosis to be found in their sensitivity to sulphonamides and antibiotics, may we not expect in the future to discover a maximally helpful bowel flora, and even a new path to therapy in some cases by reinfecting a sterilised intestine with a helpful community of micro-organisms. The problem is not simply academic. Possibly more people are chronically ill because of biochemical pathogens than because of bacillary or protozoal bowel disease as ordinarily understood.

The Khasi Hills Welsh Mission
Hospital, Shillong, Assam.

R. ARTHUR HUGHES.

PROTECTION AGAINST WHOOPING-COUGH

SIR,—For years protection against whooping-cough has been referred to indiscriminately as "inoculation," "immunisation," or "vaccination." Now that vaccines giving promising results appear to have been found, ought we not to agree firmly on the name of the procedure? May I make a plea for the exclusive use of the word "inoculation" in propaganda regarding whooping-cough, since "vaccination" is by usage almost synonymous with vaccination against smallpox, and "immunisation" with immunisation against diphtheria?

Divisional Health Offices,
Ashton-under-Lyne.

W. J. ELWOOD.

FRACTURES OF THE NECK OF THE FEMUR

SIR,—I was interested in Mr. Stamm's simplification of the procedure for Smith-Petersen nailing, published in your issue of July 12. Complementary to his method, and therefore possibly worth recording, is a minor modification I have lately practised. Two patients suggested it to me. One had a suprapubic cystotomy, and the other in a period of confusion tore off her dressings. The practically bloodless approach to the nailing operation contributed to the idea.

A $^{3}/_{4}$-in. incision is made just below the lower edge of the trochanter. This can usually be felt through the skin, and even in fat patients direction-finding seems easier from the outside. A Steinmann pin is then passed down to the bone through a small cannula, and a hole is tapped through the cortex. This gives a hole large enough to introduce a guide-pin without its direction being dictated by that of the cortical perforation.

The Steinmann pin is withdrawn; and the cannula, held against the bone, leads the guide-pin down to the invisible hole in the cortex. The rest is simply the usual technique of blind nailing by feeling one's way. Two sutures close the incision.

Finally a piece of stockinette, pulled up over the thigh and dressings, adheres by pig. mastic. co. to the skin, and saves money on strapping. A loose turn of bandage round the waist ties through a hole in the top of this over the iliac crest as an added anchorage.

The incision must of course be enlarged in the rare event of nail extraction becoming necessary.

Cheltenham. L. HENRY.

HOSPITAL ADMINISTRATION

SIR,—I worked in hospitals, as medical superintendent and otherwise, for forty-five years and can perhaps claim some understanding of their management.

I view with dismay both the suggestion that hospitals should be placed under the government of laymen and the little interest which the medical profession has evinced in a matter which so closely concerns the interests of their patients.

A layman can control no more than the business and domestic affairs of a hospital; these are indeed necessary parts of its management, but entirely subsidiary to its main purpose, in which he can play no part at all. To place him in complete and immediate charge would therefore be a retrograde step fraught with danger to the conduct of the hospital. In no other sphere of human activity would a comparable proposal be for a moment contemplated. Would the paymaster ever be placed in control of a battleship, or a bursar of a college, or one with no knowledge of its processes in charge of a factory? The question of a medical hierarchy simply does not arise. It has always existed, for there are juniors and seniors everywhere; but it goes no further. A medical superintendent does not, and never has, exercised control over the professional work of the specialist staff.

West Kent Hospital,
Bickley. H. W. BRUCE.

ANTITHYROID ACTION OF P.A.S.

SIR,—Dr. Hanngren's preliminary communication (July 19) on the antithyroid action of *p*-aminosalicylic acid (P.A.S.) and the previously described occurrence of myxœdema in patients receiving this drug are important for two reasons. Firstly and obviously, there is the undesirability of producing myxœdema in any patient. Secondly and less obviously, there is the possible effect that depression of thyroid activity may have on the tuberculous process itself.

Fishberg[1] believes that hypothyroid persons often develop progressive tuberculosis. Rich[2] says: "Some of the experimental studies[3–5] tend to support the view that underactivity of the thyroid increases susceptibility to tuberculosis, but the matter requires further study."

In 1947, working on the hypothesis that if the B.M.R. could be reduced in tuberculous patients they would be resting more effectively, I administered thiouracil to three patients, all of whom had chronic active cavitated disease, and whose general condition, although poor, had been stationary for many months. One patient rapidly gained 12 lb. in weight, but the other two developed new lesions in 6 weeks, which stabilised on stopping the drug. The spreads were not expected (neither showed evidence of myxœdema). If the thiouracil was the cause, it would seem that a careful watch should be kept on the lungs of patients receiving antithyroid drugs.

If P.A.S. depresses thyroid activity, and if hypothyroidism lowers resistance to tuberculosis, we might expect to encounter evidence of escape from its bacteriostatic effect before treatment is stopped, especially in cases where its administration has been prolonged. We must ask then, is there anything to suggest that the tuberculostatic effect of P.A.S. can, in some circumstances, be partly offset by a side action which lowers the patient's resistance? Also, can this side action, if it exists, occur without clinically obvious manifestations of hypothyroidism? The concurrent administration of thyroxine in patients who are deteriorating on P.A.S. might be attended by the risk of masking thyroid damage.

Clearly, the implications of Dr. Hanngren's observations have set the tuberculosis physician a number of problems, the solution of which may be difficult.

Grove Hospital,
London, S.W.17. F. A. NASH.

INSULIN HYPOGLYCÆMIA AND EOSINOPHILIA

SIR,—Dr. Lawrence has suggested (July 5) that the rise in the eosinophil-count of our insulin-treated psychotics is not necessarily related to hypoglycæmia and reactions thereto in hormone glands. He has observed similar rises in insulin-treated diabetics, and has ascribed these to local reactions to an injected foreign substance.

Neither Dr. Lawrence's patients (*Brit. med. J.* 1929, i, 597) nor our own (June 21) have shown clinical signs of local or general allergic reactions, and in our patients the rise in the eosinophil level was observed only after rapidly increasing doses of insulin, hypoglycæmic unconsciousness, and an eosinopenic reaction. Those patients in whom doses of insulin A.B. were inadequate in this respect, failed to show a rising eosinophil level.

Others have proved the efficacy of insulin as an adrenocortical stimulus, but the response to insulin is very complex and, unlike that to other stresses (e.g., chilling, emotional disturbances, and electroconvulsion therapy), it may give rise to eosinophilia. We do not claim to have proved that this rise is the result of hypoglycæmia, but have suggested that there may be a causal relationship between reactions to hypoglycæmia and the changes in the eosinophil-count.

Clinical Research Unit,
Three Counties Hospital,
Arlesey, Beds.
F. MACKENZIE SHATTOCK
L. P. MICKLEM.

SUCCINYLCHOLINE

SIR,—I read with great interest the article by Dr. Bourne and his colleagues in your issue of June 21. There are a few points in this paper with which I take the liberty to disagree.

The initial or single dose of succinylcholine chloride recommended by Dr Bourne and his associates was 1·1 mg. per kg. of body-weight. They state that this dose caused diffuse uncoördinated muscular contractions that were occasionally severe enough to be followed by muscular stiffness after recovery, and suggested that the use of succinylcholine might be unwise in certain fractures. They further state that "effective doses always caused respiratory arrest." This respiratory arrest was prolonged in 5 out of 546 patients.

They also describe the administration of succinylcholine chloride in a continuous intravenous drip at the rate of 10–12 mg. per minute.

I believe that both the single doses and the mg. per-minute doses recommended are unnecessarily high. We found in over 400 patients anæsthetised with sodium thiopentone that 10–30 mg. of succinylcholine chloride (or its equivalent amount of succinylcholine iodide) combined with topical anæsthesia of the larynx provided ideal conditions for endotracheal intubation. Mild muscular fasciculations were observed in only about one-third of the patients, none of whom complained of muscular soreness after recovery. Muscular relaxation was present for 2 to 3 minutes after these doses; apnœa lasting more than one minute was not seen in any of the patients.

Prolonged muscular relaxation was maintained in over 300 patients anæsthetised by sodium thiopentone

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1. Fishberg, M. Pulmonary Tuberculosis. Philadelphia, 1932.
2. Rich, A. R. Pathogenesis of Tuberculosis. Springfield, Illinois, 1946.
3. Delore, P. *C.R. Soc. Biol. Paris*, 1926, 94, 866.
4. Schroder, G. *Beitr. klin. Tuberk.* 1930, 75, 61.
5. Kallos, P., Kentzler, J. *Ibid*, 1932, 79, 584.

plus nitrous oxide and oxygen for intra-abdominal operations by the continuous intravenous infusion of succinylcholine chloride in doses of 0·8 to 5·5 mg. (average 2·5 mg.) per minute. With this dosage excellent muscular relaxation could be maintained without apnœa in all patients. The degree of relaxation could be easily regulated to the needs of the surgeon by changing the drip-rate. Respiratory depth returned to normal within 3 to 5 minutes after the *infusion* was discontinued. No postanæsthetic muscular weakness was observed.

In the light of our satisfactory experience with much smaller doses we fail to understand the use of doses recommended in British reports. The goal of the administration of muscle relaxants should be muscular relaxation and not apnœa. With the previously used muscle relaxants occasional prolonged apnœa had to be accepted as an unwanted side-effect. With succinylcholine, if administered correctly, this complication can be avoided. Just because the apnœa observed after large (80–100 mg.) doses of succinylcholine only lasts 3–5 minutes in normal persons, there is no justification in using these doses.

The duration of the effect of succinylcholine, as it has been so well demonstrated by Dr. Bourne and his colleagues and by Evans et al.,[1] depends on the plasma-cholinesterase activity. Patients with decreased plasma-cholinesterase activity caused by disease or perhaps subclinical intoxication with anti-cholinesterase insecticides[2] have been encountered. If a dose adequate to produce muscular relaxation without apnœa in a normal person is given to a patient with decreased plasma-cholinesterase activity, apnœa might develop, but it will be of very brief duration only. Should, however, such a patient receive a dose 4 to 5 times as large, prolonged respiratory arrest will ensue. Such occurrences, always after the use of much larger doses than those used by us, were recently reported.[3]

Because of its controllability, wide margin of safety, and lack of side-effects, succinylcholine chloride proved to be the most desirable of all the muscle relaxants investigated by us. It would be unfortunate if, owing to the reports of side-effects caused unnecessarily by large doses, succinylcholine were prevented from assuming its well-deserved place in the armamentarium of anæsthesiologists.

Mercy Hospital, Pittsburgh,
Pennsylvania, U.S.A.
FRANCIS F. FOLDES.

SIR,—I am particularly interested in the experiences of Dr. Bourne and his colleagues with succinylcholine in abdominal surgery, and I would like to add my own observations.

I have used succinylcholine as a continuous drip in major abdominal surgery for some time, and I have found the technique simple and the results encouraging. A delay in recovery, mentioned as one of the chief disadvantages, has not been my experience.

It is clear that the quantity of drug required for any standard operation varies considerably from patient to patient, and cannot be based on weight and physique. In 150 operations the average dose has been 480 mg. per hour; but I have given as much as 900 mg. per hour, and as little as 125 mg. per hour has occasionally been effective. Long operations have required a slightly lower average hourly dose. As these doses are lower than those quoted by Dr. Bourne and his colleagues, it is possible that they have been using larger amounts than are necessary for adequate relaxation, and that recovery has therefore been delayed.

It is my practice to use a 0·1% solution of succinylcholine in normal saline. A test dose is first given slowly by intravenous drip to the conscious patient until some effects are felt, usually a twitching sensation down the spine. This is then rapidly followed by 0·5 g. of thiopentone, and the drip-rate is increased until good relaxation of the jaw has been obtained. The larynx and trachea are sprayed with a local anæsthetic solution and intubated with a cuffed tube. Nitrous oxide saturation is achieved by overventilation for 5–10 minutes with a 3 : 1 nitrous oxide/oxygen mixture, to which 4% of carbon dioxide has been added. Anæsthesia is then maintained with a mixture of 75% nitrous oxide and 25% oxygen. Respirations are assisted, but at no time are spontaneous respirations completely eliminated. The drip-rate is adjusted from time to time to produce the required relaxation for various stages of the operation. For example, during gastrectomy, a fast drip gives good relaxation during abdominal exploration, but during the anastomosis the drip is slowed and some muscle tone allowed to return. A knowledge of the speed and methods of the surgeon are helpful in obtaining the best results.

Using this procedure, good muscle tone has returned within 5 minutes of stopping the drip in almost all cases. Frequently the patient is opening his eyes and answering questions by this time. A steady rise in blood-pressure has not been a feature in these patients, but many have had a slow pulse-rate.

I cannot agree with Dr. Bourne that the technique is cumbersome, though constant vigilance is essential.

St. Helier Hospital,
Carshalton.
RONALD GREEN.

PREVENTION OF SEASICKNESS

SIR,—The correspondence on this subject (July 12, p. 93, and July 19, p. 146) has had, at least, one valuable result: Dr. L. N. Gay, of Baltimore, who has sponsored 'Dramamine,' a combination of 'Benadryl' and chlorotheophylline, admits that he does not know the effect of chlorotheophylline in motion sickness. There is indeed, as Professor Glaser has pointed out, no evidence that dramamine has any advantage in motion sickness over its component, benadryl. I think it is important that practitioners in this country should realise this, because a similar combination (this time of promethazine) with chlorotheophylline has been put on the market and widely advertised here. Promethazine alone is much cheaper, and there is no evidence that it is less effective.

University College Hospital Medical School,
London, W.C.1.
H. HERXHEIMER.

SIR,—The relative merits of hyoscine and of different antihistaminics in the control of seasickness will not be determined by argument, by appeals to work on animals, or by the multiplication of experiments in man where arbitrarily chosen doses of hyoscine and of this or that antihistaminic are compared.

It seems likely that it is to the hyoscine-like actions of antihistaminics that any anti-emetic effect they may have is due. The degree of hyoscine action, and its rate of onset and duration, varies, like the antihistaminic effect itself, from drug to drug. Thus in any critical evaluation of antihistaminics in the prevention of seasickness these two variables—time of onset and duration of protection—must be taken into account. A good deal of information is already available on these matters and could be utilised in the design of rigorous trials.

The major points at issue, however, can only be satisfactorily settled by the determination of dosage-response curves, in experiments which take account of these other variables. In brief, it is necessary to determine the relationship between different doses and the percentage

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1. Evans, F. T., Gray, P. W. S., Lehmann, H., Silk, E. *Lancet*, 1952, i, 1229.
2. Marchand, J. F. *J. Amer. med. Ass.* 1952, 149, 738.
3. Gould, R. B. *Brit. med. J.* 1952, i, 440. Harper, J. K. *Ibid*, p. 866. Hewer, C. L. *Ibid*, p. 971. Love, S. H. S. *Anæsthesia*, 1952, 7, 113.

protection afforded by them, for hyoscine itself, and for one or more of the most promising long-acting antihistaminics with well-marked hyoscine-like effects. It would then be relatively easy to settle the minor question of whether the addition of chlorotheophylline to the antihistaminic molecule justifies the claims made for it.

An experiment of the kind suggested would be a somewhat formidable undertaking—especially if, as would be most desirable, all the observations were to be done on the same people. But it would be well worth the trouble involved and would be likely to yield information of a more valuable and reliable kind than is available so far.

Department of Pharmacology,
University of Leeds. W. A. BAIN.

TOXIC REACTIONS TO ISONIAZID

SIR,—Isoniazid (isonicotinic acid hydrazide) and iproniazid (1-isonicotinyl-2-isopropylhydrazine) are being given to many patients with tuberculosis throughout the United States and in many other countries. Toxic reactions to both drugs have been reported and, undoubtedly, more will occur. However, it is unlikely that any single investigator will observe enough of these toxic reactions in the next few months to warrant publication. The Committee on Therapy of the American Trudeau Society is anxious to collect reports of these toxic reactions, so that a consolidated report can be made available to the medical profession as soon as possible.

Any physician who is willing to submit such reports to the committee is asked to send a brief case-report to the Committee on Therapy, American Trudeau Society, Dr. D. T. Carr, 102–110, Second Avenue Southwest, Rochester, Minnesota. The report should include the patient's name or initials, his age, sex, race, diagnosis, weight, the drug administered and its dosage, the duration of treatment, and a list of other drugs being given at the same time. The toxic reaction should be described fully together with information as to its recurrence if the same drug was given later.

Copies of the consolidated report will be sent to all contributors, but will not be published in such a way as to preclude individual publications.

D. T. CARR.

REASON AND UNREASON IN PSYCHOLOGICAL MEDICINE

SIR,—I trust that the incidence of felo de se among psychiatrists will not show any steep rise following the publication of Dr. E. B. Strauss's Croonian lectures in your issues of July 5 and 12.

On second thoughts perhaps this might not be an unmitigated calamity. But it would be unfortunate if any considerable body of respectable citizens received the impression that it was necessary to go through the rather agonising permutations of metaphysical theory, indulged in by Dr. Strauss in his first lecture, in order to show that psychological medicine is, or can be, rational and scientific.

It is, of course, impossible to undertake any detailed criticism here. But as Dr. Strauss's main theme is based on the principle of causality, it is apposite to point out that in a recent book on scientific method given (astonishingly) a full-page review in the *British Medical Journal* (*The Common Sense of Science* by J. Bronowski) it is affirmed that causality is an outmoded idea—that in fact it is not now considered a scientific principle at all but "a faith," "a superstition," and merely "scholastic" like the medieval belief that everything is contained in the First Cause.

It is all very difficult, Sir. As the late Gilbert wrote and Sullivan sang: "Things are seldom what they seem, Skim milk masquerades as cream." How very true this is will be brought poignantly home to the most stubborn die-hard if, leaving verbal metaphysics aside, he will go and see the exhibition of the 20th-Century Masterpieces at the Tate Gallery. In paint as in words the tendency is the same.

London, W.1. FREDERICK DILLON.

TRAUMATIC DISLOCATION OF THE HIP

SIR,—In your issue of July 12 (p. 80) I am reported as advocating the prophylactic drilling of the epiphyseal plate in children following traumatic dislocation of the hip. If I gave this impression, let me hasten to correct it. In the first place, the incidence of aseptic necrosis in children is not known; and those authorities who, with good theoretical reasons, believe it to be much higher than in adults are none the less speculating without the evidence. However, once this complication *does* manifest itself in children, the anatomical conditions are such that revascularisation from the femoral neck cannot occur.

What I intended to convey was that in these circumstances it is reasonable to drill the epiphyseal plate. No vessels ever cross an intact epiphyseal plate; but once the integrity of the plate is destroyed by drilling, revascularisation by "creeping substitution" can occur. In children the articular cartilage can survive longer than in adults, so it is worth while.

Moreover, if the drilling is confined to the central portion of the epiphyseal plate, it does not cause premature fusion or interfere with growth.

Mansfield. E. A. NICOLL.

A BETTER NAME?

SIR,—Once again I note in your annotation of July 26 that we British, in our usual inimitable style, have coined an impossible word to describe something new. Heavens above—preregistrands! Surely there is some other way to describe newly qualified practitioners before being granted full registration. I admit that the word is more logical than, say, intern, but what a mouthful.

Newdigate, Surrey. W. F. WHEELER.

A.C.T.H. AND THE PIGMENT HORMONE

SIR,—It has recently been shown that A.C.T.H. and intermedin are closely related.[1–3] It has also been suggested that the chromatophorotropic effect may be safely used to determine A.C.T.H. in biological fluids, especially blood.[4] Dr. Morris [5] suggests, however, that the chromatophorotropic effect is not due to A.C.T.H.

Though this difficult question can be finally answered only by research it seems opportune to examine the evidence regarding these two conceptions.

The following points would indicate contamination of A.C.T.H. by a separate melanophore-expanding hormone:

1. Hogben [6] and Zondek [7–9] showed that the melanophores are under direct hormonal control by the pituitary gland. They found that, although the posterior lobe was apparently the best source of the hormone, significant amounts could also be isolated from the anterior lobe. Zondek showed that the intermediate lobe was apparently the primary site of production of the hormone, and hence coined the name intermedin. Only in primates that have no clearly defined intermediate lobe is intermedin produced mainly in the anterior lobe. This concept is also accepted by Allen, van Dyke, Houssay, Swingle, and Trendelenburg.

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1. Sulman, F. G. *Ref. Veterinarith.* 1952, 9, 1.
2. Sulman, F. G. *Nature, Lond.* 1952, 169, 588.
3. Johnsson, S., Högberg, B. *Ibid*, p. 286.
4. Sulman, F. G. *Lancet*, 1952, i, 1161.
5. Morris, C. J. O. R. *Ibid*, p. 1210.
6. Hogben, L. Pigmentary Effector System. Edinburgh, 1924.
7. Zondek, B., Krohn, H. *Klin. Wschr.* 1932, 11, 405, 849, 1293.
8. Zondek, B. Hormone des Ovariums und des Hypophysen- [illegible] p. 579.
9. [illegible] Principle of the Pars Inter- [illegible] ...dular Physiology and Therapy. Chicago, 1935; p. 133.

2. Morris[5] has recently stated: "there is little doubt that the melanophore-expanding effects observed by various workers in A.C.T.H. preparations are due to contamination." He bases his conclusions on the following findings: (*a*) Waring and Landgrebe[10] have shown that the biological potency of intermedin is actually increased by heating with 0·1 *N* NaOH, whereas A.C.T.H. activity is rapidly destroyed by this reagent even at room-temperature; (*b*) intermedin can be obtained free of A.C.T.H. potency by the carbon adsorption process of Landgrebe et al.[11]; and (*c*) A.C.T.H. can be obtained free of intermedin activity by counter-current distribution between sec.-butanol and various aqueous acid solutions.

3. Li's school has recently separated intermedin from ascorbic-acid-depleting A.C.T.H. and has consequently assumed that they are different hormones.[12] Li has based his opinion on his experience in testing a number of sheep A.C.T.H. preparations which showed no direct correlation between their titre in adrenal ascorbic-acid-depleting activity and melanophore-expansion potency. Furthermore, he succeeded in separating intermedin from A.C.T.H. by the use of a discontinuous pH gradient on oxycellulose.[13] Besides this, he has pointed out that separation has also been achieved by zone electrophoresis on paper.[14]

The following facts would indicate the existence of a chromatophorotropic factor within the A.C.T.H. complex:

1. The chromatophorotropic factor is an integral part of pituitarian A.C.T.H. and its melanogenic effect in man becomes evident by skin pigmentation in three conditions: (*a*) A.C.T.H. overproduction in pituitarian Cushing's disease; (*b*) Addison's disease with increased A.C.T.H. output as a compensatory mechanism; and (*c*) pregnancy, where A.C.T.H. production runs high, judging by both blood examinations and the effect on rheumatoid arthritis. In contradistinction to these three "natural" conditions, melanoderma produced by over-treatment with A.C.T.H. is not necessarily a proof of the chromatophorotropic effect of A.C.T.H., since it may equally be due to contamination of our A.C.T.H. preparations with chromatophore hormone. This assumption is, however, refuted by the fact that purified and concentrated A.C.T.H. preparations have a chromatophorotropic effect in green-adapted frogs in doses down to 0·01–0·001 µg., whereas intermedin itself is active only in much higher doses.[1]

2. Determination of the chromatophorotropic factor in the blood of some hundred patients has shown that production of the chromatophorotropic factor in man always parallels the A.C.T.H. output as determined by the adrenal ascorbic-acid-depletion test (Sayers). Thus the chromatophorotropic factor is abundant in the blood of patients pigmented by chronic excessive output of A.C.T.H. (e.g., in Cushing's disease, Addison's disease, and pregnancy). It is also high, for short periods, in patients with acute conditions well known to produce A.C.T.H. (e.g., mental stress, heart stress, and operational stress). This parallelism is more than mere coincidence.[15]

3. The chemical properties of A.C.T.H. and intermedin are very closely related. For this reason both hormones always appear together in nature, and it is extremely difficult to separate them completely.[16] Characteristics common to both are remarkably high solubility in alcohol, which distinguishes them from all other pituitary hormones, and liability to rapid destruction by a special enzyme in blood and urine. For this reason, early investigations on the intermedin and A.C.T.H. content of biological fluids are no longer acceptable, unless they were carried out immediately after recovery of the fluid from the body or after immediate destruction of the special enzyme by acetone, heat, or similar procedures.

This evidence clearly indicates that A.C.T.H. and intermedin are separate factors, together constituting A.C.T.H. in nature. Separation is possible, just as separation of follicle-stimulating hormone (F.S.H.) from luteal hormone (L.H.) is possible; but just as we regard F.S.H. and L.H. as part of the gonadotropic hormone complex, so must we regard ascorbic-acid-depleting A.C.T.H. factor and the chromatophorotropic A.C.T.H. factor (intermedin) as one hormone complex—A.C.T.H.

Nature makes no distinction between these factors as the biochemist does. It seems, moreover, that the A.C.T.H. complex is composed of a multitude of factors possibly distinguishable by molecular weight and other physical properties. The existence of the following A.C.T.H. factors seems now to be proved:

A = Ascorbic-acid-depleting factor.[17]
B = Basic adrenal-weight-increase factor.[18,19]
C = Chromatophorotropic factor.[1,2]

Obviously in the future the potency of A.C.T.H. preparations should be gauged by the varying content of these factors, until a routine chemical method is found for separating them in the course of manufacture.

Department of Pharmacology,
Hebrew University—
Hadassah Medical School,
Jerusalem, Israel.
F. G. SULMAN.

FEEDING DISORDERS IN INFANTS

SIR,—I should like to thank Professor Vining for his timely advice on infant feeding (July 19, p. 99). I could not agree more with his ideal feed of boiled milk and sugar, but my experience has been that 1 teaspoonful of sugar to 4 oz. is inadequate. Bottle-fed babies tend to be very constipated, unless considerably more sugar than usually advised is added to their feeds; one teaspoonful per pound of body-weight in 24 hours keeps the stools in good condition

Demand feeding, as Professor Vining says, is the feeding method of choice; but it may be quite impossible for the mother with two or three other small children. The infant's loud demands for food may (indeed often do) clash with the other children's meal. Also the baby who does not wake for a 10 P.M. feed will usually do so at 2 A.M.—a disturbance a busy mother can ill afford.

MARY ELLIS.
Hockley, Essex.

Parliament

Danckwerts Award Voted

ON July 28 the outstanding votes of the Civil Estimates were passed in the House of Commons. Class V—housing, local government, health, labour, and national insurance—includes provision for the Danckwerts award.

More Food or Fewer People

In the debate in the House of Lords on July 23 on the rising cost of food Lord BOYD-ORR, F.R.S., contrasted the price of food today and at the beginning of this century. Then food was cheap in this country, because as a largely industrial nation we could pay for all we wanted. In 1900 we were almost the sole buyers and about 80% of the world production of some foodstuffs came to this country. Today in the food-exporting countries there had been a rise in the population and in the standard of living; and these countries were now consuming more of their own food. Ten years hence Australia, for instance, might well have no food to export.

Again in 1900 it was thought that if people had enough cheap food—such as cheap meat, white bread, margarine, and jam—to satisfy their hunger the food problem had been solved. Now we realised that a more expensive diet was necessary for health and we had raised the standard of food consumption. Today not only did we have 49 million mouths to feed, but more expensive food was needed to put into these mouths. To meet this challenge we must increase home production. The Government had set its policy at a 60% increase in home

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10. Waring, H., Landgrebe, F. W. The Hormones, ed. G. Pincus and K. V. Thimann. New York, 1950; vol. 2, p. 427.
11. Landgrebe, F. W., Reid, E., Waring, H. *Quart. J. exp. Physiol.* 1943, 32, 121.
12. Geschwind, I. I., Reinhardt, W. O., Li, C. H. *Nature, Lond.* 1952, 169, 1061.
13. Geschwind, I. I., Porath, J. O., Li, C. H. *J. Amer. chem. Soc.* 1952, 74, 2121.
14. Kunkel, H. G., Tiselius, A. *J. gen. Physiol.* 1951, 35, 118.
15. Sulman, F. G. Not yet published.
16. Astwood, E. B. Personal communication.
17. Reinhardt, W. O., Li, C. H. *Proc. Soc. exp. Biol., N.Y.* 1951, 77, 229.
18. Young, F. G. *Lancet*, 1951, i, 1211.
19. Stack-Dunne, W., Young, F. G. *J. Endocrinol.* 1951, 7, suppl. 66.

production. Lord Boyd-Orr believed that if we are prepared to spend substantial capital sums on bringing marginal lands into fertility we could produce 75% or 80% of our own food.

It was only prudent to rearm, but he thought it possible that in the long run it would pay us to devote some of the money now being spent on rearmament to increasing the home output of food.

Could we also, he asked, do anything to increase world supplies so that there were surpluses for us to import. Some people held that population would always increase faster than food production, and that we should never close the gap until birth control was generally accepted. He believed that birth control would be difficult to apply in time to prevent the population of the world from reaching 3500–4000 million. If W.H.O. really got going and eliminated diseases like malaria there would be a world explosion of population. But if full advantage was taken of the resources of modern agriculture and engineering, then the practical limit of food production was the amount of labour and money we were willing to put into it. In a food shortage we were the most vulnerable country in the world because we are so dependent on imports, but we were also a politically mature nation with a great Commonwealth, and we could offer an enlightened food policy to the world. If we did, he believed we should be astonished at the extent to which it would be accepted.

Publicity for Cancer Treatment

In the House of Commons on July 23 Brigadier FRANK MEDLICOTT pointed out that the number of cancer deaths in England and Wales had risen from 26,000 in 1900 to 80,000 in 1947. Admittedly in the early days of the century diagnosis was less accurate and modern medicine enabled more people to reach an age when cancer was more likely to affect them. But however optimistically the figures might be interpreted, it was clear that the present policy of reticence about the disease needed reconsideration. Only eighteen months ago the Central Health Services Council advised that it was undesirable for any general scheme of cancer publicity to be carried out by any central government organisation. A widespread feeling existed that cancer was always fatal. It was not yet generally realised how much progress had been made in the treatment of cancer during the last fifty years. The balance against giving more publicity to the importance of seeking advice for suspected cancer had probably so far been tilted by the medical profession's fear of a great increase in neurosis or cancer apprehension. He himself believed that view to be mistaken. Because no comprehensive cure had yet been discovered, doctors were perhaps unduly modest as to what had already been achieved. He also suggested that the cancer mortality was now so high that it was pointless to pretend that the disease was something which affected only a small number of people and that the less said about it the better. Secrecy might save a certain number of people from worrying about cancer, but at the same time it was condemning thousands to die many years before they need.

Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that, despite great improvements in the methods of treating cancer, we were forced to admit that, short of some revolutionary discovery, our chief hope lay in earlier diagnosis and treatment. Cancer was not a disease which could be made notifiable, but the Ministry encouraged registration of cases which came for treatment. Radiotherapy clinics were gathering valuable information. The emphasis was on education rather than on propaganda: but the problem was not easy because they were faced with deeply divided opinion in responsible medical quarters. The objections to a widespread direct education programme to the public were weighty. It would be wrong to have a national campaign based on fear. The Minister's Standing Cancer and Radiotherapy Advisory Committee had advised against a cancer campaign addressed direct to the public. But that reply did not mean that local health authorities should omit reference to cancer in their general health propaganda; for a great deal could be done through a more restrained type of information. That could appropriately be given by the local health authorities and the voluntary associations. The Government were considering what encouragement they could best give to these bodies. A start had been made with further education for doctors and medical students in the early recognition of cancer. The Ministry had six films for showing to professional audiences.

Cancer research was world-wide, and if any country discovered a cure it would be internationally shared. This country was playing its part: many teaching hospitals were specialising in this work and a great deal of research was being carried out through large numbers of medical, surgical, and scientific bodies, including the universities. Atomic energy research at Harwell had shown how nuclear physics could provide an important method of cancer treatment, and the new types of apparatus had already been ordered by National Health Service hospitals. She did not believe that merely spending money would necessarily bring results, but the Medical Research Council had increased its expenditure. In 1945–46 it spent about £6000 directly on cancer research, in 1951–52 £340,000, and this year it would spend £410,000, including £150,000 for financing the research activites of the Royal Cancer Hospital.

QUESTION TIME

Health Service Charges

Replying to a question Mr. OSBERT PEAKE, Minister of National Insurance, said it was not the practice for Government departments to publish the executive directions which they gave to their officers and he was not prepared to ask the National Assistance Board to make an exception to that rule by publishing the instructions given by them to local offices for dealing with cases of hardship in respect of dental, ophthalmic, and prescription charges other than those on National Assistance.

Flour Improvers

Mr. D. W. WADE asked the Minister of Food what progress had been made in the provision of an alternative to the agene treatment of flour; what evidence on this subject had been obtained from the United States of America; and what had been the results of his consultations with the Medical Research Council and the Research Association of Flour Millers.—Major GWILYM LLOYD GEORGE replied: The wide scope of the investigations makes it unlikely that they will be completed before the end of the year at the earliest. My department and the other departments concerned have from the outset maintained contact with the research and developments which have taken place in the United States of America.

Iodised Salt

Sir WALDRON SMITHERS asked the Minister what steps he was taking to implement the recommendations of the Medical Research Council for the addition of iodine to all salt for human consumption.—Major LLOYD GEORGE replied: The Food Standards Committee are considering representations arising from their report on this matter. They will, I hope, be able to advise me fairly soon how best to give effect to the council's recommendations.

Replying to a further question Major LLOYD GEORGE said that he could not say how soon a decision would be reached. He was advised that there were a good many objections of a technical nature, some of which were quite serious, but he would give the information as soon as possible.

Prescription Charges

In answer to a question, Miss HORNSBY-SMITH said that the gross amount accruing from the charge on prescriptions dispensed by chemists in June, 1952, was about £418,000.

Infectious-disease Beds in London

Mr. SOMERVILLE HASTINGS asked the Minister how many beds in hospitals in the London area were reserved for the treatment of infectious disease in 1949, 1950, and 1951; and how many were occupied.—Mr. IAN MACLEOD replied: The following figures are for beds allocated to the treatment of infectious diseases in hospitals in the London postal area.

Beds	*1949*	*1950*	*1951*
Allocated	3637	3453	2973
Occupied	1201	1162	929

Obituary

CATHERINE CHISHOLM

O.B.E., B.A., M.D. Manc., F.R.C.P.

Dr. Catherine Chisholm, who died on July 21 at the age of 74, was the first woman accepted by the University of Manchester as a medical student. She fully repaid this enlightened hospitality by her years of service on behalf of the women and children of Manchester.

Her father, Dr. Kenneth Chisholm, believed in education for women, and his daughter had graduated in arts at the University of Manchester in 1898, after having won the Bishop Lee Greek Testament prize, before she asked for permission to study medicine. She took her medical degree in 1904 and after holding house-appointments in London and Yorkshire she settled in practice in Manchester.

Her special interest in the care of women and children was recognised by her appointment in 1914 as physician for children to the Northern Hospital, Manchester. The same year the medical women of Manchester opened a small hospital for the "more effective treatment of babies and very young children suffering from diarrhœa and other gastro-intestinal disorders." They felt that in a general hospital it was not always possible to offer these small patients the special attention and accommodation they needed. The number of patients was at first limited to 12, and the cost for the first year was estimated at £800. From this modest beginning grew the present Duchess of York Hospital for Babies which now has over 100 cots. In 1919 Dr. Chisholm gave up private practice, for besides being senior medical officer to the new Babies' Hospital she had been appointed consultant for children at the Hope Hospital, Salford, and clinical lecturer in children's diseases at the University of Manchester. For 36 years she was also medical officer to the Manchester High School for Girls, and she published a monograph on *The Medical Inspection of Girls.* She continued this side of her work as a member of the court of Manchester University where she did much to safeguard the health of women students.

[*F.W. Schmidt, Manchester.*

From 1928 to 1929 she was president of the Medical Women's Federation. In 1935 she was appointed C.B.E., and in 1949 the Royal College of Physicians of London chose her as the first woman to be elected to their fellowship under the by-law permitting the election of doctors who are not members. Although her activities had been curtailed during the past year, she was as interested as ever in what was going on, especially in the Duchess of York Hospital where her name has been given to the premature baby ward. She retired from the management committee only last November.

To this record of honourable service and official distinctions the words of her friends add colour and warmth.

"As a doctor," writes S. K. G., "Catherine Chisholm treated her patients, however young, as human beings and quickly secured their interest and coöperation. This recognition of the needs of the young child was one reason for the early success of the Manchester Babies' Hospital where the facilities and nursing care were, under her firm guidance, specially adapted for the small patients—a fact soon recognised and welcomed by the mothers who came with their babies. As a teacher, her students were carried forward by her intense interest and vitality, by her eager grasp of new methods of diagnosis or treatment, and her ability to stress even the smallest details of hygiene and nursing care so as to weld the treatment of the child into a complete whole. As a senior colleague, she was always ready and willing to listen or offer suggestions, while problems of clinical or administrative importance would be discussed with the whole staff. As a friend her support and encouragement knew no bounds. She would go out of her way to help people. Many medical women—and men too—owe their advancement to her, for she opened the way and enabled them to move forward with confidence. I remember with warm gratitude her support during difficult times, her pleasure in the achievements of others, and her unfailing interest in the personal life of those around her. Many children, and those now grown-up as well, will always think with affection of 'Chisio' and her breezy visits, sometimes with an unexpected gift such as a longed-for book. For her wide knowledge, her sound wisdom, and her warm good fellowship she will be missed by many all over the country."

C. E. W. mourns her friend in the words of the Gael: Yesterday a mountain in my sight, and today, my grief, a shadow.

"The personality and intellect of Catherine Chisholm," she continues, "were indeed a mountain of an infinite and contradictory variety of aspect. She had Highland imagination in her appreciation of literature and the arts, especially music, and in her intuitive understanding of the child and the rebel. She had Lancastrian shrewdness in assessing the worth of others, so that she gathered round her generation after generation of able juniors. She had the proper male contempt for domestic trivia, and an intensely feminine interest in dress and manners. She had tremendous courage, whether putting a needle into a baby's longitudinal sinus, driving on to a rickety Highland ferry, or boarding some august philistine for his subscription or his signature. She was the bonniest fighter—went in without fear, stayed in without loss of temper or dignity, and won without malice. With courage went generosity as reckless, shown in nothing more than in her friendships, which were many and embraced not only friends but their children and grandchildren ripening with their ripening years, and extended also to her staff in hospital and household.

"She looked and spoke charmingly at the dinner given in her honour by the Manchester branch of the Medical Women's Federation after the award of the fellowship of the Royal College of Physicians. This was the same Catherine Chisholm who had cowered under the weather gunwale on the way to Mull in a squall, or sat, booted, be-knapsacked, and happy on Helvellyn or Snowdon, or some height in Ireland or abroad, after a morning's scramble. At the day's end the 'crack' was seldom of 'causes,' for she could bandy the best of nonsense, solve puzzles, play children's games, and follow the complications of a Wild Western at the cinema.

"Yesterday a mountain, today a shadow—tomorrow perhaps a legend, and all legends have served as rallying cries."

Births, Marriages, and Deaths

BIRTHS

BROWN.—On July 23, at the Sussex Maternity Hospital, Brighton, to Elizabeth (née Cumberlege), wife of Dr. P. B. Brown—a son.

BUXTON.—On July 24, at King's College Hospital, to Diana Margaret (née Borrow) and Dr. Roger St. John Buxton—a son.

DAVIES.—On July 24, at Churchill Hospital, Oxford, to Alison, wife of Dr. J. O. F. Davies—a daughter.

EDNEY.—On July 14, at Faversham, to Mary, wife of Dr. Roy Edney—a daughter.

FAIRBAIRN.—On July 19, to Marcia, wife of Dr. A. S. Fairbairn—a daughter.

FISHER.—On July 21, in Belfast, to Sheila (née Penny), wife of Dr. Oliver D. Fisher, M.R.C.P.—a son.

GELLATLY.—On July 16, at Perivale Maternity Hospital, to Audrey (née Norris) and Dr. Edward Gellatly—a son.

WOOTTON.—On July 14, at Hammersmith Hospital, London, to Veryan, wife of Dr. I. D. P. Wootton—a son.

MARRIAGES

BENNISON—UNDERWOOD.—On July 19, Robert John Bennison, M.B., of Harrogate, to Kathleen Mary Underwood, M.B., of Nottingham.

FRANKS—DOUHAN.—On July 19, in London, Raymond Basil Franks, M.R.C.P., of Wimbledon, to Ulla Margareta Douhan, of Stockholm.

GREY TURNER—TOMLINSON.—On July 26, Elston Grey Turner, M.C., M.R.C.S., of Huntercombe Manor, near Taplow, Buckinghamshire, to Lilias Tomlinson, of Credenhill Court, Herefordshire.

DEATHS

CAMAC.—On July 19, James Camac, M.B. Belf., of Church Gresley, Derbyshire.

CHISHOLM.—On July 21, at 34, Broadway, Withington, Manchester, Catherine Chisholm, O.B.E., B.A., M.D. Manc., F.R.C.P.

NOBLE.—On July 22, at Lowthorpe, 31, Queen's Park Avenue, Bournemouth, John Allen Noble, M.C., M.A., B.M. Oxfd.

PYRAH.—On July 9, in hospital, Reginald Smith Pyrah, M.B. Leeds, of Farnley, Leeds.

Notes and News

RESEARCH IN SCOTLAND

At the start of the National Health Service in Scotland the endowment funds of the voluntary hospitals were transferred to the new hospital boards of management. The funds now amount to some £13 million and the Hospital Endowment Commission has been considering, under the chairmanship of Sir Sydney Smith, how they can best be used. Part of the money, the commission consider, should be set aside to provide amenities for hospital patients and staff beyond what the N.H.S. "can reasonably be expected to finance." The substantial remainder, they suggest, should be used to finance medical research in Scotland, and they have set out their proposals in a white-paper to the Secretary of State for Scotland (H.M. Stationery Office. 6*d*.).

The commission recommend that a small number of trustees, broadly representative of the whole of Scotland, should be set up under statutory powers to work in close association with the Advisory Committee on Medical Research in Scotland. They estimate that the funds likely to be available under the trustees would produce an income of some £120,000 a year. Any research-worker or team would be entitled to apply for help, and the commission think that research should be looked at in its widest sense and "not merely as a matter of laboratory investigation."

Many boards of management have only small endowments or no endowments at all at present, while others have large funds for which there is no sufficient outlet. The commission would like to see part of the money redistributed in such a way that every board of management will have reasonable funds at its disposal for research as well as other purposes. They propose to provide also for the constitution of small funds under the control of each regional hospital board.

THE AGE OF ENTRY TO NURSING

The leaders of the nursing profession have long believed that girls entering nursing training should not be under the age of 18. In August last year recruitment had reached the highest figure ever known up to that time (though it has since gone a little higher), and the General Nursing Council and the Ministry of Health agreed that a regulation should be made—which is coming into force on Aug. 1, this year—fixing the minimum age of entry at 18. Girls under that age who have begun their training will be allowed to continue. Those who have joined cadet schemes or prenursing courses will have to wait six months longer before beginning their hospital training, but will not otherwise be affected. In hospitals where recruitment is likely to be seriously reduced the G.N.C. have discretion to relax the rule until the situation adjusts itself.

APPROVED NAMES FOR DRUGS

The British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Alphameprodine	α-3-Ethyl-1-methyl-4-phenyl-4-propionoxy-piperidine.
Betameprodine	β-3-Ethyl-1-methyl-4-phenyl-4-propionoxy-piperidine.
Hydroxyprocaine	2-Diethylaminoethyl 4-aminosalicylate.
Isoniazid	*iso*Nicotinhydrazide. Cotinazin; Hydrazid; Mybasan; Pycazide; Rimifon; Tubomel.
Penethamate hydriodide	Benzylpenicillin 2-diethylaminoethyl ester hydriodide. Estopen.
Pyrimethamine	2 : 4-Diamino-5-*p*-chlorophenyl-6-ethylpyrimidine. Daraprim.

THE GOLD MINERS OF WEST AFRICA

The health of the mining community of the Gold Coast is the subject of a report [1] by Prof. G. Macdonald to the Ross Institute Industrial Committee. The gold mines (together with others that work bauxite, manganese, and diamonds) employ some 34,000 persons, of whom about 12,500 work underground. A large number of these are seasonal workers, who form part of an annual migration of 200,000 persons from the healthy but infertile interior to the fertile coast. The migration, which has been going on for centuries, starts in August and September, and the return journey is in the spring. The journey of over 350 miles is made partly on foot, partly on overloaded lorries. Three major rivers have to be crossed by ferries; these are quite inadequate, and lorries may be held up for a week. During the long journey neither feeding nor sanitary arrangements are organised. Both during the journey and on arrival at the coast the labourer depends on agents and moneylenders for his immediate necessities, and usually he starts his season's work heavily in debt. Yet these migrants are the wealth of the Gold Coast Colony; so, as Professor Macdonald points out, both the health and the economy of the Colony would benefit if the journey could be made "reasonably civilised for all." But it is not clear whether he regards this as more properly a task for the mine owners or the government.

At the mines themselves the hospital arrangements are "creditable." But there is no organised industrial or preventive medical service amongst the community. Hot underground workings impose a severe environmental strain on many workers, and the most important industrial hazards are probably accidents and tuberculosis. Many of the miners live in villages where housing, sanitation, and feeding are far from adequate; but some mines have excellent housing arrangements for their labour and well-run canteens. Many of the men prefer to live in squalor in the villages, often amongst a tribal group, where a natural leader maintains the tribal organisation and discipline; but such leaders apparently fail to instil standards of conduct and hygiene suitable to an industrial community.

The Gold Coast miners present a fascinating problem in social medicine. The Ross Institute sees clearly the elements of the solution, and, as an outside body, should be well fitted to bring about the necessary coöperation between the mine owners, the government, and the miners and so create new attitudes to health. In this, as in nearly all difficult public-health problems, much rests on education.

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[1] Obtainable from the Organising Secretary, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Gower Street, London, W.C.1.

University of London

The title of professor emeritus of bacteriology has been conferred on Prof. S. P. Bedson, F.R.S., and the title of professor emeritus of chemical pathology on Prof. J. R. Marrack, on their retirement from their chairs at the London Hospital Medical College.

The title of professor of pharmacology and therapeutics has been conferred on Dr. C. A. Keele in respect of his post at the Middlesex Hospital Medical School, and the title of professor of chemical pathology on Dr. N. H. Martin in respect of his post at St. George's Hospital Medical School. The title of reader in biochemistry has been conferred on Mr. William Klyne, PH.D. (Postgraduate Medical School of London), the title of reader in bacteriology on Dr. B. W. Lacey (Westminster Medical School), and the title of reader in morbid anatomy on Dr. A. D. Morgan (Westminster Medical School).

Royal College of Physicians of Edinburgh

At a meeting of the college on July 22, with Dr. W. A. Alexander, the president, in the chair, the following were elected to the fellowship:

Daw Yin May, Maung Shwe Zan, W. J. G. Barrie, J. W. Rae.

The following were elected to the membership:

A. F. S. Perera, Mohd Ayub Khan, W. S. Watson, W. J. Abel, Nimai Krishna Mitra, Andrew Bogdan, G. H. Templeman, Arthur Jarrett, M. W. J. Boyd, N. S. Chalk, Pathiyil Karthiyayani Krishnankutti, Sureshwar Prasad Jha, J. B. Cromie, H. G. Morgan, C. D. R. Pengelly, Harry Altman, Eveline P. Forbes, Leo Schamroth, L. H. Moffin, P. G. Aungle, Janet L. P. Hunter.

Queen's University, Belfast

At recent examinations the following were successful:

M.D.—Sarah L. Campbell, R. A. N. McMath, Thomas Wilson (with commendation); R. N. Beck, P. J. Blaney, E. W. T. Henry, J. C. Hewitt, R. J. Marshall, Frances L. J. Robinson, K. L. Stuart, A. P. Trimble.

M.B., B.Ch., B.A.O.—F. C. O. Allen, R. F. C. McDowell, J. J. H. Stewart (with second-class honours); C. A. C. Abraham, D. A. Aiken, Goordeealsing [illegible] bin, S. C. Bateman, R. C. Bloomfield, C. [illegible] P. Boyle, Eileen S. Browne, John Carroll, T [illegible] orkey, C. E. Cosgrove, E. C. Cowan, G. E. Crawford, Margaret H. Dales, S. N. Donaldson, Domnall Duffin, Desmond Duignan, T. L. Dunn, D. S. Fullerton, Dorothy Gilpin, Florence C. Gordon, W. H. Graham, T. M. Hannigan, K. K. A. Hofheinz, H. B. Kean, John Lowry, Matthew Lowry, S. J. H. Lowry, W. N. C. McCleery, J. W. McKay, T. J. McLister, Elizabeth G. H. McLucas, J. B. H. Martin, J. S. Y. Mathewson, E. S. Mitchess, James Moore, A. L. Murphy, Frances M. Murphy, R. C. W. Murphy, Betty Nicholl, Margaret Nicholl, R. M. Nicholl, P. J. O'Neill, B. Z. Rosensweig, David Ross, G. M. Scott, Anthony Smyth, Mabel M. Stevenson, E. M. W. Stuart, Zoe Waddington, Margaret G. Warwick, Madge G. Watson, Mary J. Watson, A. G. C. Wilson, A. J. Woods, J. H. Woolf.

D.P.H.—John Andress, T. L. Gracey, G. A. Kernohan, Anne W. Kilpatrick, E. I. Mulholland, C. R. C. Rainsford, Sarah E. M. Sherrard, H. P. Swan.

Royal College of Surgeons of Edinburgh

At a meeting of the college held on July 21, with Prof. Walter Mercer, the president, in the chair, the following were admitted to the fellowship:

V. P. Amato, Manilal [illegible] Chand Bhandhela, [illegible] J. R. Conacher, [illegible] Adly Hammouda [illegible] G. Munro, Nanalal Ranchhodji Patel, A. I [illegible] William Seright, B. L. Shaff, Abdel Hamid Shouman, E. M. Sparrow, K. S. Stewart, J.G. Stonham, Willoughby Wilson.

Scottish Conjoint Board

At recent examinations of the board of the Royal Colleges of Physicians and Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow the following were successful:

Ranjit Singh Ahluwalia, Mavis F. Anderson, F. J. Badenhorst, J. B. B. Baird, C. E. Barth, G. A. C. Binnie, E. H. Brown, D. G. Chambers, Brian Cornes, W. A. Dalgleish, E. A. Ehlinger, Sydney Fogel, Brenda Gale, Colina Graham, Ruth E. Graham-Yooll, J. M. H. R. Hardy, A. R. Isaac, Amirali Husein Kassam, Viljoen Kritzinger, C. H. Lalgee, Pamela M. Lambden, P. A. Lowe, W. A. Mahon, Pearl K. Malasky, Christine W. Mann, R. W. S. Miller, E. C. Moffat, J. I. Morrison, J. A. McIlvride, Agnes F. Mackay, Arnold Orwin, Joyce E. A. Ovens, Hedwig M. M. Papigay, Audrey Pilbeam, Jean M. Price, R. A. W. Ratcliff, Margaret H. Rodger, Enid Sagar, Ralph Shabetai, Thelma D. Standing, Robert Steele, Alexander Stevenson, Cyril Ward, M. H. Weinberg, M. M. Wiener.

Royal College of Obstetricians and Gynæcologists

At a meeting of the council held on July 26, with Dame Hilda Lloyd, the president, in the chair, the following officers were elected:

President, Mr. A. A. Gemmell; vice-presidents, Prof. Gilbert Strachan and Mr. A. J. McNair; hon. treasurer, Mr. A. C. H. Bell; hon. secretary, Mr. H. G. E. Arthure; hon. librarian, Mr. A. J. McNair; hon. curator of the museum, Mr. Aleck Bourne; hon. treasurer of the Australian regional council, Prof. Bruce Mayes; hon. treasurer of the New Zealand regional council, Mr. H. K. Pacey. Sir Stanford Cade was invited to attend meetings of council as representative of the council of the Royal College of Surgeons.

The following were elected to the membership:

Janki Devi Arora, Lily Arratoon, J. L. M. Bean, Anil Chandra Bhoumik, C. H. Borsman, G. H. Burgess, G. G. Champion, Sivaccolunthu Chinnatamby, G. R. Clare, J. F. Correy, N. K. Crooke, G. E. Cummins, A. M. Dawson, R. D. De Vere, D. T. Dodds, C. P. Douglas, Robert Dowie, Sunit Kumar Dutt, Aileen C. Foley, M. S. Forrest, D. F. P. Gordon, W. J. Gordon, J. J. Handler, Alexander Hunter, Daphne M. E. Kayton, I. A. McDonald, Margaret W. Macgregor, T. P. Magee, T. M. McNie, A. G. Mathew, P. R. Myerscough, J. G. O'Sullivan, Marjorie M. Paterson, Alexander Persey, Evelyn Peters, G. W. Prueter, Delmont Puflett, Marie Quadros, M. B. Quane, Bibhuti Bhusan Rakshit, Harry Rees, Dia Seif-Eldin, C. A. Simmons, E. L. Trott, Mary E. Walker, R. A. Warren, H. B. Watson, J. A. Williams.

Royal Australian College of Surgeons

Alan Newton prize.—This essay prize was established last year in recognition of the services to the college of Sir Alan S. Newton.

It is to be offered biennially to fellows of the Royal Colleges of Surgeons of Australasia, of England, of Edinburgh, in Ireland, and of the Royal Faculty of Physicians and Surgeons of Glasgow.

The subject for the first essay is to be the Pathology and Surgery of Diseases of the Parathyroid Glands, and entries should reach the secretary of the college on or before Dec. 1, 1954.

Royal Medical Benevolent Fund

At the annual general meeting of the fund held on July 24 the following officials were re-elected: president, Lord Webb-Johnson; hon. treasurer, Mr. F. A. Juler; and hon. secretary, Dr. R. Cove-Smith. During 1951 £36,500 was distributed in grants, gifts, and annuities.

Blood Donors

There are now more blood donors in England and Wales than at any time since the late war. During the March quarter this year 17,269 new donors joined the National Blood Transfusion Service bringing the total to 470,574. Over 170,000 more donors are needed to keep pace with the growth of the service and to provide a reasonable reserve of blood plasma.

W.H.O. Tuberculosis Appointment

Dr. Johannes Herman Holm, of Copenhagen, has been appointed chief of the tuberculosis section of the World Health Organisation. He succeeds Dr. J. B. McDougall who has held the post since W.H.O. was established.

Dr. Holm, who was born in 1902, studied medicine at the University of Copenhagen. He has lately obtained an M.P.H. at Harvard. Among the positions he has held are the following: chief of the tuberculosis division of [illegible] consultant to the Danish national [illegible] U.S. Public Health Service, chair[illegible]mittee on tuberculosis, and director of the International Tuberculosis Campaign.

Société Française de Biologie Médicale

This new French society has lately been set up under the presidency of Prof. Henri Benard. The secretaries are Dr. M. Lamotte, 48, rue du Docteur Blanche, Paris, and Dr. M. Durupt, 20, rue de la Pompe, Paris.

The Largest Medical Library

Lieut.-Colonel Frank B. Rogers has been appointed director of the recently established Armed Forces Medical Library in Washington. Colonel Rogers has served since 1949 as the director of the Army Medical Library, which is the nucleus for the new establishment. The new library is to serve as a central medical library for the United States Army, Navy, and Air Force, and as a national library for medicine and related sciences.

Committee on Venereal Infections and Treponematoses

At the fourth session of the World Health Organisation's expert committee on this subject, which opened in London on July 28, speakers reviewed the work of W.H.O. in this field during the last four years which has ranged from demonstration projects against the venereal infections to mass treatment campaigns against yaws in Indonesia and Thailand, and against bejel in Iraq. The experience gained in the treatment of treponemal infections by repository penicillin therapy was also discussed.

The Doctor's Signature

The *Manchester Guardian* of July 25 records that at a meeting on the previous day the London Executive Council was informed by its general benefits committee that on some prescription forms the doctor's signature is indecipherable. If the doctor for any reason is liable to a surcharge it is then impossible to trace him. The council has decided to ask the Executive Councils Association to consider whether the Ministry of Health should be asked to put a distinguishing number or mark on prescription forms so that the practitioner can be readily identified.

Lord Horder has accepted an invitation to become the first president of the United Hospitals Festival Choir.

Appointments

Howat, D. D. C., M.B. Lond., D.A.: consultant anæsthetist, St. George's Hospital group, London.

Pleydell, M. J., M.C., M.D. Lond., D.P.H.: deputy county M.O.H., Northamptonshire.

Rutherford, H. W., M.B. Aberd., D.P.H.: asst. tuberculosis officer, North-Eastern R.H.B.

Birmingham Regional Hospital Board:

- Ansari, A. H., M.A. Camb., M.R.C.S., D.M.R.D.: asst. radiologist, Dudley and Stourbridge and West Bromwich group of hospitals.
- Kershaw, R. A., M.B. Manc., M.R.C.P.: asst. chest physician, South Worcestershire group of hospitals, and Worcestershire county council.
- Paul, M. B., M.A., M.D. Camb.: consultant chest physician, Burton-on-Trent group of hospitals.
- Sanderson, J. M., M.B. Birm., F.R.C.S.: part-time consultant thoracic surgeon, Stoke-on-Trent group of hospitals.

East Anglian Regional Hospital Board:

- Chalmers, R. D., M.R.C.S.: asst. chest physician, Peterborough chest clinic.
- Love, W. J., M.B. Belf.: anæsthetic registrar, United Norwich hospitals.
- Wolff, F. W., M.B. Durh.: medical registrar, West Suffolk General Hospital.

Manchester Regional Hospital Board:

- Brown, C. P., M.B. Manc., D.A.: consultant anæsthetist, thoracic surgery team, Blackpool.
- Hassall, Harold, M.B. Manc., F.R.C.S.: consultant general surgeon, South Cheshire hospital centre.
- Marsden, H. B., M.B. Manc., D.C.H.: asst. pathologist, Salford.
- White, T. A., M.B. Birm., D.C.P.: asst. pathologist, Withington Hospital, Manchester.

North-East Metropolitan Regional Hospital Board:

- Brimblecombe, F. S. W., M.D. Lond., M.R.C.P., D.C.H.: part-time consultant pædiatrician, Harold Wood Hospital.
- Cohen, E. L., M.A., M.B. Camb.: part-time consultant dermatologist, Oldchurch Hospital.
- Edkins, J. R. P., M.D. Manc., D.P.M.: consultant psychiatrist, Brentwood Mental Hospital.
- Gray, P. W. S., M.B. Lond., D.A.: consultant anæsthetist, Chase Farm Hospital and other hospitals within the group.
- Marks, Morton, M.R.C.S., D.L.O.: part-time consultant E.N.T. surgeon, Mile End and St. George-in-the-East Hospital.
- Sefton, Louis, M.R.C.P.E.: part-time consultant dermatologist, Whipps Cross Hospital.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

THERAPEUTIC TRAUMA OF THE BRAIN*

P. MACDONALD TOW
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BEIT MEMORIAL RESEARCH FELLOW
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IT has not always been accepted that the brain was the organ of mind; or, to put it less equivocally, that it was the physical organ of any psychological activity. This alone may explain why manipulation of the organ was not proposed earlier as a cure for diseases of the psyche. One of the early pronouncements on the subject was made by Hippocrates:

> "It ought," he wrote, "to be more generally known that the source of our pleasure, our merriment, laughter, and amusement, as of our grief, pain, anxiety and tears, is none other than the brain. It is especially the organ which enables us to think, see and hear, and to distinguish the ugly and the beautiful, the bad and the good, the pleasant and the unpleasant. Sometimes we judge according to convention; at other times according to the perceptions of expediency.
>
> "It is the brain, too, which is the seat of madness and delirium, of the fears and frights which assail us, often by night, but sometimes even by day; it is there where lies the cause of insomnia and sleep-walking, of thoughts that will not come, forgotten duties, and eccentricities."

But it was over 2000 years before the connection was therapeutically exploited.

A trial of cerebral surgery was made in 1890, following on the animal experiments of Goltz. The pioneer was G. Burckhardt, physician in charge of a small Swiss mental hospital, who removed part of the temporo-parietal cortex in a few severe psychotics. But, though one patient appears to have been considerably benefited, Burckhardt met with much opposition and his work ceased and was forgotten. Very different was the reception accorded Egas Moniz of Lisbon, sixteen years ago, when he described the results of operating on the brains of 20 insane persons. Far from receiving intense opposition, his method was quickly taken up by Freeman and Watts in America and others elsewhere, and was soon well on its way to extensive trial. Yet, though thousands of patients have been leucotomised in the succeeding years, we are still far from certain of the value of the operation: as Professor Lewis (1950) has aptly put it. "Some of the successes attained by the operation in apparently hopeless cases indicate that its risks and crudity do not put it out of court; it is still in many respects on trial, but has respectable testimony in its favour."

EFFECT OF LEUCOTOMY

If these operations are traumatic, where exactly is the trauma? There is, of course, the surgical trauma. Apart from a few excursions down into the thalamus, this, up to now, has been confined to the frontal lobe; but this trauma is deliberate. There may be minor accidental trauma to the autonomic system and to purely intellectual activity: but the body as a whole and all the senses are unimpaired. The major damage is to certain aspects of the character or personality.

For almost a decade after the initial dramatic success of Moniz and Freeman, and, curiously enough, especially towards the end of that period, it was repeatedly and indignantly denied that the operation resulted in any trauma to the person as a whole. Patients were apparently being cured right and left, and were *often* discharged from hospital to the ordinary social and domestic backgrounds of everyday existence. Such patients were in fact sent away from the physicians' constant observations; and with so few workers in the field it may be understandable that their later fate was lost sight of in the zeal to cure more urgent cases.

Moniz published his first communication in
In 1939 appeared the classic monograph of Pro
Rylander on his study of patients who had had
frontal lobes removed for tumour—the first full ps
logical study of surgical cases of this sort. His num
findings included not only psychological data fr
series of tests but also an account of the various a
malities of behaviour which he discovered onl
visiting the homes of the lobectomised subjects.
for some reason his example was not heeded, and
leucotomy patients were rarely given anything
than a conventional psychiatric examination.

That the operation of leucotomy is therapeu
now beyond all doubt. It produces a consid
amount of relief in intolerable mental illness. The
disorderly schizophrenic frequently becomes quie
manageable; the depressive is often relieved
sadness and suffering; the tense obsessional be
relaxed; and the anxious hypochondriac ceas
complain. Often, though not always, the distr
symptoms which form the core of the presenting
are removed.

The topical question, however, is not how much
these operations will do, but rather how much
they may cause.

HOW MUCH HARM?

I believe that in any large hospital for the c
insane—say with 2000 beds—one could justifiably
out the hundred worst patients and deprive th
part of their frontal lobes. One would inevitably
certain amount of good, and the little bit of ba
would do, also inevitable, would in such cas
negligible. It would certainly be more logical
leucotomising every obsessional patient ill for more
two years.

In well-preserved patients with the common for
neuroses the results from the purely clinical po
view are about the same (Tow 1950); but it is in
cases that one sees after operation the various
malities of temperament and character which a
meat of the present arguments about the do
ethics of the operation. Some of these abnorm
such as emotional barrenness, gross egocentricity
of responsibility towards others, and lack of ap
tion of moral and spiritual values, are in particul
basis of outcries about the wickedness of the proc

I have suggested one reason why such obv
serious complications passed unnoticed at first. An
probably, was that gross abnormalities of this ki
definitely rare; so in the early days the relatively
number of cases then available could not yield
such examples. A further reason was that most of
early patients were in the worst wards of a
hospital, and among a group of dirty, degenerate s
phrenics it is hardly surprising that one of
leucotomised, might not be conspicuous by his
rude or inconsiderate table manners. At any rat
asocial tendencies and inconsiderate behaviour
hardly be observed with any thoroughness, and no
significance would be attributed to them, agains
abnormal psychological environment of the c
hospital ward.

The background against which the early postope
changes were observed was in fact the worst p
for their detection, and the entirely hopeful and
peutic orientation of the observers may not have
discovery of the type of change which sometimes occ

But it was not long before the operation was
tively performed on sane patients—patients with v
severely disabling neuroses, but with a basic perso
still essentially intact. What happens if we i
frontal cortex in such patients? Roughly the sa
with the psychotics, if they have been well sel

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* From an address to the Medical Society of London.

In half, the illness is relieved, and perhaps a few are cured. The others are essentially unaltered; they may be slightly better, or, more rarely, slightly worse.

Here again similar circumstances vitiated the results. A neurotic was seen, for example, in the consulting-room and recommended leucotomy; when he was seen later the operation had produced the effect desired. Often, however, it had also produced an undesired effect, a certain damage to the personality, and this was missed because the symptoms and signs which made it up did not reveal themselves in the physician's normal sphere of work. If he sought such information by direct questioning, he would probably be met by a bland denial of any egocentricity, unkindness, or volubility. Such characteristics are hardly those to which the average patient would be eager to lay claim; though a further reason might be the lack of insight with which these symptoms were associated.

To all this I believe we can add another explanation —a halo effect. Even if a patient has some insight into his failings (which, as a matter of fact, he usually euphemistically interprets and describes as a little irritability or impatience), or if they are brought to his notice by his friends or relatives (in any case an unlikely event) he will be reluctant to complain of them to the doctor who has helped him and removed him from an existence of misery and anxiety to show him promise of a full and happy life.

These, then, are some of the reasons why the early results of leucotomy were rather poor prognostic guides as to its ultimate usefulness and application. Moreover, the complacency, which not unnaturally developed from the apparently uncomplicated early successes, probably hindered any extensive inquiry into the social and civil aspects. But when these were adequately investigated many kinds of alteration of the personality were determined and analysed (Freeman and Watts 1950, Hutton 1947a and b, Knight 1943, Meyer and McLardy 1946, Partridge 1950, Rylander and Sjöqvist 1946, Rylander 1947a and b, Ström-Olsen 1945, Ström-Olsen and Tow 1949). Now Partridge (1950) says that every patient has deficits of some sort; though he rightly prefers to refer to them as trends rather than as fixed characteristics. It is important to pay particular attention to the patients' capacity for work and pleasure, their inner feelings, their judgment, and their acceptability to others.

IN THE HOME

Patients in their own homes are often found to be dirty and untidy in their dress and habits. It is easy to understand how such a thing might have been previously obscured by their being washed and made presentable by their relatives for the day they came to the clinic for their routine follow-up. Often at home they are found to be irritable or overbearing. One woman, previously in the depths of depression and inertia, would rant and rave for no cause at quite inoffensive members of the household. She would dust through the dining-room in the middle of a meal, and might insist on taking up the carpet when others wanted to settle down to listen to the wireless; all of which activities would be carried through in the face of all reasonable objection.

Many patients become obstinate and self-willed, and if not allowed to have their way become explosively aggressive. One, for example, was so euphoric and joyous, but at the same time so overbearing, that her family actually said, "Of course for *her* the operation has been a miracle; but *we* wish we had not got to live with her." One good lady always contrived to monopolise the conversation with irrelevant nonsense whenever visitors appeared in the house; while another would walk boldly in the middle of main roads, expecting all traffic to get out of her way.

Some retire very much into their own shell and either refuse, or do not want, or have not the initiative, to go out at all. One woman, preoperatively very active and adept at all the numerous activities to which a parson's wife must turn her hand, afterwards rarely did more than look at the morning paper. One husband complained that his wife neglected all household duties and was always out on the spree. She might condescend to a little cooking, but would throw the ingredients together with an abandon which had variable and unexpected results.

In others the symptoms may be more distressing or objectionable. One girl developed a postoperative hobby of writing me a regular stream of demanding and sometimes abusive letters, packed with the most descriptive neologisms. And there was, of course, the patient of Partridge whose flippantly amorous behaviour embarrassed even her husband. Though several became excessively conceited or just bluntly tactless, it was exceptional to find one who resorted to persistent lying.

I should state that Partridge has not placed nearly so much weight on some deficits as I have myself, though I think it fair to say that disagreement is largely one of incidence, and could be due to different types of material.

One could give numerous examples, but I will just add that, in general, some patients become unkind or inconsiderate, and occasionally cruel and callous; and some do, indeed, seem to develop a certain spiritual apathy, and a dwarfing of ethical standards. I do not mean that they steal or lie, for there has been an unexpected lack of obvious and overt manifestations of conventionally unacceptable conduct; but there is sometimes a disregard of what I would say are more significant things, such as the right and wrong way of treating a child, the kind and proper way of behaving towards invalids, or tolerance and understanding of the aged.

These conclusions can be expressed by saying that there is a discrepancy between the state of patients as assessed medically by established methods of clinical examination and their state as assessed socially, in the workshop, and at play. In other words, the operation has two effects—one may call them the therapeutic and the traumatic—and hence come the questions as to its ultimate usefulness or ethical justification. (Perhaps I should point out, in passing, that in any one patient the operation only produces one total set of changes.) In properly selected cases it may cure the illness; but in these—and of course in others—it damages important aspects of the person. For surely those aspects are important which determine the patient's social and cultural existence, his ability to work, his pleasures, his acceptability to his fellows, and, for all we know, his spiritual, as well as his emotional experience.

GAINS AND LOSSES

In a recent annotation (*Lancet* 1952) this matter was most accurately and pertinently discussed. After saying that "in many cases the state of the patient is otherwise so miserable and hopeless that few would question the wisdom of operating," the writer continues:

> "When, however, the operation is advised for relatively benign states of psychoneurosis, or for the relief of pain, it becomes necessary to examine very critically the balance between gain and loss. . . .
>
> "The 'cured' patient is likely to be emotionally blunted and may become friendless. The finer human relationships depend on a delicate balance of feeling which cannot survive the tactless remark, the thoughtless act, or the failure to show understanding. When are we therefore ethically justified in advising a procedure which, though it relieves the misery of neurosis or of pain, will also dull the patient's sense of responsibility, conscience, and feeling for others?"

Even so, the operation has already produced a vast mount of relief from chronic mental suffering. In a ertain proportion of disturbed and tense psychotics it s now, in my opinion, often the treatment of choice; nd in these cases I think it is necessary to make a arge incision. This will produce the undesirable comlications of which we are now aware; but in such opeless invalids surely we are justified, if not in ignoring hese complications, at least in regarding them as we lo the addiction to morphine which results in the heavily rugged case of cancer. I have felt that the deplorable reoperative state of many of these patients is often not ully realised by some critics of the operation.

It is in the relatively benign cases that we must veigh carefully the gains against the losses before dvising trauma to a healthy brain. Bearing in mind the operative mortality of 3–5%, the varying and often arge incidence of epilepsy, a number of deaths due to ater physical complications which we still do not fully understand, and the intellectual and personality changes —which may have significance in spheres other than medicine itself—I think we must be cautious in operating on the better type of patient.

The issues raised on the ethics and usefulness of the procedures would seem to lead to two essential questions for any one operation: Is it any good? Is it justifiable? With this in mind there should, while these empirical procedures remain a practical necessity, be two trends: (1) the gradual restriction of the original major incision to very ill patients where the therapeutic gain is obvious; and (2) the trial, and careful and *adequate* appraisal, of small localised ablations performed initially in skilled hands.

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ACTION OF BELLADONNA ON GASTRIC MOTILITY IN MAN

W. FERGUSON ANDERSON
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CONSULTANT PHYSICIAN, FORESTHALL HOSPITAL, GLASGOW; FORMERLY SENIOR ASSISTANT, MEDICAL UNIT, CARDIFF ROYAL INFIRMARY

DESPITE the widespread use of belladonna, the action of this drug on the human stomach has not been adequately investigated.

Textbooks agree that it controls excess motor activity —e.g., hyperperistalsis and pylorospasm—but only slightly decreases the volume of the gastric juice. Douthwaite (1947), working with *l*-hyoscyamine, the alkaloid to which the main effects of belladonna are attributed, concluded that belladonna does not affect the acidity of the stomach, but he observed radiologically much diminution in the gastric contractions. Schick (1910) had previously declared that the chief action of belladonna lay in overcoming pylorospasm. Croxon Deller (1948) stated that belladonna was of great value in relaxing spasm at the pylorus or at the site of peptic ulceration.

Anderson and Morris (1943) have shown that atropine sulphate has a biphasic effect on the pulse-rate and gastric motility. At first it slows the pulse-rate and stimulates the gastric contractions; and later it quickens the pulse-rate and stops stomach movements.

METHOD

This investigation was made on thirty-two people, of whom twenty-nine had no apparent abnormality of the gastro-intestinal tract, two had duodenal ulcers, and one had ulcerative colitis. The experiments were conducted in a quiet room, with the subject fasting and under continuous observation. The pulse-rate was recorded every 5 minutes for 20 minutes before, and for 1–3 hours after, the administration of belladonna. In two cases continuous electrocardiographic tracings were taken. The contractions of the fasting stomach were recorded by a modification of Carlson's balloon method (Anderson 1943).

Tincture of belladonna (*B.P.*) was given by mouth in doses ranging from 5 to 60 minims made up to 2 fluid oz. with water. To compare the effects of belladonna with those of atropine, 1 mg. of atropine sulphate was given orally in the same amount of water and, in another set of experiments, in a teaspoonful of 70% alcohol diluted to 2 fluid oz. with water. This latter method was used to ensure a solution of atropine similar in quality to the tincture used in the tincture of belladonna. As a control for these experiments, the approximate amount of alcohol in 60 minims of the tincture of belladonna—i.e., 60 minims of 70% alcohol—was given in 2 fluid oz. of water on eight occasions to seven people. Pulse-rate and gastric contractions were recorded as described above.

So far as gastric motility is concerned, it must be emphasised that, in both the controls and with belladonna, cold water given orally stops gastric contractions. This was first described by Carlson (1916) and confirmed by Anderson (1943). The inhibitory effect of 4 oz. of water usually lasts 10 minutes, and with 2 oz. of the mixture of alcohol, atropine, or belladonna gastric motility was commonly inhibited for 2–4 minutes. The only exception to this finding was in the presence of a duodenal ulcer; in such cases the usual inhibitory effect does not take place (Anderson 1943, Kay 1947).

In the recordings of gastric motility three phases were seen: active contractions, tonus rhythm, and relative quiescence. The active contractions were sharp spike-like waves lasting 30–40 seconds. Tonus rhythm was composed of regular flat-topped waves, each of which lasted 90 seconds. Relative quiescence was the nearest approach to complete rest found in the fasting stomach; it was characterised by undulating waves of low amplitude lasting about 2½ minutes.

Drugs may have varying effects on gastric motility according to conditions existing at the time of administration. If the stomach is showing active contractions, the drug may stop them, increase their frequency and/or amplitude, or leave them unaltered. The result of a single experiment is worthless because these periods of contractions are self-limiting, and, though normally lasting ½–1 hour, might be ending spontaneously at the time of administration of the drug. Therefore conclusions about the action of a drug depend on the repeated demonstration of a particular pattern of stomach movements.

RESULTS

Controls

With one exception, all the cases showed no alteration in pulse-rate after the administration of alcohol in water. In the one exception the pulse-rate slowed by 7 beats per minute immediately after the dose and returned to its previous level in 10 minutes.

In every case, after the inhibitory effect of the fluid administered had passed off, gastric motility remained unaltered for 23–37 minutes, and the pattern of the

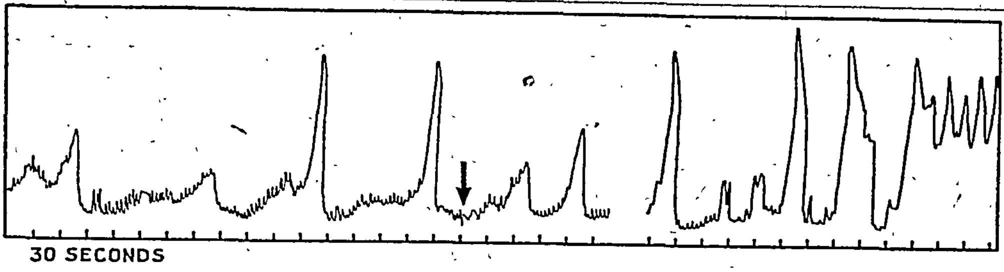

Fig. 1—Gastric motility in case 4 (table I): *arrow*, tincture of belladonna minims 5 given orally during active contractions. Increase in frequency and amplitude came on in 12 minutes and reached tetanic spasm in 20 minutes. The tracing has been condensed by omitting the middle part.

gastric movements never resembled that noted after belladonna or atropine.

Belladonna 5–15 Minims

Tincture of belladonna 5–15 minims was given by mouth on eight occasions to six people. The effects on gastric contractions and on the pulse-rate are shown in table I, and a typical result is illustrated in fig. 1. In every case the administration of belladonna was followed by slowing of the pulse-rate; this took place 5–10 minutes after the belladonna was given, and lasted for up to an hour. No increase in the pulse-rate was noted.

TABLE I—EFFECTS OF BELLADONNA ON PULSE-RATE AND GASTRIC CONTRACTIONS

Preparation	Case no.	Time after administration (min.)			
		5–20		21–120	
		Pulse-rate	Gastric motility	Pulse-rate	Gastric motility
Tincture of belladonna: Minims 5	1	–	+	0	+ +
	2	–	+ + +	–	+ + +
	3	– –	+ +	–	+ +
	4	– –	+ +	– – –	0
Minims 10	5	–	0	–	0
Minims 15	6	– –	+	– –	+
	7	–	+ +	– –	+
	8	– –	0	–	0
Minims 30	9	–	+ +	– – –	+ +
	10	–	+ + +	– –	+ + +
	11	Not recorded	+ + +	Not recorded	– – –
	12	– –	0	– – –	0
	13	–	+	+	– – –
	14	–	0	+ +	0
Minims 45	15	–	+	– – –	+
	16	– –	+ +	+ + +	– –
	17	– – –	– – –	+ + +	– – –
	18	– – –	+ + *	– –	+ +
	19	– –	0	+ + +	– –
	20	–	+ +	+ + +	– – –
	21	– –	+ + +	+ + +	– – –
Minims 60	22	–	+ +	+ + +	– – –
	23	– –	+	+ + +	–
	24	–	+ +	+ + +	– – –
	25	– – –	0	+ + +	0
	26	– –	+ +	+ + +	+ +
Minims 45 after a week's belladonna	27	0	+ +	+ +	–
	28	–	– – –	+	– – –
	29	0	– – –	+ + +	– – –
	30	0	+ +	+ + +	–
Atropine sulphate: 1 mg. in water orally	31	– – –	0	+ + +	+ +
	32	– – –	+ + +	+ + +	+ + +
	33	– –	+ +	+	–
	34	– – –	Recording unsuccessful	+ +	Recording unsuccessful
	35	– –	+	+ + +	–
	36	– –	+	0	0
1 mg. in 1 drachm of 70% alcohol diluted with water	37	– –	+ + *	+ +	– – –
	38	– –	+ +	+ + +	– – –
	39	– –	0	0	–
	40	– –	Recording unsuccessful	0	Recording unsuccessful
	41	– – –	– –	+ + +	– – –
	42	–	+ + +	– – –	+ + +

Symbol	*Pulse-rate*	*Gastric Motility*
+	Increase of 3–5	Increase in amplitude or in frequency
+ +	,, 6–10	,, ,, and frequency
+ + +	,, 11–20	Onset of active gastric contractions
–	Decrease of 3–5	Decrease in amplitude or in frequency
– –	,, 6–10	,, ,, and frequency
– – –	,, 11–20	Onset of relative quiescence

* Increase in frequency and amplitude occurred 33 minutes after administration.

In five out of seven occasions when active gastric contractions were present at the time of administration, contractions were increased in frequency and amplitude after 5 to 12 minutes. Once, when no active contractions were noted before the belladonna, contractions started 6 minutes after it was given. On two occasions the contractions continued unaltered. In no experiment did the belladonna inhibit gastric contractions, and there was always a close time-relation between the slowing of the heart and the increase in frequency and amplitude of gastric contractions.

After belladonna had been given, the greatest increase in gastric motility and the greatest slowing of the pulse-rate took place in 13–35 and 5–45 minutes respectively. People aged less than 40 showed more slowing of the pulse-rate than did those aged more than 40.

Belladonna 30 Minims

Tincture of belladonna 30 minims was given orally on six occasions to five people. In each case there was a preliminary slowing of the pulse-rate in 5–20 minutes, which lasted for at least 1 hour. In two cases, where the pulse-rate was recorded for a longer time, the rate increased by 4–7 beats a minute, and this took place 80 and 90 minutes after the belladonna had been given.

The effects on gastric motility were varied. In two cases, where the belladonna was given during a phase of relative quiescence, active contractions ensued in 6 minutes, and in a further two cases active contractions, already present, increased in frequency and/or amplitude. In the remaining two cases no alteration in the gastric motility was noted. In two of the above subjects, where an increase in gastric motility was first recorded, there was a later phase of relative quiescence, and the initial slowing of the pulse-rate was followed by a quickening when the decrease in gastric motility was noted.

In all the experiments increase in gastric motility and slowing of the pulse-rate were greatest 12–29 and 15–40 minutes respectively after the belladonna. Again the pulse-rate slowed more in the younger people.

Belladonna 45 Minims

Tincture of belladonna 45 minims was given orally to seven people, as shown in table I. In every case there was well-marked initial slowing of the pulse-rate in 5–10 minutes, which lasted 20–85 minutes. In two cases the pulse-rate remained slow for 80 and 85 minutes after the belladonna. In the remaining five cases this initial slowing was followed by a quickening, which took place in 21–40 minutes.

As regards gastric motility, in four cases active contractions already present were augmented in 5–20 minutes, and these times corresponded fairly closely to the onset of the slowing of the pulse-rate. In one case, when the belladonna was given during relative quiescence, active contractions started in 14 minutes. In three of the subjects showing an increase in gastric movements, as a second effect the active contractions abruptly diminished in frequency and amplitude and continued thus until the recording was stopped (fig. 2). This occurred at the same time as the pulse-rate quickened. In the remaining two cases an inhibitory effect was observed in 16 and 27 minutes after the belladonna. After belladonna had been given the maximum slowing of the pulse-rate took place in 10–50 minutes and the gastric contractions were greatest in 12–40 minutes.

TABLE II—TIME-RELATIONS OF CHANGES IN PULSE-RATE AND GASTRIC MOTILITY

Dose	No. of cases	Time of onset after dose (min.)				Time of maximum effect after dose (min.)		Maximum effect on pulse-rate (beats per min.)	
		Pulse-rate		Gastric motility		Pulse-rate	Increased gastric contractions		
		Slowing	Quickening	Increased	Diminished			Slowing	Quickening
Tincture of belladonna									
5–15 minims	8	5–10	..	5–14	..	5–45	13–35	12	..
30 minims	6	5–20	80–90	6–29	15–20	15–40	12–29	21	7
45 minims	7	5–10	20–40	5–20	16–54	10–50	12–40	14	31
60 minims	5	5–15	20–60	7–13	14–40	15–30	8–37	11	30
45 minims after previous administration of belladonna	4	5 (1 case)	20–50	8–26	9–54	15 (1 case)	24–26	4 (1 case)	28
Atropine 1 mg. in water	6	10–20	40–135	8–38	28–29	30–45	16–54	31	22
Atropine 1 mg. in alcohol ..	6	5–30	35–100 (no quickening in 3 cases)	14–33	10–65	20–65	16–54	17	30

Belladonna 60-Minims

The results found when 60 minims of the tincture of belladonna were given by mouth to five people are shown in table I. In every case there was a preliminary slowing of the pulse-rate 5–15 minutes after the belladonna, and this was followed by an increase in the rate 20–60 minutes after the belladonna. In one case no effect on gastric motility was observed, but in the other four there was a preliminary increase in the frequency and amplitude of active contractions 7–13 minutes after the belladonna. In one case, no inhibition was evident, but in the remaining three the gastric contractions stopped 19–40 minutes after the belladonna. A typical result is shown in fig. 3. Further, in these four cases (table I) there was a close time-relation between changes in the pulse-rate and changes in gastric activity.

Repeated Medication

It has been previously shown that a small dose of atropine has a parasympathomimetic action, increasing the frequency and amplitude of the gastric contractions and slowing the pulse-rate; it has also a sensitising effect whereby antiparasympathetic action is obtained from a second small dose (Anderson and Morris 1943). A single dose of 45 minims of the tincture of belladonna was given orally to fasting people after a week's continuous administration of 15 minims three times a day. In these experiments only one of the four persons investigated showed a preliminary slowing of the pulse-rate. It will be recalled that this slowing of the pulse-rate is a constant feature when a single dose of 45 minims is given without previous medication. The action on gastric motility varied, tending to be sedative at the time when the pulse-rate was most rapid. The preliminary phase of increased gastric motility was smaller than usual, and in every instance the pulse-rate was quickened as a second effect.

Atropine Sulphate

Atropine sulphate 1 mg. was given orally to compare the action of belladonna with that of atropine. The atropine was given dissolved in 2 fluid oz. of water and, to a separate group of people, in a teaspoonful of 70% alcohol. In this latter series water was added to 2 fluid oz. to compare the atropine more accurately with the tincture of belladonna. The amount of alcohol present was about equivalent to that in 60 minims of the tincture of belladonna.

When 1 mg. of atropine sulphate in 2 fluid oz. of water was given orally, all six people showed a preliminary slowing of the pulse-rate in 10–20 minutes. In five of the six the pulse-rate increased in 40–135 minutes after the administration of atropine. In one case the recording of gastric motility was unsuccessful, and in the other five the motility increased 8–38 minutes after atropine sulphate. In one of these cases, two phases of slowing of the pulse-rate were found, together with a corresponding alteration in the gastric motility. Initially, 12 minutes after atropine was given, the gastric contractions increased in frequency and amplitude and the pulse-rate slowed. The gastric contractions ceased, and at the end of this sedative phase the pulse-rate increased. Then, 44 minutes after administration of the atropine, the contractions began again, and in 58 minutes the pulse-rate slowed again. The contractions finally ceased 78 minutes after the atropine had been given, and at the same time the pulse-rate quickened. In a further case, after the initial increase in gastric motility, the contractions became less frequent 28 minutes after the atropine (table I).

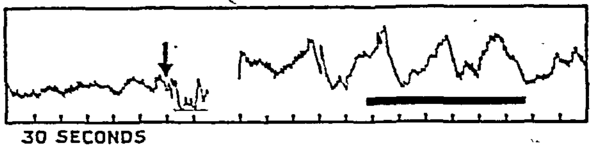

Fig. 3—Gastric motility in case 22 (table I): arrow, tincture of belladonna minims 60 given orally during active contractions. Increase in frequency and amplitude of contractions came on in 7 minutes and lasted 21 minutes. Black line shows time during which pulse-rate was slowed. The tracing has been condensed by omitting the middle part.

When 1 mg. of atropine sulphate dissolved in 1 fluid drachm of 70% alcohol, and diluted to 2 fluid oz. with water, was given to six people an initial slowing of the pulse-rate occurred in 5–30 minutes in every instance. In three of the six cases an increase occurred in 35–100 minutes, whereas in the remaining three people no such increase was recorded. In three of the five successful gastric recordings gastric motility increased in 14–33 minutes. This was followed in two cases by diminished gastric

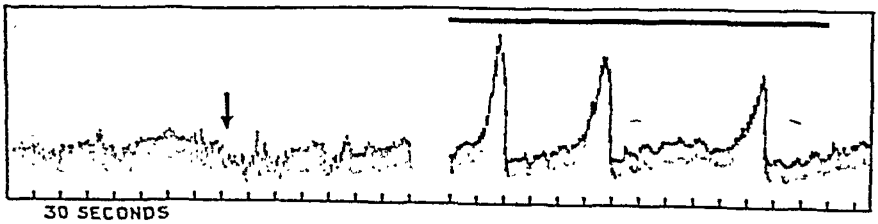

Fig. 2—Gastric motility in case 16 (table I): arrow, tincture of belladonna minims 45 given orally during very weak active contractions. In 5 minutes stronger contractions came on and remained of high amplitude for 25 minutes and then abruptly ceased. Black line shows time during which pulse-rate was slowed. This abbreviated tracing shows the last three contractions only.

activity in 50–57 minutes after the atropine. In one case no initial change in the motility was produced, but in 65 minutes contractions became less frequent, and in another case the frequency and amplitude of contractions decreased in 10 minutes and relative quiescence was achieved in 54 minutes.

Electrocardiography confirmed the changes in heart-rate following the administration of belladonna and atropine noted above. Electrocardiograms showed only findings associated with bradycardia and tachycardia.

DISCUSSION

Slowing of the pulse-rate and increased gastric motility quickly follow the oral administration of belladonna. Table II shows the times of the various actions, and it will be noted that, apart from a slightly slower onset of effect, atropine given orally seems to have the same action as belladonna. In the past belladonna has often been prescribed for its slower absorption, but no evidence in support of this contention has been obtained. With both atropine and belladonna the slowing and increase of pulse-rate occur at about the same times as the stimulation and cessation of gastric motility respectively.

Steinmann et al. (1948), investigating the effect of 'Bellafolin' (an alkaloid preparation of folia belladonnæ) on the circulation of healthy persons, found that the effect varied with the dose: a small dose slowed the pulse-rate, whereas larger doses increased it, usually with a preliminary phase of slowing. Goodman and Gilman (1941) describe the biphasic action of atropine on the pulse-rate; the temporary slowing with small doses they ascribed to the slight stimulant action of atropine on the medullary vagal centre. This slowing, they state, is rarely well marked or significant. Anderson and Morris (1943) have shown that parenteral atropine has a parasympathomimetic action, increasing the frequency and amplitude of active gastric contractions and slowing the pulse-rate. These doses have also a sensitising effect whereby an antiparasympathetic action is obtained from a second small dose. In large doses atropine inhibits the movements of the stomach and quickens the pulse-rate. With small doses of belladonna this slowing of the pulse-rate is the usual result and is accompanied by an increase in the frequency and amplitude of active gastric contractions. It is tempting to postulate that both these effects are due to central stimulation of the vagus. These effects are well marked, and it is therefore difficult to believe that they are of no clinical significance. Previous administration of belladonna has been shown to interfere with this central effect, the slowing of the pulse-rate being usually absent, and the initial increase in gastric motility being almost abolished.

From the present experiments it seems reasonable to use the pulse-rate as a guide to the action of belladonna on the stomach movements.

Belladonna must be given in a dose of at least 45 minims of the tincture if inhibition of the gastric contractions is desired from a single dose. Even with this dose this effect is by no means constant, and it may take as long as 40 minutes to appear. When repeated doses of belladonna are given they should be as large as the patient will tolerate, because only then will gastric motility be decreased. These repeated doses are much more likely than a single large dose to have an inhibitory effect.

It seems possible that the stimulating action of small doses of belladonna has some clinical use. The benefit obtained with belladonna in pyloric stenosis of infants and adults has never been explained. It is usual for substances which increase the motility of the stomach to relax the pyloric sphincter; and it may be that this stimulating effect on gastric movements initiates this usual pattern of motility—i.e., active peristalsis is associated with relaxation of the pyloric sphincter.

SUMMARY

Tincture of belladonna in small doses given by mouth has a parasympathomimetic action, slowing the pulse-rate and increasing the frequency and amplitude of active gastric contractions.

With larger doses, after a preliminary phase of slowing of the pulse-rate there is an increase in the rate. This biphasic effect can sometimes be demonstrated on the fasting contractions of the stomach, a short phase of increased movements being followed by the cessation of gastric contractions.

After preliminary medication with belladonna a large single dose does not produce the usual slowing of the pulse-rate, and the initial increase in gastric motility is less.

Electrocardiography after belladonna confirms these findings and gives tracings indistinguishable from those seen in simple tachycardia and bradycardia.

Given by mouth, atropine sulphate has the same action as when injected parenterally—i.e., it causes a slowing of pulse-rate followed by an increase, and an initial stimulation of gastric movements succeeded by diminution. These effects are produced rather more slowly than those produced by belladonna. It was thought that this action might be due to the alcohol content of the tincture of belladonna. Atropine was therefore given in an alcoholic solution about equivalent to the tincture, but no change in the speed of action of the atropine was observed.

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ON THE TREATMENT OF ANOGENITAL PRURITUS

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So much has been written recently on the psychogenic origin of pruritus ani and pruritus vulvæ that dermatologists and gynæcologists alike are not only becoming convinced that these difficult cases are the result of some past emotional disturbance but are also only too thankful to argue that, if there is a psychological cause, it must be dealt with before irritation can cease (e.g., Cormia 1951). Thus psychiatrists are reaping an embarrassing reward for the researches of their fellows, in spite of the fact that it has never been claimed that psychiatric treatment can necessarily cure all, or even a large proportion, of those who suffer from disorders which may have originated from mental trauma. Perhaps because anogenital pruritus is such a difficult and unrewarding condition to treat, or perhaps because most dermatologists and gynæcologists fight shy of becoming too deeply involved with the souls as well as with the bodies of their patients, our approach to the subject has become confused and an attempt should be made to understand it more clearly.

CAUSE AND EFFECT

A girl has a brutal and drunken father and is overfond of her mother. To escape from home she marries young, but sees much in her husband that reminds her of her father. She derives little satisfaction from sexual intercourse, becomes frigid, and, as time goes on, spends more and more time at home with her mother. Her mother dies, and by this time her husband is quite understandably losing interest in her. She becomes lonely and has no-one to comfort her. She begins to itch.

This facile and entirely fictitious history might easily be extracted from a woman of 30 with severe pruritus vulvæ which has been present for ten years. Here is our cause—the failure to establish a satisfactory marital relationship because of an unsatisfactory home life in childhood. Our logic, our very philosophy, makes us work backwards from the present state to its beginning ten years before, and there we find what we believe to be its origin. Yet this origin itself is a compound of cause and effect—the early environment and the reaction to marriage. Can we be sure that cause and origin are the same? Does the origination of a process, or its cause for that matter, determine its duration? If not, what does? Perhaps our hypothetical girl has a sister who also married, in which case we wonder if the sister's marriage was a success as our patient's was not; perhaps the sister's marriage also proved a failure, but we doubt if she too developed pruritus vulvæ. Our cause is becoming a little less definite, but our effect remains; our patient still sits before us complaining bitterly that the irritation is intolerable, that it is keeping her awake at night, that she "can't leave herself alone."

Let us suppose, however, that our patient's symptoms did originate as a direct result of her unhappy circumstances. All this was ten years ago. What is the relationship between cause and effect over this period? What has happened during the ten years? Why is she still itching? Mankind has proved itself the most adaptable of creatures, and it seems most unlikely that during the years there has been no change of circumstances, no rearrangement of personality, no compensation found other than itching. Can the origin also be the continuing cause, or has something else kept the irritation going? It is surely more reasonable to suggest that, whatever may have initiated the trouble, some more simple mechanism, common to other cases and to skin in other areas, has perpetuated it.

Let us turn now to some more material cases:

> A woman, an older woman, has pruritus vulvæ and is found to be a diabetic. Her diabetes is treated, and she passes no more sugar in her urine, but her irritation unexpectedly persists.
>
> A man has pruritus ani. He is found to have threadworms, and these are eradicated, but his irritation does not cease as was hoped.

There is one thing in common in these cases—a fairly long history, six months or more in each of them. It seems that, after a time, anogenital pruritus may become self-perpetuating, whether its original cause is still present or not; and so it becomes of equal importance to seek out and attack the continuing cause as well as the origin of the complaint.

PRESENT CONDITION

I have tried to show the relative unimportance of the origin of the irritation in these patients and to focus attention on them as they are when they present themselves for treatment after months or years of symptoms. Let us now examine our patient. The first complaint is itching, severe and continuous, and almost always worse at night. This leads directly to scratching by the patient, at first just in spasms and fairly well controlled, but later more and more uninhibited and unrestrained, especially in bed at night, until in the final and most common stage this scratching becomes a habit, an unconscious "spinal reflex," which continues during sleep until it becomes violent enough for the patient to wake himself up, though he seldom admits or even realises this, but says it is the irritation which wakes him. By this time the patient's sleep has usually become so interfered with that his life is becoming a misery, what self-control he had is lost, his work is suffering, and, as he often puts it, "his nerves are going to pieces." It is my impression, though it is hard to be certain, that it is only at this stage that he can be induced to go to the doctor, as by then he is at the end of his tether, and this may partly explain the usual long history.

Other factors must be considered before deciding on a rational form of treatment for anogenital pruritus, and most important among these is the attitude of the patient to his affliction. First there is often a strong sense of shame, of inadequacy, and a reluctance to expose themselves for examination, which may also help to explain the long period before advice is sought. Then there is very often the fear of infection (or malignancy) which often gets woven into a most complex but entirely fictitious history naming the time and place of the contagion. These sensations of fear and shame further add to the patient's discomfiture and, I am quite sure, often play just as important a part in the present psychological state as the now intangible happenings of long ago. The patient has in fact developed a neurosis as the result of his physical state, and here the words of Sargant (1951) are well worth quoting:

> "The presence of obvious functional components does not necessarily mean that they are the cause of the illness. One reason for attributing too many physical illnesses to psychological disorders may be that some people, when they get physical disorders, also become neurotic about them, whereas others do not. Those who become neurotic about their disability are the group most often seen by psychiatrists. The finding of neurotic traits may lead to the false conclusion that these are causal, whereas it may only indicate that those with tendencies to neurosis are the most likely persons to become neurotic about added physical disabilities."

PAST TREATMENT

The last factor I wish to consider is the failure of past treatment to relieve the irritation. If a doctor has been consulted, it is always demoralising for the patient if his treatment has failed. Also these people have usually tried out many applications themselves, often with disastrous results, though they may not realise it. For instance, a lady told me proudly that the best treatment she had found for her pruritus vulvæ was to paint herself with pure lysol. This, she assured me, entirely removed the irritating skin and so, though painful, cured her itching for the time being. And yet, what other rationale is there for vulvectomy in these cases? There is no doubt that, just as deeply as cause and effect are linked in our philosophy so are crime and punishment, and a shameful disease demands exorcism in many minds. This is very often seen in skin patients, who are not the least upset if some ointment violently irritates their lesions but, on the contrary, are delighted that "it is driving it out," as is shown by the profuse serous exudate so caused. Thus some patients with pruritus vulvæ or pruritus ani will take tremendous punishment under the impression that this is doing them good, and sometimes in telling their story it is quite clear that they are referring as much to their souls as to their bodies, and often confusing the one with the other. So to the trauma of scratching is not infrequently added the trauma of unsuitable medication, leading to further irritation and further scratching.

TREATMENT

We have discussed some remote causes, psychological and physical, and the continuing causes—namely, scratching, unsuitable medicaments, and the psychological results of long-continued and disabling irritation—and we should now be able to compose a logical scheme of treatment for these cases. The one factor of paramount importance is continual scratching, and this must be impressed on the patient first, last, and all the time. He or she must be told that the whole and only object of any treatment is simply to help to break the scratching habit—it is for the patient to do the rest. If there is no more scratching, the skin will *get better by itself*, as it surely will. From this homily on scratching it naturally follows that there is *no infection present to be feared*, and if there is anything to be ashamed of it is nothing more serious than being so foolish as to have gone on scratching for so long. Most patients will accept this explanation quite readily and often with obvious relief, but will reply with sudden and surprising candour that the trouble is that they cannot help scratching. They must then be told quite explicitly how it is proposed to help them. In the first place they must sleep well. They are unlikely to scratch very much in a deep sleep, and after a week or two of sleeping well their morale will be restored and their general health improved, and they will be much less troubled by any irritation they may still experience. The actual hypnotic chosen is not of great importance provided it achieves its object. It is my practice to use 'Sodium amytal' gr. 3 or gr. 6, and I believe that this type of barbiturate is preferable to phenobarbitone, which leaves the patient with more of a "hangover" next day.

Though ample sedation at night is probably the most important consideration in managing these cases, local applications are of considerable help, and some form of tar preparation is still the most useful. The following paste, though messy, is a powerful antipruritic and forms part of my routine treatment:

Crude coal tar	5%
Zinc oxide	5%
Starch	45%
Soft paraffin	45%

This is a greenish-black paste and is applied at night. Since it will otherwise make a mess of the bed-clothes, it is easy to induce patients to wear a thin pair of pants under their night clothes which makes scratching more difficult, and it is easy for them to tell by their blackened fingers in the morning if they had lapsed during the night and been scratching in spite of everything.

In the morning they are instructed to clean themselves thoroughly with cetrimide 1% and, in the cases of pruritus ani, to do so after they have had their bowels opened. This latter instruction ensures a good standard of hygiene and encourages attention to the bowels in those liable to be constipated, and who consequently suffer added discomfort from the passage of hard stools. Then again the knowledge that they are using a good "skin antiseptic" helps to dispel any lingering doubts about infection in the less believing patients, and makes it unnecessary for them to fall back on the secretive use of more irritating applications.

During the day, when the irritation is less and there is less opportunity or incentive for scratching, some bland and clean cream is applied. Ung. aquosum *B.P.* and 'Anthisan' cream are equally effective.

Finally, to guard against the lapses liable to occur early in treatment, the patient must be instructed to keep the finger-nails cut as short as possible.

Many applications containing local anæsthetics have been recommended in the past, and perhaps anthisan is useful because it has a mild local anæsthetic action. Preparations containing benzocaine are dangerous if used for any length of time, because some people become sensitised to this with disastrous results. As a sole approach to treatment *local anæsthetic ointments* are remarkably unsuccessful.

By far the greater number of cases of anogenital pruritus have very little to show in the way of visible changes, and it is probably this as much as anything that encourages the psychological approach so much favoured today. In many cases the skin looks normal, and in many more there is only a little lichenification of the perianal or vulval skin. If the scrotum is affected there is usually a definite thickened plaque, and such cases are usually more resistant to treatment but are fortunately less common. In any of the above, excoriation from scratching may be seen and occasionally some local œdema, especially of the labia majora. All may be treated with the routine tar paste. A few patients, especially those who are fat, have intertriginous lesions in the groins, and then it is advisable to begin with something more bland—e.g., calamine liniment—to settle the intertrigo before going on to the full routine, and it is often a help to put such patients to bed in hospital for a few days. Their general handling, however, is the same.

There is one type of patient, fortunately rare, in which the treatment outlined above is liable to fail, and that is the one who manifestly enjoys scratching and obtains an erotic satisfaction from it that is barely if at all concealed. This is commoner in the male with pruritus ani. There is a small group, usually in their twenties, who approach one with none of the diffidence to be anticipated in those suffering from such a complaint, and who have the disconcerting habit of dropping their trousers more quickly than expected and of thrusting their posteriors up at one. Their hygiene is usually not of the highest. The anal sphincter often seems to be deeply depressed at the bottom of a "funnel" between the buttocks. The skin around is invariably normal. They seldom complain much of irritation, except inasmuch as they find it embarrassing socially to be seen scratching themselves. Diagnosis is important from the doctor's point of view to save him wasting his time by attempting to treat such cases, and possibly to help him to understand why some of the more barbarous treatments of the past were ever devised.

RADIOTHERAPY

Radiotherapy is a most useful weapon in countering anogenital pruritus, but *it should not be used alone*; nor in my opinion should it be used when the patient is first seen. The mode of action of X rays in countering skin irritation is not understood, but there is no doubt that, in small amounts, they do depress or abolish itching *for a short time*. We are considering the treatment of a chronic condition, perpetuated by constant rubbing and scratching, and it is worse than foolish to offer a temporary alleviation of symptoms without making use of this period to help break the scratching habit, or without giving the patient something *to use* to help stop *scratching* when the irritation returns, as it invariably does a few weeks after the last treatment.

X rays must only be given as a part of the general management of the case, and for this reason, if for no other, the dosage and timing must be under complete control of the dermatologist. They are *only* needed in cases in which the treatment outlined above has failed to enable the patient to stop scratching, and once again it must be clearly explained to the patient that X-ray treatment will not cure the irritation, but it will give a period of relief which must be taken advantage of, as only a certain amount of X rays can be given without danger. He or she must be warned at the onset that after a few weeks there will be some return of the irritation, and that this will be the testing-time. *If scratching* starts again, the irritation will persist and get worse again, but if not it will rapidly fade away. With the patient understanding the object and limitations of the treatment, *X rays will often* prove the decisive factor in coping with these cases. A course of 3 or 4 exposures once a week of 75 or 100 r is adequate, and there is little or no advantage to be gained from larger doses.

TREATMENT OF COEXISTING CONDITIONS

Hæmorrhoids.—If we consider what common conditions pruritus ani and piles are, it is almost surprising that they are not found together more often. Patients with anal irritation often speak of their "piles" as a convenient excuse for their itching, and when they are examined there are none to be seen. If hæmorrhoids are present they should be treated on their merits, but not for the sake of any accompanying pruritus.

Fissures and Skin Tags.—Skin tags are of no significance and should not be allowed to become an excuse for surgical interference. Fissures are usually the result of previous lichenification. The thickened and hardened skin often cracks, especially immediately behind the anus, and these cracks are often painful. There is unfortunately little that can be done for these beyond attention to the condition as a whole. Excision and cautery are not recommended.

Vaginal Discharge.—Anything the gynæcologist can do to lessen or abolish vaginal discharge is of great help, because constant moisture of the over-sensitive skin of the labia tends to increase and perpetuate the irritation. Until the discharge can be controlled, such patients are better with a paste during the day as well as at night, because this gives some "waterproofing" to the affected areas. Ordinary Lassar's paste is as good as anything.

Leukoplakia Vulvæ.—I do not intend to discuss the treatment or diagnosis of this condition. Areas of leukoplakia are, however, found in some cases of pruritus vulvæ and must be recognised because of their liability to malignant change. The pain and irritation of these patients can usually be lessened considerably and sometimes abolished: but the routine of treatment described above should always be given, though X rays are better withheld. It seems reasonable to suggest that the less the leukoplakia areas are subjected to the mechanical trauma of scratching, the less is the likelihood of malignancy.

Lichen Sclerosus et Atrophicus of Vulva and Anus.—It is curious that this condition, which is usually without symptoms when it occurs elsewhere on the body, should cause irritation when it involves the anogenital area. There is unfortunately no known successful treatment for it, but once again elimination of scratching is of great help.

Psoriasis and Lichen Planus.—These two diseases may be responsible for irritating lesions in the groins and perineum. Lichen planus may produce white patches on the mucosal surfaces of the labia which may be mistaken for leucoplakia. Flexural psoriasis may closely resemble intertrigo. Treatment in both conditions must be largely symptomatic, and the principles mentioned above will be found useful, but the prognosis for recovery is that of the appropriate disease.

Diabetes and *threadworms* must be treated if present.

PSYCHIATRY

I do not propose to discuss the merits of psychiatry or the psychiatric methods to be adopted, for I am unqualified to do so. I merely wish to set psychiatry in its proper perspective and to point out that alone, and in detachment from other forms of treatment, it is as unlikely to succeed as is radiotherapy alone.

The state of mind of patients with severe and long-standing anogenital pruritus has already been discussed, as has the importance of restoring sleep, removing fears of infection, and explaining the nature of the complaint, so as to give them some insight and enable them to help themselves and be helped. It often happens that these patients tell of periods of stress at the time of onset of their pruritus or during its course, and they often wonder themselves if this stress played any part in the initiation or perpetuation of their itching. The following case serves as a good illustration:

An unmarried nurse, aged 55, complained of very severe irritation of her groins and vulval and anal regions, which had been going on for four years and getting worse all the time. For the last six years she had been nursing her sister, who was apparently mad and extremely difficult to live with. At last, six months ago, she had agreed to lay down her burden and allow the sister to be certified insane, a course she had strenuously opposed previously, insisting on assuming full responsibility for her. Soon after her sister departed to an institution the patient's pruritus became worse than ever. She was convinced she had "caught a germ" and, though at last free to do so, she feared to resume her nursing career in case she "passed it on to someone."

On examination she showed the severest lichenification of the groins, vulva, and anal cleft that I have ever seen. This patient had evidently had a very grim time looking after her sister, and I have very little doubt that she went through a period of acute misery before and after deciding to allow her to be removed to a mental hospital. It is quite possible that the feelings of guilt at quitting the job she had tackled for so long coincided with the acute exacerbation of her symptoms after the sister's departure. However, the above-mentioned routine of treatment, together with three weekly X-ray treatments of 100 r led to her losing all her irritation in from six weeks to two months, and she has had no relapse in the year that has followed.

Such patients are relatively common, but the coexistence of worry and pruritus does not necessarily imply cause and effect. The two interact on each other, but abolishing the worry will no more cure the pruritus than abolishing the pruritus will cure the worry, though it often helps considerably. It is not the worry, "the nerves," that produce the lichenification but the finger-nails.

In such patients psychiatry is seldom either necessary or desirable. The patient should be able to control his scratching himself, if helped as I have described, and it is a mistake to infer that he needs extra help; in fact it is tantamount to saying that the condition is beyond his control and so offering a cloak to hide his weakness.

The indication for psychotherapy is now plain—it is simply the utter incapacity of the patient to stop scratching.

CASES AND RESULTS

About 50 patients have now been treated along these lines in the last eighteen months with remarkably few failures or recurrences so far as is known, but only 32 have been followed up personally for six months or more, and only these will be briefly discussed. These patients are entirely unselected except inasmuch as they were all seen in the outpatient department of a general hospital at the request of their general practitioners, whose treatment had not succeeded in relieving their irritation. No case of any specific condition—e.g., psoriasis and lichen sclerosus—is included, but several patients had some complicating intertrigo. 14 were males, and 5 in addition to pruritus ani had irritation extending forwards in the perineum to the base of the scrotum; 18 were females, of whom 16 had pruritus vulvæ, and 8 of these had anal irritation also.

Of these patients 20 (10 male and 10 female) were aged 40–60 when first seen, 5 were aged less than 40, and 7 more than 60. The average duration of symptoms for the males was 3·3 years and for the females 4·8 years, but these figures do not mean very much, because the histories varied from 4 months to 20 years. 2 of the female cases had begun as diabetic vulvitis six months and a year before, and in each case the diabetes had been well controlled for several months and there was no apparent abnormality of the irritating skin. One man was reputed to have had threadworms eighteen months before and had been treated; no threadworms were found when he came to hospital.

All of these cases were improved with treatment, and 28 of the patients lost all their irritation in two months or less. In these 28 radiotherapy was used three times only. There has been no recurrence in any of these cases over a period of at least six months. 3 of the remaining patients have improved greatly but have occasional bouts of irritation and for this reason keep attending hospital, mainly for encouragement. All have been put back on the full routine of treatment from time to time and have settled down again. 2 have had a course of X-ray therapy. The remaining patient has only improved slightly:

She is now aged 36, and her pruritus vulvæ began when she was 16. It got much worse immediately after her marriage at the age of 25. Three years later, because there was a little vaginal discharge, a hysterectomy was done at another hospital, apparently in the hope that this might help her irritation. She had no children. As might be expected, she then became much worse and has been having treatment unsuccessfully ever since. There was gross œdema of the left labium majus, presumably due to lymphœdema following the repeated infection of fissures in the lichenified skin. There were numerous boils in the vicinity. She was admitted and put on the usual routine. The boils cleared up quickly simply with repeated cleaning with cetrimide, and there was fairly rapid improvement at first, but she could not stop scratching, especially at night. Increasing doses of sodium amytal up to gr. 12 were given at night, but she was repeatedly seen by the night staff scratching in her sleep. Unfiltered X rays 300 r were given in divided doses without helping her in the least. After discharge from hospital her improvement was maintained for a while, but she could not control her scratching, on her own admission, and she was referred to Dr. J. Gilroy for psychotherapy. Dr. Gilroy confirmed the existence of a sexual neurosis but does not hold out very much hope of success, because of the chronicity of the psychiatric as well as the physical condition. This treatment has not yet begun.

This case has been described in some detail because I had the opportunity of observing her closely, and though she has proved the only failure so far she has confirmed the concept that scratching is the continuing cause.

COMMENTS

The results obtained with this routine of treatment have been most encouraging, and so far there have been few relapses, because the patients understand, to their own satisfaction, the nature of their trouble, and know what to do about it if there is any mild return of their irritation. It will be appreciated that I am considering pruritus ani and pruritus vulvæ simply as instances of lichen simplex chronicus occurring in special areas, and it is probably only because the type of sensation arising from the anogenital area differs in quality from that of the rest of the skin that irritation there is more distressing than that from patches of lichen simplex elsewhere on the body. It therefore seems unnecessary to endow irritation from this part of the body-surface with a greater significance of psychiatric disturbance than when it occurs elsewhere. We are all familiar with the picture of the old sow solemnly scratching her back against a post and obviously deriving considerable pleasure from doing so. She would not dream of complaining to her doctor about her beloved itch, but might do so vehemently to the farmer if he removed the post. It is also a common sight on the part of Dartmoor where I live to see wild ponies scratching their nethermost regions. The most favoured method is to use the wire guy ropes supporting telegraph poles. The tail is looped over the wire and the hind quarters are pressed against it and the animal will rub away, often for a long time. Such an animal may become separated temporarily from its herd, and I have even heard it said that "scratchers" may lose condition because they do not take off sufficient time to feed. I feel, however, that it would hardly be acceptable to postulate that the lonely pony, pining for its strayed companions, sought consolation in scratching its backside. We are now back where we started—which is the cause and which the effect? Perhaps we do not know, but the pony, and the patient, are still scratching.

SUMMARY

The origins of anogenital pruritus are discussed and the reasons for its persistence. Scratching is the continuing cause.

The state of the patient, both mental and physical, is described, and from this is deduced a rational form of treatment.

The relative usefulness of X rays and psychiatry is discussed, together with the indications for using them.

Anogenital pruritus is usually only a variant of lichen simplex. It is perpetuated by scratching and not by whatever initiated the scratching. The precipitating cause has usually long since ceased to operate.

I wish to thank Dr. H. J. Wallace for his encouragement and kindly criticism in the preparation of this paper.

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INCIDENCE OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI IN A HOSPITAL

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In previous papers (Rountree and Thomson 1949, Rountree et al. 1951) we reported the incidence of penicillin-resistant strains of *Staphylococcus pyogenes* in a general hospital, and the subsequent emergence of strains also resistant to streptomycin. Here we record the incidence of such strains during the thirteen months from Jan. 1, 1951, to Feb. 1, 1952. In addition we record the incidence of strains resistant to aureomycin, terramycin, and chloramphenicol, since these antibiotics became freely available during this period. Observations on the nasal carrier-rate in the staff are also included, and their significance is discussed.

The laboratory methods used are similar to those previously described, with the addition that tests for sensitivity to aureomycin, terramycin, and chloramphenicol were made with filter-paper discs impregnated with solutions of these substances 5 mg. per ml.

The monthly incidence of antibiotic-resistant strains isolated from 915 inpatients between Jan. 1, 1951, and Feb. 1, 1952, is shown in table 1 together with the figures for 157 outpatients' strains isolated in the same period.

RESISTANCE TO PENICILLIN

Of the inpatients' strains 592 (64·7%) were penicillin-resistant. In comparison with the figure obtained during the period April, 1949, to March, 1950, which was 53·4% of 603 strains, there was an increase of 11·3%. This is statistically significant ($\chi^2=8{\cdot}15$, $P<0{\cdot}01$). The frequency distribution of phage-types among these strains is discussed below in connection with the carrier state of the staff. There was also an increase in the incidence of resistant strains from outpatients, the incidence rising from 24·6 to 36·3%.

RESISTANCE TO STREPTOMYCIN

All the strains resistant to streptomycin were also resistant to penicillin. The monthly incidence of these strains in the inpatients fluctuated from 18·3 to 33·8%, with a mean value of 27·6%. This is about the

TABLE I—INCIDENCE OF ANTIBIOTIC-RESISTANT STRAINS OF *Staph. pyogenes* ISOLATED FROM OUTPATIENTS AND INPATIENTS BETWEEN JAN. 1, 1951, AND FEB. 1, 1952

	No. of patients	No. yielding strains resistant to			
		Penicillin	Streptomycin	Aureomycin and terramycin	Chloramphenicol
Outpatients	157	57 (*36·3%*)	17 (*10·8%*)	2 (*1·3%*)	—
Inpatients					
Jan., 1951	63	40 (*63·5%*)	22 (*34·9%*)	..	..
Feb. ,,	68	48 (*70·6%*)	19 (*28·0%*)	..	..
March ,,	70	41 (*58·5%*)	23 (*32·8%*)	..	..
April ,,	83	49 (*59·0%*)	16 (*19·3%*)	1	..
May ,,	77	45 (*58·4%*)	25 (*32·4%*)	2	..
June ,,	57	34 (*59·7%*)	13 (*22·8%*)	2	..
July ,,	51	37 (*72·5%*)	13 (*25·5%*)	1	1
Aug. ,,	86	59 (*68·6%*)	18 (*20·9%*)	8 (*9·3%*)	1
Sept. ,,	82	48 (*58·5%*)	15 (*18·3%*)	9 (*11·0%*)	1
Oct. ,,	66	44 (*66·6%*)	22 (*33·3%*)	11 (*16·6%*)	2
Nov. ,,	78	57 (*73·1%*)	22 (*28·2%*)	14 (*18·0%*)	1
Dec. ,,	62	42 (*67·7%*)	21 (*33·8%*)	12 (*19·0%*)	1
Jan., 1952	72	48 (*66·6%*)	24 (*33·3%*)	12 (*16·6%*)	4
Total	915	592 (*64·7%*)	253 (*27·6%*)	72 (*7·9%*)	11

same as that found in the period December, 1949, to March, 1950. There is reason to believe that most of these strains were the result of cross-infection in the hospital wards. Of the 157 outpatients' strains 17 (10·8%) were streptomycin-resistant. Most of these were obtained from varicose ulcers treated with local streptomycin.

RESISTANCE TO AUREOMYCIN AND TERRAMYCIN

These two antibiotics are considered together because it has been found that every strain resistant to one of them has also been resistant to the other.

The first resistant strain was isolated in April, 1951. Thereafter there were 2, 2, and 1 strains isolated in May, June, and July respectively. In August 8 strains were isolated, and in December 12 of 62 strains (19%) were resistant.

There are two points of interest about these strains—their sensitivity to other antibiotics, and their origin.

Sensitivity to Other Antibiotics

The sensitivity records show that 86 cultures were examined from the 72 patients yielding these strains with the following results:

	No.
Resistant to penicillin	84 (*97·7%*)
Resistant to penicillin and streptomycin	57 (*66·3%*)
Resistant to penicillin, streptomycin, and chloramphenicol	11 (*12·8%*)
Sensitive to penicillin, streptomycin, and chloramphenicol	2 (*2·3%*)

With the 2 exceptions, which were cultures from a patient treated with aureomycin for a staphylococcal skin infection, all the strains were resistant to penicillin, 57 (66·3%) were resistant to both streptomycin and penicillin, and 11 (12·8%) were resistant to all five antibiotics.

Origin

To ascertain whether the resistant strains had arisen as a result of conversion during therapy or were due to cross-infection, the case-records of 61 of the 72 patients were examined. The sources of the strains were as follows:

Infected surgical wounds	21
Infected burns	2
Infected ulcers	7
Urine	17
Sputum	8
Miscellaneous skin infections	6

Seven strains were isolated from urine showing no cellular evidence of infection and were considered to have been contaminants introduced in the ward after the specimens had been voided. All came from one ward, in which there had been considerable cross-infection. Of the remaining 54 cases none could be regarded as having been infected outside the hospital:

In 6 cases there was clear-cut evidence of conversion to resistance during therapy; 4 of these patients had received aureomycin and 2 terramycin. In all 6 the strain was identical in phage-type with that previously isolated as a sensitive strain. 4 strains came from infected surgical wounds, 1 from a case of osteomyelitis, and 1 from a chronic ulceration of the leg. 3 of these strains were isolated in April, May, and June.

There were 33 patients who had received no aureomycin or terramycin therapy, and these may be regarded as certainly cross-infected in hospital.

In the remaining 15 patients the data available were insufficient for us to make a definite decision on the origin of their strains. They had received aureomycin or terramycin therapy before the strains were isolated, but no sensitive strain had been isolated before the resistant one. In 10 of them the case-histories suggested that the strains were due to cross-infections.

In the early stages of the investigation phage-typing was only partially useful in identifying the strains, since many of them were apparently insensitive to the typing phages. Those in which conversion to antibiotic resistance had occurred were, however, identifiable, 3 belonging to type 47, and 1 each to types 7/47, 47C, and 31B. It was later found that most of the non-typable strains were only partially phage-resistant, and when tested with phages they proved to be type 47. Of 17 cultures all were thus identified as type 47. 30 of the cultures had been discarded without being tested with the undiluted phages, but in view of the later results probably most of these also belonged to type 47.

RESISTANCE TO CHLORAMPHENICOL

Only 11 strains were resistant to chloramphenicol. All were in addition resistant to the other four antibiotics. In 3 there was evidence of conversion to resistance during chloramphenicol therapy. Of the 11 resistant strains, 4 were isolated in January, 1952, and their incidence may be expected to increase in future months.

NASAL CARRIER-RATES OF ANTIBIOTIC-RESISTANT STRAINS IN HOSPITAL STAFF

In a previous paper (Rountree and Thomson 1949) it was shown that many of the hospital staff (nurses and doctors) were nasal carriers of strains similar to those isolated from patients cross-infected in hospital, and that certain penicillin-resistant phage-types were the predominant staphylococci in the hospital environment. It was later found (Rountree and Barbour 1951) that nasal carriage of these hospital strains was established in new nursing trainees within a few weeks of their entering the hospital wards, particularly if they were non-carriers on entry. Whether nasal carriers among the staff constitute a reservoir of infection for the patients or are merely infected from the same source as the patients—e.g., contaminated dressings, bed-clothes, and dust—the distribution in the staff of antibiotic-resistant strains and of the phage-types of these strains should be similar to that in the cross-infected patients.

Accordingly in February, 1952, we swabbed the noses of 200 of the nurses and doctors to find out what proportion were now carrying antibiotic-resistant strains, and what was the distribution of antibiotic resistance and phage-types among such carriers.

109 (54·5%) of the staff were nasal carriers of *Staph. pyogenes*, a carrier-rate similar to that found on other occasions. The following is the distribution of antibiotic resistance among these 109 strains:

	No.
Resistant to penicillin	88 (*80·7%*)
Resistant to penicillin and streptomycin	51 (*46·8%*)
Resistant to penicillin, streptomycin, aureomycin, and terramycin	17 (*15·6%*)
Resistant to penicillin, streptomycin, aureomycin, terramycin, and chloramphenicol	3 (*2·7%*)
Sensitive to penicillin, streptomycin, aureomycin, terramycin, and chloramphenicol	21 (*19·2%*)

Only 21 of the people swabbed were carrying penicillin-sensitive strains, and it is significant that 10 of these 21 were first-year trainee nurses who had been in the hospital for only a short time. The remainder (80·7%) were carrying penicillin-resistant strains. More than half these strains were also streptomycin-resistant. Strains also resistant to aureomycin and terramycin were obtained from 17 persons, and all were of type 47. In addition, 3 nurses were carrying strains resistant to all five antibiotics; these also were of type 47. Comparison of this distribution of resistant strains among the nasal carriers with that found in the patients in January, 1952, shows a reasonably close correspondence between the two sets of figures. The incidence of penicillin-resistant and of penicillin-and-streptomycin-resistant strains is lower in the patients than in the staff (66·6% compared with 80·7%, and 33·3% compared with 46·8% respectively). However, the patients' over-all percentages will include strains present when the patients were admitted to hospital; since the majority of these will be antibiotic-sensitive, the incidence of antibiotic-resistant strains calculated as percentages of the total will be lowered.

The two series of strains may be compared with reference to the phage-types they comprise. This information is set out in table II. In compiling the table, strains have in some cases been grouped into related phage patterns rather than differentiated on small variations in pattern. For example, all strains lysed by one or more of the phages 3A, 3B, 3C, and 51 have been grouped together, and within the groups denoted as 7/47/31B and 29/31/52 there are strains of various patterns. For the purposes of comparison, however, this arrangement is a convenient one.

There is close correspondence between the phage patterns of the strains of the two series, all patterns, with the exception of 6/47, being present in both groups. Correspondence between the frequency distributions, on the other hand, is less close. Since we are comparing a series of strains obtained from patients over a period of thirteen months with that obtained in a survey lasting two weeks at the end of the thirteen-month period, and since we know that these frequency distributions are dynamic rather than static, very close correspondence in actual percentages is not to be expected. There is also one obvious source of error in the figures for the patients' strains; included in the "not-typable" strains are a number of the aureomycin-terramycin-resistant strains isolated early in the investigation, which in the light of later findings may reasonably be considered to have been type 47. When all these factors are taken into consideration, the conclusion that the frequency distribution of strains among the nasal carriers of the staff reflects that found in the patients' lesions is justifiable.

DISCUSSION

Claims have been made that one of the advantages of aureomycin is that resistance to it is rarely developed. We found, however, that, after aureomycin therapy a number of strains resistant to *Staph. pyogenes* appeared in lesions. These strains were of the same phage-type as the sensitive organisms previously present in the lesions, and we conclude that resistant variants were selected as the result of the therapy. Moreover, such strains always became resistant also to terramycin. There were also 2 cases in which resistance to aureomycin and terramycin followed local terramycin therapy. From these observations it follows that if a staphylococcal infection fails to respond to aureomycin therapy it is useless to treat it with terramycin, and vice versa. Herrell et al. (1950) have already reported this linked resistance in strains made resistant in vitro.

TABLE II—PHAGE PATTERNS OF PENICILLIN-RESISTANT STRAINS OF *Staph. pyogenes* ISOLATED FROM PATIENTS' LESIONS AND FROM NOSES OF THE HOSPITAL STAFF

Phage pattern	Patients' strains	Staff strains
3A/3B/3C/51 ..	13 (*2·2%*)	1 (*1·2%*)
6/47	25 (*4·2%*)	..
6/7/47	17 (*2·9%*)	1 (*1·2%*)
7/47/31B	113 (*19·1%*)	14 (*15·9%*)
29/31/52	42 (*7·1%*)	5 (*5·7%*)
31B	92 (*15·6%*)	9 (*10·2%*)
42F	18 (*3·1%*)	4 (*4·5%*)
47	131 (*22·1%*)	35 (*39·7%*)
47C/47D	20 (*3·4%*)	5 (*5·7%*)
Not typable ..	112 (*18·8%*)	13 (*14·7%*)
Other types ..	9 (*1·5%*)	1 (*1·2%*)
Total	592	88

Chloramphenicol resistance following therapy can also occur. Among the 11 cases yielding strains resistant to all five antibiotics, there were 3 with clear-cut evidence of such a change. In 1 of these, the original infecting strain was resistant only to penicillin; but after therapy with aureomycin, streptomycin, and chloramphenicol it became resistant to all five antibiotics.

The emergence of the aureomycin-terramycin-resistant strains followed a course similar to that of the streptomycin-resistant strains in 1949. In the first few months following the introduction of the new antibiotics an occasional strain appeared after therapy with the antibiotic in question and was due to conversion to resistance. After a period of some months there was a sudden increase in the incidence of the resistant strains, and the majority of these were the result of cross-infection. These cross-infections apparently occur when the new strains have become well established in the hospital environment, probably both in the bed-clothes and dust of the wards and in the noses of the nurses and doctors.

An interesting point emerged on re-examining the results of the previous investigation of the first-year nursing trainees (Rountree and Barbour 1951). The first group of these nurses entered the wards in August, 1949, when there was little cross-infection with the penicillin-streptomycin-resistant strains, and only 1 out of 15 penicillin-resistant strains acquired by these nurses was streptomycin-resistant. The next group entered the wards six weeks later when cross-infection with the penicillin-streptomycin-resistant strains was occurring, and among this group all 7 penicillin-resistant strains acquired were also streptomycin-resistant, suggesting that in the six weeks' interim the new strains had become well disseminated in the wards.

The longer the nurse or doctor stays in the hospital, the more likely is he or she to become a nasal carrier of the hospital strains of *Staph. pyogenes*. In the three years that have elapsed since our first survey of nasal carrier-rates in the staff there has been a significant increase in the incidence of penicillin-resistant carriers, which now represent 8 in every 10 carriers compared with 6 in every 10 in the previous survey. Furthermore, half the carriers of penicillin-sensitive strains found in the present series were newcomers to the staff.

That the strains present in the hospital are constantly changing is shown by the differences between the incidences of phage-types and of antibiotic-resistant strains found in the patients and staff in the two surveys. In 1948–49 the majority of the penicillin-resistant strains belonged to one particular type, 31B. In the latter part of 1949, penicillin-streptomycin strains of types 47, 47/31B, and 31B appeared. Although type 31B is still found in both staff and cross-infected patients its incidence is now much lower and strains falling into patterns of 7/47/31B and 47 are now the predominant organisms in both groups of people Furthermore, concomitantly with the increased incidence of aureomycin-terramycin-chloramphenicol-resistant strains of type 47, we find these particular strains also among the staff nasal carriers.

Of the staff swabbed on previous occasions, 25 were included in the 200 examined in the present survey. In only 4 of these is their nasal carrier state the same as it was eighteen months to three years ago. 3 have been non-carriers on all occasions and 1 is still carrying the same strain as that isolated three years ago. The remainder are carrying strains different from those previously isolated.

The question whether the staff or the ward and theatre environment is directly responsible for the infection of patients seems to be unanswerable. Indeed, one is tempted to ask whether it is not redundant. Clearly, both routes of infection are practicable, and it will depend on particular circumstances which one operates. In our series of cases there was evidence of infection of wounds occurring in the theatres, and one nasal carrier of the penicillin-streptomycin-aureomycin-terramycin-resistant strain was found among the theatre sisters. There were also a number of infections which had obviously occurred in the hospital wards.

Finally, the emergence of strains resistant to all antibiotics at present available cannot be regarded without apprehension. In the present series there were 3 cases in which an antibiotic-resistant staphylococcal pneumonia was superimposed on other clinical conditions. Of these cases 2 had a fatal termination to which the pneumonia contributed.

It should, however, be emphasised that these antibiotic-resistant staphylococci appear to be confined to hospital environments. In a survey of blood donors carried out in April, 1951 (Rountree 1951), only 7 of 97 nasal carriers were carrying penicillin-resistant strains and no streptomycin-resistant strains were found. This was a similar incidence to that found in 1949. Similarly, Anderson (1951) reported that 100 strains of *Staph. aureus* isolated from lesions in casualty patients at their first attendance at the hospital were aureomycin-sensitive. It is only in the hospital environment that conditions obtain which permit the selection of the resistant variants and their subsequent spread to large numbers of people.

SUMMARY

Of 915 strains of *Staph. pyogenes* isolated from inpatients between Jan. 1, 1951, and Feb. 1, 1952, 592 (64·7%) were resistant to penicillin, 253 (27·6%) to streptomycin, 72 (7·9%) to aureomycin and terramycin, and 11 to chloramphenicol.

All the strains resistant to aureomycin were likewise resistant to terramycin, and vice versa. 98% of these strains were resistant to penicillin and 66% to penicillin and streptomycin. None of these strains was acquired outside the hospital. The first strains isolated were converted to resistance during aureomycin or terramycin therapy. Subsequently the strains were isolated from cases of hospital cross-infection.

A survey of the nasal carrier-rates in 200 of the hospital staff showed that 54·5% were carriers of *Staph. pyogenes*. Of every 10 carriers, 8 were carrying penicillin-resistant strains. 47% were carrying penicillin-streptomycin-resistant strains, and 17 carriers of penicillin-streptomycin-aureomycin-terramycin-resistant organisms of one particular phage type were found.

There was a close correspondence between the distribution of phage-types and antibiotic resistance in the strains from the patients and the noses of the staff.

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THE MAINTENANCE THERAPY OF PERNICIOUS ANÆMIA WITH VITAMIN B_{12}

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VITAMIN B_{12} is being widely used in the treatment of pernicious anæmia. So far all the evidence shows that the initial response is good, but clinical and laboratory studies must be made over several years before vitamin B_{12} is fully accepted as the best maintenance therapy. It must be shown that adequate blood levels are maintained and that no neurological complications ensue. Also the patient's opinion of the new injections has to be considered, as well as the opinion of the neurologist and hæmatologist, for it is important to maintain well-being in addition to hæmatological and neurological perfection.

This study is based on 36 patients with pernicious anæmia who had previously been treated with liver preparations for at least a year (most of them for over five years) and now have been changed to a preparation of vitamin B_{12} for more than twenty months. They had their own opinions about the change of therapy, and these were recorded. Full clinical examinations and blood-counts were done at the time of review.

DOSAGE

At first small doses were given at short intervals, but with increasing knowledge we have come to rely on larger doses given every two to four weeks. At present the doses vary between 50 µg. every four weeks and 100 µg. every two weeks.

On liver therapy the patients required an average of one injection every nineteen days. On vitamin B_{12} they required an average of one injection every twenty-five days.

The cost of liver extract varies with different preparations. Our patients had been treated with one or more of five well-known proprietary preparations at an average cost per patient of £2 10*s.* a year, whereas treatment with a proprietary vitamin-B_{12} preparation ('Cytamen') cost on the average 9*s.* 4*d.* a year.

PATIENTS' OPINIONS

The following questions were asked of each patient: "Your injections were changed in ——. Have you been better or worse since then?" "Which injections do you prefer?"

3 patients felt worse since their injections were changed; 13 felt no difference; and 20 felt that they had improved.

Of the 3 patients who felt worse the 1st said: "I feel weak and I'm all of a shake." He has a senile tremor which has been becoming more severe for five years. Clinical examination revealed no evidence of subacute combined degeneration of the cord, or of peripheral neuritis, and a blood-count was normal, with 5,000,000 red cells per c.mm. The 2nd patient has had severe subacute combined degeneration of the cord since 1944. She complained that there was more cramp in her leg muscles at night. On examination there was no change in the physical signs, and a blood-count was normal. Her dosage was inadequate and has since been increased from 50 to 100 µg. every two weeks, with complete relief of her recent symptoms. The 3rd patient is a woman, aged 75, with chronic bronchitis. She complained that she was not so robust, and that her appetite was poor. On examination there were no abnormal signs, except those due to her bronchitis, and a blood-count was normal, with 4,600,000 red cells per c.mm. Review of her old notes revealed the same complaints recurring many times during the past ten years while she was having liver injections.

13 patients had noticed no improvement. Without exception these patients had had no symptoms when their therapy was changed. As one said, "I feel lovely, but I felt all right before."

The other patients, who all felt better, may be quoted verbatim:

(1) "I'm much better since I changed the injections. My breathing is better."

(2) "I think they're wonderful. I'm better this last eighteen months. Now I can do some housework, and before I couldn't hardly do anything. It is definitely better. I am so much better in myself."

(3) "They're better than the ones we had before. Not so tired."

(4) "I have been much better than on the other. I've always thought so. There's nothing wrong with me now. I've felt more life."

(5) "I've felt ever so much better, doctor. My cramp is much better."

(6) "I haven't been so tired. My legs haven't ached so much."

(7) "I am much better than I was with those dark injections. I feel better in myself. I can walk better." (This patient has angina of effort.)

(8) "These suit me well. I've felt much better since I've had that."

(9) "Better. Before I used to be tired. Now I just get on with my work."

(10) "I feel better."

(11) "I think I have felt definitely better. I can do more than what I did. I noticed it about six months after I changed."

(12) "I'm better. I have more go in me. I don't get so tired. I seem to be more energetic."

(13) "I know it was changed and I've been pleased ever since. It seems to suit me."

(14) "I feel a lot better in my health and everything. I don't want those first ones (liver) again. I feel champion."

(15) "I've been a lot better in all respects. I'm not so short-winded. I'm not so tired."

(16) "Ever so much better on this stuff. Now I feel quite normal. I don't feel tired or anything."

(17) "I have been better. I am not so short of breath. I have more go in me. I have more energy."

(18) "I am definitely better."

(19) "This treatment is superior to the other. I don't get so fatigued in the evenings."

(20) "I'm definitely better. The pains in the chest have gone (angina of effort). The pins-and-needles are better. I wouldn't like to change back, because there has been a definite improvement."

CLINICAL EXAMINATION

All the patients were examined clinically at the time of review. In no case was there clinical evidence of deterioration. Particular attention was paid to the nervous system. As already described, one patient complained of increased night cramp. No other new complaints and no new physical signs were elicited. No patients had developed neurological complications, and of 5 cases of subacute combined degeneration of the cord only the 1 case could be considered to be in any way worse than before the change of therapy. At the same time 3 of these patients said that their symptoms were less or that their walking had improved. In no case was there striking improvement.

BLOOD-COUNTS

Extensive laboratory investigations were not made. Hæmoglobin, red-cell count, packed cell volume, and blood film were done in all cases at least once at the time of review. These results will not be discussed except to say that all the counts were considered to be within normal limits. In no case was the red-cell count below 4,000,000 per c.mm. for women or 4,400,000 per c.mm. for men.

REACTIONS

Of the 36 patients who had had liver therapy for more than a year 13 (36%) had experienced unpleasant reactions after liver injections at some time. The commonest reaction was flushing of the face. As one patient said, "My face came up scarlet in the bus on the way home from hospital. I felt terrible, and there was no life in me. Sometimes I nearly fainted. But I was better the next day." One patient with chronic bronchitis experienced increased wheezing and dyspnœa for twenty-four hours after an injection. Fifteen patients complained that the liver injections they had had were painful. Sometimes the pain was such that they were unable to turn over in bed for two or three nights. In most instances these unpleasant reactions had been avoided by changing to another liver preparation.

In our experience of vitamin-B_{12} therapy there have been no reactions following about a thousand injections given to 40 patients. No patient found the injections painful, and in no case did a sterile abscess form.

DISCUSSION

During this investigation the most striking finding was the patients' enthusiasm for this treatment. Over half of those questioned stated clearly that they felt better and that symptoms had been relieved. Since their injections had often been changed before (from one brand of liver to another) they were not specially biased in favour of a new type of injection.

The subjective changes experienced by patients with pernicious anæmia are an important feature of this disease. Further, it is well known that many of the symptoms are not directly related to the anæmia or to neurological complications. This is shown most clearly when a case in relapse is treated with vitamin B_{12} or liver extract. Indigestion, vomiting, fever, lethargy, and mental symptoms may improve within a few hours. The appetite returns, and there is a feeling of well-being. All this happens before there is any change in the peripheral blood. Similarly, when a case begins to relapse, there are sometimes vague symptoms at an early stage before there is an appreciable alteration in the blood-count. The patient loses his sense of well-being.

Although our patients may feel better because of more adequate treatment of their pernicious anæmia, it is also possible that this improvement is due to a non-specific "tonic" effect. Such an effect has been attributed to vitamin B_{12} when given to patients with general debility. It seems impossible to determine which is the more important factor, but this does not detract from the value of the improvement.

CONCLUSION

Vitamin B_{12} is popular among patients who have pernicious anæmia and must have regular injections for the rest of their lives.

It is cheap, relatively painless, and free from unpleasant reactions. Its potency is reliable.

We wish to thank Dr. George Discombe, Dr. H. B. W. Greig, and the hæmatology technicians for their assistance in this work.

"When the physician takes the history of a patient with whom he has had no previous acquaintance, the interrogator's attitude toward that person and his reaction to his complaints will create more of an impression than his technical skill. The ability to be interested, unhurried, careful, tactful and considerate rather than amused, supercilious, distracted, bored or inconsiderate of the patient's sensibilities might well be called the essence of the art of medicine. . . . the student . . . should be reminded of the possible dire consequences of *showing the pity which he may feel for* an incurably ill patient, and the tragedy which may result if the patient, rather than a responsible member of his immediate family, is frankly told the truth."—SIMON S. LEOPOLD. *Principles and Methods of Physical Diagnosis.* Philadelphia and London, 1952; p. 403.

FURTHER OUTBREAK OF BORNHOLM DISEASE ASSOCIATED WITH COXSACKIE VIRUS

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SIX weeks after the localised outbreak of Bornholm disease in a suburb of Manchester, reported by Metcalfe Brown et al. (1952), another occured in a village in Saddleworth urban district 20 miles away. From 2 patients during this second epidemic Coxsackie virus was isolated which was of the same serological type as that found in the first epidemic.

This second outbreak took place between July 19 and 30, 1951. Of the 21 patients seen, 16 were children and 5 adults. Most of the children were attending two schools, situated at either end of the village, which appeared to be the foci from which the disease was disseminated: 13 patients were either at, or in contact with children attending, one school, and 7 were associated with the other. There was only 1 case, that of an old man, in which contact with the schools could not be established.

In the school initially affected the first 5 cases occurred in the infants' class within four days of each other: these were followed by 4 more cases four to eight days later, 2 in the same and 2 in another class. Of the children in this school, 1 infected a child of pre-school age who passed on the disease to his parents. Four days after the first case appeared, 2 older children attending the other school became ill, and 1 of them transmitted the disease to his mother and sister. Four days later 2 more children were taken ill at this school, but with the closing of the schools for the summer holidays the outbreak ceased abruptly.

As the majority of cases were contacts one with another, there was no reason to think that the infection was conveyed by vectors such as flies. The incubation period appeared to be two to four days.

CLINICAL FEATURES

Three different clinical types were noted, and these would have been attributed to different infections had it not been for their close association and the results of the virus studies.

TABLE I—CLINICAL SUMMARY

—	Types 1	2	3
No. of cases	11	5	6
Age-group			
3–5	9	1	0
7–10	2	4	0
Adults	0	0	6
Duration of illness			
1–3 days	11	5	2
1–2 weeks	0	0	4
Clinical symptoms			
Pyrexia	9	5	6
Sore throat	1	0	2
Muscle pain:			
generalised	0	0	2
abdominal	10	0	2
chest	2	0	1
limb	3	0	1
Neck pain or stiffness	1	1	4
Lassitude	2	3	0
Headache	3	4	6
Dizziness	2	2	2
Anorexia	0	1	3
Nausea or vomiting	5	3	1
Loose stools	0	2	0

Type 1.—These were typical cases of Bornholm disease with pyrexia and acute abdominal or chest pain, occurring mostly in the younger children.

Type 2.—In these cases the main symptoms were pyrexia and headache with occasional pain or stiffness in the neck, nausea or vomiting, and lassitude. The older children tended to present this sort of clinical picture in which there was no definite muscular involvement.

Type 3.—This type was characterised by headaches, neck stiffness, generalised or localised muscular pain, and sometimes dizziness. This syndrome was confined to the adults, in 4 of whom it lasted for a week or more.

A sporadic case (X.Y.) of this last type occurred in a village 3 miles away the day before the main outbreak. As serological studies were performed on the patient (table II) she was included in our summary of age-distribution, duration of illness, and symptoms (table I). Evidence of salmonella, shigella, or brucella infection was sought in 3 cases with negative results.

TABLE II—SERUM-NEUTRALISATION TESTS

Patient	Age	Clinical type	Days after onset of symptoms	Serum + 100 I.D.$_{50}$ virus. No. of infected mice/no. injected at a serum dilution of 1 in 10	1 in 50	1 in 250	1 in 1250
H.I.	29	3	6 21 103 278	6/6 0/8 0/7 0/6	8/8 3/7 0/8 5/5	— 7/8 5/5 —	— — — —
J.K.	32	3	4 18 100 275	6/6 0/7 — 1/8	5/5 1/6 0/7 3/8	— 6/6 3/6 7/7	— — — —
C.B.	34	3	16 43	— —	0/6 0/7	3/5 1/6	— 6/6
X.Y.	20	3	12 30 111 286	0/6 — — 0/8	2/6 0/7 0/4 0/5	5/5 8/8 5/5 7/7	— — — —
D.E.	9	2	3 17 101	5/5 0/8 —	7/7 0/7 0/8	— 3/5 0/8	— 7/7 5/6
L.M.	10	2	8 22	0/7 0/7	0/7 0/8	6/6 4/7	— —
F.G.	75	3	2 16	4/8 0/6	7/7 0/8	— 5/5	— —

CASE-HISTORIES

The histories of 3 cases occurring in one family and 2 others are given below to illustrate the different clinical syndromes.

The Family Outbreak

A schoolboy (A.B.), aged 7, complained of a sore throat and malaise on the morning of July 23, and in the afternoon was seized with acute pain in the lower chest. This persisted until the evening, but next morning after vomiting once he was quite well.

Four days later, while out for a walk, his sister (B.B.), aged 4½, complained of pain in her legs and hips. This pain then moved to her abdomen and slowly abated and by next day, except for one bout of vomiting, she was perfectly well again.

Three days later her mother (C.B.) started to experience malaise, headache, sore throat, and pain in her upper abdomen. Next day she had a temperature 101°F with headache and pain in the back of her neck and back. Chloramphenicol was administered, but her pyrexia and pain lasted ten days. A sample of serum taken on the sixteenth day from the onset of symptoms gave a high titre to the isolated strain of Coxsackie virus (table II).

Type 2

A boy (D.E.), aged 9, complained of malaise and dizziness on July 28, with pyrexia (104·5°F) and some vomiting. Next day he passed three loose stools but by the third day was quite normal. A rising titre to the isolated strain of Coxsackie virus was demonstrated in his serum (table II).

Type 3

An old man (F.G.) of 75, under regular medical supervision for arteriosclerosis and subject to headaches and palpitations, suffered from a severe acute headache and dizziness and vomited several times. He was pyrexial and complained of stiffness of his neck and palpitations. His illness lasted seven days and he was still weak ten days later. A rising titre to the Coxsackie virus was demonstrated in his serum (table II).

VIRUS INVESTIGATION

Single specimens of stools were obtained from 7 patients between the second and twenty-first day after the onset of symptoms and from 2 of these the same serological strain of Coxsackie virus was isolated. One of these fæcal samples had been taken on the fourth and the other on the eleventh day of illness. Stools from all these 7 patients and from 6 others were again tested two months later but no virus was isolated.

Neutralisation tests using the isolated strain were performed in paired serum samples obtained from 7 patients and the results are shown in table II. These were performed in mice less than one day old. A significant rise in titre was obtained in 4 cases in which the first sample was taken within the first six days of illness, but in the other 3 taken later antibody was present to a high level in all specimens. Four serum samples were also tested for antibodies three to four months after infection, and these all showed as high a level of antibody as those taken after two to six weeks. One of three sera taken nine months later showed little if any drop in titre, but in the other two it had decreased —in one considerably. The sera of 4 adults living in the village who had slightly different pyrexial attacks were negative.

Histologically the strain of Coxsackie virus which was isolated produced lesions in fat, brain, and to only a very slight extent in muscle in mice one to two days old, and produced no visible signs in three-weeks-old or adult mice. However, histological examination of 6 three-weeks-old mice six and ten days after inoculation with a large dose showed an acute pancreatitis in one of them. These findings would place this agent in Dalldorf's group B. Involvement of the pancreas in older mice by a strain of this group was first reported by Pappenheimer et al. (1951) in the U.S.A. and has also been found in strains in Australia (Atkinson et al. 1951), and in Oxford (Sanders 1952).

By cross-neutralisation tests the virus from our Saddleworth cases was found to be of the same serological type as that isolated from the neighbouring epidemic in Baguley (Metcalfe Brown et al. 1952), but it was not related to the B1 strain, Conn 5 (see table III). The virus was not neutralised by antisera prepared against the group A strains 1, 2, 4, "Grey," and "Northwich," the last two strains being isolated in this country, "Grey" by Prof. C. H. Stuart Harris and "Northwich" (which is not identical with but is related to A1) by Forrester and Tobin (1951).

DISCUSSION

It is almost certain that members of the Coxsackie group of viruses are the causal agents of epidemic Bornholm disease. The close association of this illness with this type of virus infection has been shown in the United States, on the Continent, in Australia, and in this country. Recently Lepine et al. (1952) have isolated strains from muscle biopsy material taken during an epidemic and have noted the same histological response in the human subject as was seen in suckling mice. That cases of the three clinical types described here were suffering from the same virus infection was indicated by the virus studies. The virus was isolated from cases of type 1 and type 2. Previous work had shown that this strain had been associated with the type-1 clinical

of antibody was demonstrated in another case of type 2 and in 3 cases of type 3. The other 3 cases investigated serologically had large amounts of antibody in each sample of serum, but in all of these the first specimen had been collected after the first week of illness. To demonstrate a significant rise in titre the first serum sample should be taken within six days of the onset of the illness and preferably in the first one or two days. Neutralising antibodies appeared within the first week and rose steeply to a high level which was maintained for three to nine months but then slowly declined.

Two serum samples taken four months after the patients had had Bornholm disease were received from Dr. R. J. F. H. Pinsent of Birmingham, and three from Dr. J. Sandilands of Kirkcaldy; and all of them contained high levels of antibodies to this strain. Epidemics of the disease had occurred in both areas during the summer, one of which was reported by McNeish and Stewart (1952).

During the summer and autumn of 1951, 6 sporadic cases of myalgia from the North-West, 4 of which occurred in pairs, were tested against this strain with negative results. However, another serological type of Coxsackie virus was isolated from the son of one of the patients. This boy had a lymphocytic meningitis. The sera from 5 of these cases all contained antibody to high titre to this second type. The exact relation of this strain to the sporadic cases of Bornholm and to cases of aseptic meningitis has not yet been determined.

TABLE III—CROSS-NEUTRALISATION TESTS

Virus strain	Antiserum (Lowest dilution showing complete inhibition with approx. 100 I.D.₅₀ virus)				
..	Saddleworth	Baguley	Conn 5	A1, 2, 4	Grey and Northwich
Saddleworth ..	1/250	1/1250	<1/10	<1/10	<1/10
Baguley ..	1/250	1/1250	<1/10	<1/10	<1/10
Conn 5 ..	<1/10	<1/10	1/250	<1/10	<1/10

The rôle of Coxsackie virus in lymphocytic meningitis is still far from clear. The cases of headache and neck stiffness reported during the epidemic described here might suggest a meningeal reaction, but there was no clinical evidence to justify lumbar puncture. 9 cases of lymphocytic meningitis of unknown ætiology occurring in the North-West of England during the summer and autumn were investigated for neutralising antibodies against the Saddleworth strain of Coxsackie virus but all were negative. Of these 9 patients 3 lived in the affected village, but they were taken ill some weeks after the epidemic had finished. Of these cases, 2 failed to neutralise the second strain.

At the moment it would appear that in the North-West of England the explosive outbreaks and a few of the sporadic cases of Bornholm disease were due to the same type of virus, while the more sporadic cases were probably caused by another type occurring simultaneously in the locality. Whether the difference in epidemiology of these strains is related to a biological as well as serological difference has not yet been decided, but comparison between other strains isolated elsewhere in the country may provide the answer.

SUMMARY

An outbreak of Bornholm disease associated with a Coxsackie virus is described. Three different clinical types of infection were noted and case-notes are given to illustrate each. The relation of *Coxsackie* virus to myalgia and lymphocytic *meningitis* in the North-West

Our thanks are due to Dr. D. McCracken and Dr. R. S. Holgate for reporting cases; to Dr. M. T. Parker, Dr. W. H. Patterson, and Dr. K. Rawnsley for samples of serum from sporadic cases of myalgia; and to Dr. A. D. Macrae for strains of Coxsackie virus.

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INTRA-ARTICULAR HYDROCORTISONE ACETATE IN RHEUMATOID ARTHRITIS

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A FEW reports have appeared in America on the use of hydrocortisone acetate (Compound F) in rheumatoid arthritis (Thorn, G., cited by Hollander et al. 1951, Stevenson et al. 1952) but so far there has been none in this country. We are therefore presenting this preliminary report comparing its effects with those of cortisone (Compound E) when injected into affected joints.

In 11 patients with rheumatoid arthritis 32 intra-articular injections of hydrocortisone acetate were given into 14 different joints.

In 3 patients whose two knees had been affected for about the same time and were about equally swollen, cortisone was injected into one knee and hydrocortisone into the other. In a second series of 8 cases, 13 joints were injected first with cortisone and later with hydrocortisone.

Each injection consisted of 50 mg. of cortisone or 50 mg. of the saline suspension of hydrocortisone acetate; the patients did not know which drug was being administered. Progress was assessed every other day, the range of movement, circumference of the joint, and amount of tenderness being recorded on a graph. The injections were not repeated until the symptoms returned.

In the 3 patients given cortisone into one knee and hydrocortisone into the other, the knees injected with cortisone showed only slight improvement lasting for about three days. But of the 3 knees injected with hydrocortisone, 2 showed dramatic improvement, lasting for eight days in one and fifteen days in the other, after a single injection; the third knee was slightly improved for three days after each of two injections—an effect comparable with that of cortisone in the opposite knee.

In the 8 cases treated first with cortisone and then with hydrocortisone, 5 of the 13 knees injected with cortisone showed slight improvement for twenty-four to forty-eight hours, the others being unaffected. However, 4 of these 8 cases reacted sharply to hydrocortisone, the average duration of improvement after each of 17 injections into 8 joints being fourteen days. In 1 case there was complete freedom from symptoms in both knees a month after the last injection; 1 case showed moderate improvement for three days only; 1 case showed slight improvement after the first two injections, moderate improvement with the third, and no benefit at all from the fourth, fifth, and sixth injections. One case, which had proved completely resistant to systemic cortisone and intravenous adrenocorticotrophic hormone, did not respond to the injection of hydrocortisone into a wrist, but a single injection of hydrocortisone into a recently swollen knee somewhat reduced both pain and swelling (Kersley et al. 1952).

In 5 cases where eosinophil-counts were done, there was a 50% fall in 2 cases after cortisone but in only 1 case after hydrocortisone. As these patients were having both knees injected at the same time, their total dose of cortisone and hydrocortisone was 100 mg.

In 6 cases synovial fluid was withdrawn for examination just before and two days after hydrocortisone injection, the aim being to draw off 2–3 ml. the minimal amount needed for these investigations, but in only 3 was enough fluid obtained on both occasions to compare the viscosities. In all 6 cases the total cell-count and percentage of polymorphs were reduced, with a relative increase in lymphocytes; and in the 3 cases where it was estimated the viscosity was increased (see table). In 6 instances intra-articular cortisone caused either no significant change or an increase in the synovial-fluid cell-count and had no significant effect on the ratio of lymphocytes to polymorphs; in 1 case out of 4 the viscosity was appreciably increased (see table).

In no case did any joint other than the one injected appear to benefit from the cortisone or hydrocortisone, and there was no apparent systemic effect. After the injection of hydrocortisone, improvement was usually noticed within about six hours and reached its peak in forty-eight to seventy-two hours. Of the 32 injections given, 22 produced striking improvement and only 4 were completely ineffective.

SYNOVIAL FLUID BEFORE AND 2 DAYS AFTER INTRA-ARTICULAR INJECTION OF 50 MG. OF CORTISONE OR HYDROCORTISONE

Drug injected	Total cells per c.mm.		Lymphocytes %		Polymorphs %		Viscosity	
	Before	After	Before	After	Before	After	Before	After
Hydrocortisone	7400	4500	22	47	76	21	750	1200
Hydrocortisone	60,800	29,500	7	10	92	83	340	1000
Hydrocortisone	36,000	30,000	6	25	92	69	820	2400
Hydrocortisone	19,000	8000	14	45	82	43	..	..
Hydrocortisone	68,800	11,150	8	39	86	59	..	..
Hydrocortisone	36,200	3400	8	51	88	31	..	..
Cortisone ..	37,200	31,000	7	7	91	88	..	
Cortisone ..	30,600	68,800	9	8	85	86	960	1157
Cortisone ..	27,200	35,600	8	10	85	88	680	487
Cortisone ..	32,000	66,000	8	4	88	94	910	1100
Cortisone ..	9900	13,800	26	16	71	76	..	
Cortisone ..	18,200	17,700	8	18	90	80	1200	6500

From this preliminary experience, hydrocortisone seems likely to have several valuable applications in the treatment of a refractory joint in a patient whose disease is otherwise well controlled, in monarticular cases, and as an adjunct to manipulation or orthopædic surgery, with the object of minimising joint reaction and subsequent formation of adhesions.

Hydrocortisone costs considerably more than cortisone at present, but when supplies improve the small quantity required should make it an economic proposition for selected cases.

We are indebted to Messrs. Merck and Co., for the hydrocortisone acetate used in this trial.

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PANCREATICOGASTROSTOMY

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THE best method of establishing in man a communication between the canal of Wirsung and the alimentary canal after partial pancreaticoduodenectomy is still under discussion.

Wells and Annis (1949) showed th[illegible] trostomy was feasible in dogs, and [illegible] and Dill-Russell (1952) report the successful performance of this operation in man.

When one of us (R. I.) did his first pancreaticoduodenectomy three years ago, the pancreatic remnant was anastomosed not to the jejunum but to the stomach, on the supposition that the stomach, being more substantial than the jejunum, would hold the suture better than the jejunum would. Moreover, it was thought desirable to get rid of the hydrochloric acid of the stomach, which might perhaps destroy the trypsin secreted by the pancreatic remnant; and in any case it would be impossible to confirm postoperatively the presence of trypsin in the acid milieu of the stomach. In both the cases reported here I resected the antrum of the stomach, so that it contained no free acid postoperatively. This made it possible to test for pancreatic enzymes in the stomach after pancreaticogastrostomy. The investigations were made at the Physiological Institute of the University of Oslo under the direction of the other author (E. L.).

After excision of the head of the pancreas with the duodenum, resection of the gastric antrum, choledochojejunostomy, jejunogastrostomy, and pancreaticogastrostomy, a test-meal withdrawn from the stomach may contain trypsin, lipase, and diastase secreted by the pancreatic stump implanted in the gastric wall, diastase from the saliva, pepsin and lipase from the stomach, and erepsin and bile from the intestine. Hydrochloric acid is not to be expected, because the antrum is excised, but bile is always present. If trypsin is found, it means that the pancreatic stump, implanted in the gastric wall, is secreting; for trypsin is the proteolytic enzyme of the pancreatic juice and is the only enzyme which splits true proteins (e.g., serum-proteins) into amino-acids. The splitting takes place only in an alkaline milieu, the optimum pH being about 8·5.

Erepsin is the proteolytic enzyme of the intestinal juice. It does not act, however, on true proteins, though it catalyses the splitting of peptones in an alkaline milieu. Pepsin splits proteins into peptones but not further, and is active only in an acid milieu. Since the contents of the stomach after [illegible] are not acid, pepsin does not [illegible]ion in an alkaline milieu. One may conclude that trypsin is present if serum-protein is used as the substrate in an alkaline milieu and hydrolysis is demonstrated. If peptones are used as the substrate in an alkaline milieu, hydrolysis is effected by erepsin as well as by trypsin.

METHODS

Two simple methods can be used:

(1) 1 ml. of stomach contents is mixed in a glass with 10 ml. of 4% peptone solution, and 1 ml. of stomach contents in another glass with 10 ml. of serum-protein solution. To each glass is added *N*/10 sodium hydroxide to bring the pH to 8·3. The two solutions are kept at a temperature of 37°C and examined at intervals for turbidity when 1 ml. is mixed with 10% trichloracetic acid. Amino-acids give no turbidity. Trypsin gives turbidity in both solutions. Erepsin gives turbidity with peptone but not with serum-protein.

(2) Formol titration is a quantitative method which may be used for qualitative analysis: 50 ml. of 4% peptone solution and 50 ml. of 4% serum-protein solution are each mixed with 5 ml. of stomach contents. The blank value is determined in 10 ml. of the mixture, which is next kept at a temperature of 37°C. Formol titration of 10 ml. is done after 2 hours, 5 hours, and 24 hours. The titration acidity, expressed in ml. of *N*/10 sodium hydroxide, will be the same as the blank value if trypsin is absent. If trypsin is present, formol titration with serum-proteins will show that the solution contains an enzyme hydrolysing proteins in an alkaline milieu and that the hydrolysis goes further than to peptones.

The pancreatic juice also contains a very active lipase which acts in an alkaline milieu, splitting neutral fat to glycerol and fatty acids. If an emulsion of neutral fat, with a pH of 8·5 and containing an enzyme, changes from alkaline to acid, and if lipolysis can be proved again and again after the acid mixture has once more been made alkaline, we may conclude that lipase is present. A lipase with these qualities is found only in the pancreatic juice.

CASE-RECORDS

Case 1.—A man, aged 55, was admitted to the University Hospital on Feb. 12, 1949, with five weeks' history of abdominal pain, chills, fever, and jaundice. Radiography showed no calculi in the gall-bladder, or elsewhere. A gall-stone in the common bile-duct was diagnosed.

Operations.—Laparotomy on Feb. 13 revealed a carcinoma of the head of the pancreas. No calculi were found. A cholecystogastrostomy was done successfully, and the jaundice and fever subsided. At laparotomy two months later no metastases were found, and a pancreaticoduodenectomy was performed (carcinoma of the pancreas was confirmed histologically), the gall-bladder and the antrum of the stomach were removed, the common bile-duct was anastomosed to the jejunum, the remnant (about half) of the pancreas histologically free from cancer was sutured in three layers into an opening in the posterior wall of the stomach, the duct of Wirsung was dilated rather easily, and the stomach was anastomosed to the jejunum, end to side.

Postoperative course was uneventful and without glycosuria. An Ewald test-meal showed no free acid and a total acidity of 13.

Formol titration of the gastric contents for pancreatic enzymes after a test-meal of 200 ml. of barley-soup withdrawn after 1 hour (the stomach had been evacuated by aspiration just before the test-meal was given) gave the following results:

	Peptone	*Serum-protein*
0 hr.	5·0 ml. *N*/10 NaOH	1·9 ml. *N*/10 NaOH
2 ,,	5·6 ,, ,,	2·2 ,, ,,
5 ,,	6·6 ,, ,,	3·2 ,, ,,
24 ,,	12·0 ,, ,,	3·3 ,, ,,

This showed that trypsin was present.

The presence of lipase was proved by shaking a sample of the stomach contents with olive oil in water, with phenolphthalein added as an indicator, and *N*/10 sodium hydroxide to pH 8·3, and leaving the mixture until the red colour had disappeared, adding *N*/10 sodium hydroxide until it became pale rose, then leaving it again till this colour disappeared, and adding *N*/10 sodium hydroxide again, and so on.

Follow-up.—Three months after the pancreaticoduodenectomy the patient resumed his former occupation. Four months later he had two hard tumours in his abdomen, each as big as a child's fist—evidently recurrent cancer—and he died shortly afterwards. There was no necropsy.

Case 2.—A man, aged 51, was admitted to the University Hospital on Nov. 17, 1949, with four weeks' history of diarrhœa, loss of weight, itching, dark urine, and progressive jaundice. There was no pyrexia. Obstructive jaundice, probably caused by a tumour, was diagnosed.

Operations.—On Dec. 21 laparotomy revealed an induration of the lower right corner of the pancreas. The gall-bladder, which was much dilated but had no calculi, was anastomosed to a loop of the jejunum, the two limbs of the latter being connected to each other by an entero-anastomosis. It proved impossible to pass a sound to the duodenum through a choledochotomy. After the patient had recovered from this operation and the jaundice had subsided, a pancreaticoduodenectomy was performed on Dec. 30. The dissection of the duodenum from the posterior abdominal wall was rather laborious, the tissue here being sclerotic. Tumour tissue had grown far and deep through the wall of the duodenum into the retroperitoneal tissue and had spread along the sheath of the vena cava. Cancer here was verified histologically, the tumour being an adenocarcinoma originating from the ampulla of Vater. Radical excision was impossible for remnants of tumour tissue were sure to be left behind. This only became evident, however, when the operation had gone too far. The common duct was anastomosed to the loop of jejunum already connected to the gall-bladder. The pyloric antrum of the stomach was resected, and an end-to-side gastrojejunostomy was done. The cut end of the pancreas was implanted into the posterior wall of the stomach by sutures in three layers.

The postoperative course was uneventful and without glycosuria. On admission to the surgical department on Dec. 6, 1949, the patient had weighed 62·8 kg., and on discharge on Feb. 27, 1950, 58·7 kg. On two occasions the stomach contents were examined for pancreatic enzymes, and trypsin was found, though in considerably smaller amounts than in case 1.

Follow-up.—On March 31, 1950, the patient weighed 62 kg. He then went away and we did not see him again, but his doctor reported that he died with cachexia six months after the pancreaticoduodenectomy.

SUMMARY

In two patients the stump of the pancreas was implanted into the stomach after pancreaticoduodenectomy, an extensive resection of the gastric antrum being done at the same time to get rid of the gastric hydrochloric acid.

Both patients made a good postoperative recovery. Both gained weight, and one of them resumed work. In both cases pancreatic enzymes were found in the gastric contents after the operations.

The operations therefore seemed to be technically and physiologically successful.

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Wells, C. A., Annis, D. (1949) *Ibid.* i, 97.
— Shepherd, J. A., Gibbon, N. (1952) *Ibid.* i, 588.

RECOVERY FROM A SHOT IN THE BACK OF THE NECK

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M.D. Budapest

In the case reported here a pistol shot was fired at close quarters at the back of a woman's neck without killing her; in fact later she was restored to perfect health.

CASE-RECORD

A woman, aged about 30, well developed, strong, and otherwise healthy, was blindfolded and led to the edge of a deep ditch. There she was shot in the back of the neck with a pistol and fell into the ditch, breaking a few ribs and acquiring a hæmothorax. After some time she regained consciousness, tried to climb out, and was seen by passers-by, who carried her away for proper medical treatment.

On examination the back of her neck showed a fresh bullet-wound in the midst of hair sticky with blood; no exit wound could be detected. Radiography revealed a pistol bullet in the midline behind the posterior tubercle of the atlas (fig. 1).

Treatment.—The bullet was removed *secundum artem*, and the patient recovered completely in spite of the most unfavourable circumstances then prevailing (1944).

DISCUSSION

A shot fired at close quarters at the back of the neck from the direction indicated by the arrow in fig. 3 practically always causes death. After breaking through the occipital bone, or piercing the foramen magnum, and entering the skull the projectile will either damage the brain directly or hydrodynamically, or, without penetrating the skull, injure the vital organs passing through the foramen magnum—the medulla oblongata, the vertebral artery, the spinal arteries, the accessory nerve, and the 1st cervical nerve. Therefore this type of shot is well known for its lethal effect and is used in practice. It may be applied, though with some difficulty, to one's own neck for suicidal purposes, as reported by Maschka and by Haberda at the end of the last century.

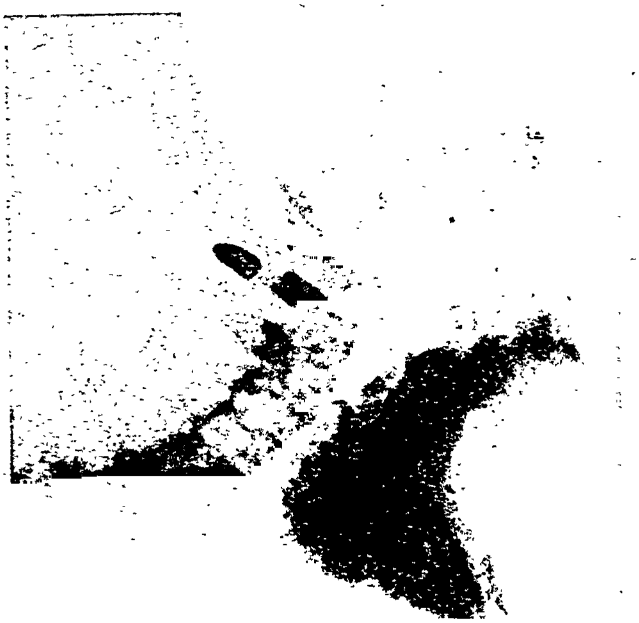

Fig. 1—The pistol bullet behind the posterior tubercle of the atlas and pointing outwards.

Radiography in the present case showed that the bullet had turned completely round to point to the surface again and had become bent in the process (fig. 1). The bullet had finally come to rest behind the posterior tubercle of the atlas. These three facts show that the bullet must have ricochetted from the skull, missing the vital parts of the neck. The radiogram did not show any fracture.

The wound presented a strange feature: the small perforation of the entrance wound communicated, immediately under the skin, with an egg-sized cavity with uneven walls lined with shreds of soft tissue and containing clotted blood and the bullet.

The fact that the bullet neither entered the skull nor penetrated deeper into the neck may be explained by the circumstance that the bullet, passing through and being retarded by the ligamentum nuchæ (fig. 2), struck the external occipital crest at an acute angle. Here the force of impact slightly bent the bullet and deflected its course. The diverted bullet could hardly pierce the relaxed septum nuchæ, because its kinetic energy had been spent on complicated rotations destroying the surrounding tissues instead of driving itself forward in the prolongation of the trajectory (fig. 3).

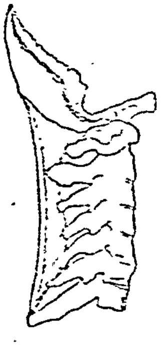

Fig. 2—The ligamentum and septum nuchæ.

This explanation is supported by the following facts:

(1) The patient was young, with well-developed bones and elastic tissue.

(2) The occipital bone is thickest in the midline, where the bullet struck; here it is formed by the external and internal occipital protuberances and the external and internal occipital crests.

(3) The ligamentum and septum nuchæ (fig. 2) are thick, very tough, and extremely elastic, apt to reduce or damp the motion of a projectile.

(4) A projectile ricochetting within the body may perform all kinds of rotatory movements and dig a cavity. Thus, by

tearing and heavily damaging the surrounding organs, its kinetic energy is consumed almost on the spot and it either does not move forward at all or only a little.

(5) In the case of a shot fired at close quarters, the force of the impact depends not so much on the distance travelled by the bullet within the body as on the violence of the explosion.

(6) Elastic tissue, when relaxed, *resists a projectile*, gradually giving way like a spring; but, when *stretched, will not stop the projectile.*

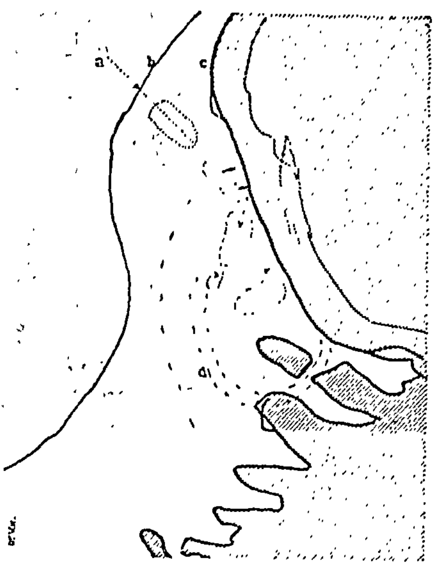

Fig. 3—Key to fig. 1 : *a*, presumed course of bullet ; *b*, external surface of soft parts of nape ; *c*, external occipital protuberance ; *d*, wall of cavity excavated by bullet.

Most probably the bullet struck the occipital bone at *an acute angle—i.e., grazed it—and the septum nuchae* was relaxed when the shot was fired, for we may assume that the victim had lifted her chin and bent her head somewhat back purposely to try to see from under the bandage over her eyes while being led to the ditch, and as a reflex action when her neck, bandage, or hair was touched with the barrel of the pistol.

The fact that a shot which is commonly lethal proved ineffective in the present case supports Kenyeres's statement that "one should be very careful as to the expression of an opinion about danger and recovery in gunshot injuries." It also confirms Kogel's view of the value of evidence : "no photograph, no evidence, no decision." Radiograms should be taken of every gunshot injury ; in fatal cases they should be taken before necropsy. The projectile may sometimes be found facing an unexpected direction and surprisingly far from or, as in the present case, near the wound. *In addition to showing the nature of the fracture, if present,* and the anatomical position of the projectile, radiography enables conclusions to be drawn about the type of weapon used and the direction and distance at which it was fired.

SUMMARY

An unsuccessful attempt at execution is described. A pistol-shot fired at close quarters into the back of the neck did *not kill the victim, who made a complete* recovery.

Presumably the bullet glanced off the occipital bone and spun round, damaging the soft tissues alone.

The *importance of radiography even in fatal cases of* gunshot wounds is emphasised.

Preliminary Communication

BACTERIOPHAGE AS A FACTOR IN EPIDEMIOLOGY AND BACTERIAL EVOLUTION

LYSIS OF DIPHTHERIA BACILLI BY STAPHYLOCOCCAL BACTERIOPHAGE

Like those of other bacteria, strains of the diphtheria bacillus *differ widely in virulence, growth characteristics,* and fermentation reactions, and more than 60 different serological types have been described.[1] The ordinary processes of bacterial variation and natural selection do not adequately account for this diversity of strains. For, although mutation is known to occur in bacteria as in other living organisms, the presence of one mutant bacterium in a population of say *100 million*, would not be expected to affect the behaviour of the culture as a whole. *Of course, if the mutant had superior survival-powers* and multiplied more rapidly it might in time overgrow other organis[illegible] become predominant. But if this [illegible] strains would inevitably become more and more coarse-growing, whilst slow-growing and fastidious pathogenic organisms would disappear. The frequent occurrence of strains *of pathogenic organisms of widely different properties,* and the absence of any apparent evolution towards coarser and less fastidious growth requirements, suggests the presence in Nature of selective agents favouring the multiplication of mutants regardless of the general vigour of their growth.

EXPERIMENTAL EVIDENCE

I have lately been able to show[2] that, in relation to the diphtheria bacillus, bacteriophage is just such an agent. Diphtheria bacteriophages are type-specific and when added to a culture they lyse the great majority of the organisms, leaving intact only mutant bacteria which differ from the other cells in the culture in being resistant to the *bacterial virus.* Not *only do the* organisms which grow out from a lysed culture differ from the parent strain in being resistant to the lethal and lytic action of the bacteriophage, but they often differ in other characters as well.

As an example, the case of *mitis* type III diphtheria bacilli may be considered. A phage was isolated which *lysed a strain of this type,* but when it was tested against other strains of the same type only some of these were found to be susceptible to its action and the others were completely re[illegible]. Although identical serologically, as tested by [illegible] the *mitis* type III strains were thus divisible into two subtypes, *according* to their phage-susceptibility. Furthermore, the phage-*resistant strains* were all virulent and toxigenic, *whereas* the susceptible strains were avirulent and *produced* no diphtheria toxin. When the susceptible strains were subjected to the action of the bacteriophage, organisms grew out which were resistant to lysis ; and a number of these phage-resistant mutant strains were found to be fully virulent and toxigenic. Thus phage had been shown to be an agent capable of *completely transforming* the biological characters of a bacterial *strain* in a single subculture.

That this transformation is not an isolated phenomenon is confirmed by the recent work of Freeman,[3] Parsons and Frobisher[4] and Freeman and Morse,[5] who describe a bacteriophage which in contact with an avirulent strain of *diphtheria bacilli produced* virulent organisms. The presence of carriers of avirulent diphtheria bacilli among fully immunised children, as recently reported by Bradshaw et al.[6] cannot be dismissed as of no significance, since, in the presence of bacteriophage, avirulent strains can become virulent and *might* start an epidemic among unimmunised contacts now that the proportion of immunised *children is declining.*

Thus it has been demonstrated that bacteriophage is an agent capable of selecting mutant strains and completely altering the characteristics of pathogenic organisms; but it remains to be shown that this happens often enough to be of epidemiological importance. When eight diphtheria strains, selected at random, were investigated it was found that five of them were carrying bacteriophage and this property persisted on subculture. The bacteriophages did not lyse the strains which were carrying them but could readily be adapted to lyse a wide variety of strains of other serological types. It appears, therefore, that a considerable proportion of diphtheria strains occurring in infections carry bacteriophage. Should a patient be infected with both a phage-carrying strain and a strain susceptible to the phage, modification of the susceptible strain would occur. The susceptible organisms would be lysed, and only phage-resistant mutants would survive; so contacts of the patient would be exposed to infection with mutant strains differing from the parent strain.

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[1] Hewitt, L. F. *Brit. J. exp. Path.* 1947, 28, 338.
[2] Hewitt, L. F. *J. gen. Microbiol.* (In the press).
[3] Freeman, V. J. *J. Bact.* 1951, 61, 675.
[4] Parsons, E. I., Frobisher, M. *Proc. Soc. exp. Biol. Med.* 1951, 78, 746.
[5] Freeman, V. J., Morse, I. U. *J. Bact.* 1952, 63, 407.
[6] Bradshaw, D. B., Dixon, C. W., Mawson, F. M., Turner, G. H., Zinnemann, K. S. *Lancet*, 1952, i, 558.

A mechanism exists, therefore, by which infections can change their character; but, for this mechanism to operate, the patient must be infected by more than one strain of the diphtheria bacillus. Such multiple infection has been observed from time to time and is probably commoner than is generally supposed. Usually the pathologist has to be content when he has isolated a single strain of the diphtheria bacillus from a patient, and he cannot undertake, in each case, an exhaustive investigation of a statistically significant number of bacterial colonies.

However, even if it is accepted that infection with more than one strain of *Corynebacterium diphtheriæ* does occur in a number of patients, it must be conceded that the coincident occurrence of a phage-carrying and a phage-susceptible strain in the same patient must be comparatively rare. If bacteriophage is to be incriminated as the principal agent controlling the frequent variation in strains which is encountered in infections, a more likely conjunction of circumstances must be sought.

The question arises whether the only kind of phage that can alter the character of a micro-organism is one carried by another organism of the same species. Perhaps a strain can be altered by phage from some quite different organism which the patient happens to be harbouring?

Staphylococci are present in so large a proportion of nose and throat swabs that we can be sure that almost all diphtheria strains have been in contact with staphylococci at some stage in their history. Moreover, I have noticed that diphtheria strains isolated from swabs heavily contaminated with staphylococci often show modified properties. Accordingly, I have investigated the possibility that staphylococcus bacteriophage can affect diphtheria strains.

When *Staphylococcus aureus* bacteriophage no. 47 (which had been propagated on *Staph. aureus* strain 36) was tested against various diphtheria strains, there was no visible effect. However, after a few subcultures of the bacteriophage with diphtheria strains, filtrates were obtained which lysed the diphtheria strains. Thus staphylococcus phage had been converted to diphtheria phage. To confirm this finding, three more staphylococcus phages were examined (phages 58, *muscæ*, and 3A, which had been propagated on *Staph. aureus* strains OxH, *muscæ*, and 284 respectively) and each of them yielded phages which lysed diphtheria strains after a few subcultures with the appropriate diphtheria strain. Like diphtheria phages obtained from phage-carrying diphtheria strains, those obtained from staphylococcal phages were type-specific but could readily be adapted to lyse a variety of other types of *C. diphtheriæ*.

COMMENT

The observation that staphylococcus bacteriophages can readily be adapted to lyse diphtheria bacilli provides a reasonable explanation of the wide variety of diphtheria strains encountered in infections, since the presence of staphylococci in the nose and throat of diphtheria patients is very common. I do not, of course, suggest that this relation between bacteriophage and bacteria of different species is confined to *Staph. aureus* and *C. diphtheriæ*. On the contrary, through the intervention of bacteriophages from phage-carrying strains, coincident infection with different bacteria may modify the character of many other pathogenic organisms. Indeed, the apparently inexplicable rise and fall in the severity of epidemics may be explained, at least in part, by the selective action of bacteriophage. One would expect that in the intestinal tract the complex interplay of phage-carrying organisms and susceptible strains would result in modification of the flora by the selection of resistant mutants; and this may account for the wide variations seen, for example, in the salmonella group.

The origin of "specific" bacteriophages, apparently active only against one type of organism, is more intelligible when one recognises that phages active against one species of bacterium can be adapted to lyse not only different serological types but also different species of bacteria.

There has been a tendency to regard bacteriophage as of mere academic interest, or at most as a useful laboratory tool for the typing of strains. But it now seems probable that phages are important agents in the modification of infections and epidemics and in the evolution of bacteria.

I am indebted to Dr. R. E. O. Williams for samples of staphylococcus phages and the *Staphylococcus aureus* strains on which they are propagated.

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Director

New Inventions

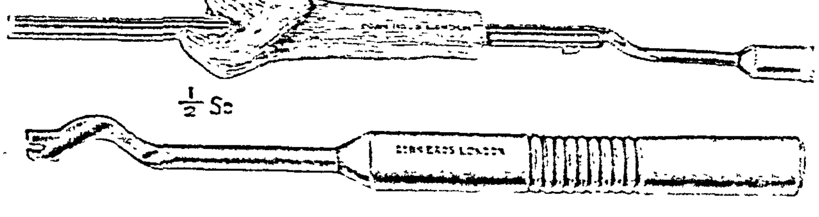
INSTRUMENT FOR RETROGRADE NAILING

ONE of the few disadvantages of the retrograde method of inserting intramedullary nails has been the technical complication necessary to avoid blunting the ends of the nail. The instrument illustrated, used in conjunction with a standard nail slotted and sharpened at both ends, provides a simple means of driving a nail in either direction without damage to the cutting surfaces, by enabling the driving force to be applied directly to the slot.

The original model was made for me by Mr. Robert Fraser, chief orthopædic technician, Stracathro Hospital, Brechin, and the model illustrated has now been made by Messrs. Down Bros. & Mayer & Phelps, whose help I gratefully acknowledge.

Royal Infirmary,
Aberdeen.

N. G. C. HENDRY
M.B. Aberd., F.R.C.S.E.



Reviews of Books

Causes and Prevention of Tuberculosis

BRICE R. CLARKE, M.D., consultant physician, Northern Ireland Tuberculosis Authority; lecturer in tuberculosis, Queen's University of Belfast. Edinburgh: E. & S. Livingstone. 1952. Pp. 288. 32*s*. 6*d*.

THIS book comes at an opportune moment to correct the present tendency to separate the preventive and curative sides of the tuberculosis services. Surprisingly, Dr. Clarke does not mention this unfortunate effect of the National Health Service Act, probably because a special authority to deal with all aspects of tuberculosis work has been established in Northern Ireland.

The first two-thirds of the book set out what is known of the pathogenesis of tuberculosis. The references are unusually full for a textbook. The various causative relationships are described, but it is doubtful whether the balance between them is fairly held. The genetic factor receives less than its due, since Dr. Clarke avowedly believes in the major part played by infection, even in family contacts. The last chapters deal with the prevention of infection, and methods of immunisation and of preventing disease in the infected individual are also discussed. Dr. J. Ritchie contributes a chapter on mass miniature radiography.

The presentation is clear throughout, but it is a pity that in quoting from Scandinavian sources Dr. Clarke has copied the meaningless term "inversion" of the tuberculin reaction where most English doctors would use "conversion."

Rheumatic Diseases

Based on the proceedings of the Seventh International Congress on Rheumatic Diseases. Editor: CHARLES H. SLOCUMB. Philadelphia and London: W. B. Saunders. 1952. Pp. 449. 60*s*.

THERE is a place in any subject for something between a formal textbook and current literature. This is such a book, and is the result of wise exploitation of the proceedings of the seventh International Congress on Rheumatic Diseases. Over ninety papers are presented here, a few in abstract but most in full; and to some of the more important papers reports of the discussions are attached. Some—such as the early reports on the use of cortisone and A.C.T.H. in the treatment of rheumatoid arthritis—are by now distinctly dated; but papers on other, slower-moving topics—such as the relation of the group-A hæmolytic streptococcus to acute rheumatic fever—are well up to date. The twenty chapters range through general information about the rheumatic diseases to rheumatic fever, rheumatoid arthritis and its variants, fibrositis and psychogenic rheumatism, osteo-arthritis, various approaches to treatment of rheumatoid arthritis, uncommon rheumatic syndromes, and reports of experimental work in all fields. Careful editing and indexing, and good printing, unify the diversity of these contributions and make most of them interesting reading.

The Alkaloids

Chemistry and Physiology. Vol. 2. Editors: R. H. F. MANSKE and H. L. HOLMES. New York: Academic Press Inc. 1952. Pp. 587. $14.50.

THE first of the projected four volumes of this treatise appeared in 1950 and was reviewed in these columns.[1] This second volume contains nine monographs, each written by an expert and dealing with a group of chemically or biologically related alkaloids, such as the indole group and the alkaloids of Erythrina spp., which are of special interest because of the diligence with which they have been examined, and the curare-like activity of the alkaloids. Most of the monographs are followed by comprehensive tables giving, with references, the principal physical constants of the alkaloids discussed, and of their derivatives and degradation products. The book is thus well documented and should prove a useful and convenient source of information.

The monographs on the Strychnos alkaloids and the morphine group, contributed by H. L. Holmes, are, in two parts, the first in each case being the original monograph, and the second (written partly with G. Stork for the morphin group) an addendum recording recent developments. Inconveniently for readers part I of the section on the Strychno alkaloids comes at the end of vol. 1, while part II is at th end of vol. 2. The chemistry of these two groups is comple and difficult, and Holmes has been remarkably successful i presenting a clear and interesting account, generously illustrated by graphic formulæ, of the vast amount of practica and theoretical work on their structure.

The other monographs are rather more conventional i treatment and are also well done. J. W. Cook and J. D Loudon tell the full story of colchicine, with its occurrence estimation, extraction, and characteristic reactions, givin a lucid and readable statement of its structural chemistry and ending with a comprehensive discussion of its biologica effects, including its mitotic poisoning effect, the attempt to apply it to the treatment of tumours, and its use in th production of polyploidy in plants.

Freezing and Drying

Report of a symposium held in June, 1951. Editor: R. J. C. HARRIS. London: Institute of Biology. 1952. Pp. 206 15*s*.

IN this book there is something for everyone interested in drying by sublimation, from high-powered technicalitie to the problems of drying an infusion of tea (which, incidentally, loses its characteristic bouquet in the process). The drying of antibiotics and foodstuffs form an introduction to the greater difficulties in achieving functional survival after the freezing and partial dehydration of skin grafts, tumour cells, blood corpuscles, spermatozoa, and "vinegar eels." The evidence is conflicting on the effect of extremely rapid freezing—vitrification—in preventing the formation of ice-crystals, and of the speed of thawing the frozen material, but it is agreed that glycerol or glucose exert some protective action essential for functional—as distinct from structural—survival of tissue cells.

Viability in dried bacteria and viruses depends more on the suspending fluid than on the method of the drying process; some technically inefficient methods seem to give as good survival-rates as those which are theoretically more efficient. Vacuum-freeze dehydration can be used by histologists to replace the older fixation methods, and seems to be particularly useful in combination with fluorescent microscopy; it can be applied to thin slices of tissue embedded in collodion to make preparations for electron microscopy. In cytochemical work the freeze-dried tissue has advantages over the chemically fixed in that the cell constituents are retained unaltered both in site and in composition.

The report includes good reproductions of photographs of apparatus and many fine micrographs of tissues.

Survey of Compounds which have been tested for Carcinogenic Activity

(2nd ed.) JONATHAN L. HARTWELL, National Cancer Institute, National Institutes of Health, Bethesda, Md. Public Health Service publication no. 149. Washington, D.C. 1951. Pp. 583. $4.25.

THIS survey covers publications dealing with chemical compounds tested for carcinogenic activity from 1880 to the end of 1947. In all, 1329 compounds are listed, of which 322 were reported to cause malignant tumours and 35 benign. The corresponding figures for the previous edition up to the end of 1939 were 696, 169, and 23. No mixtures such as tar or articles of diet are included. Data are tabulated with references to authors in chronological and alphabetical order, of animals used, strain, type and sex, preparation, dose solvent, site and route, animals with tumours, survival-time, and duration of experiment. The type of tumour is given in a footnote. Apart from these items the scope of the publications referred to is not indicated. Thus each must be consulted for other purposes. Warning is given not to carry over, without reservation, to man conclusions based on animal experiment. In the monkey none of the powerful carcinogens has been shown to produce tumours. A bibliography, indices of compounds tested, route and site of application, tumour site, species including man, and vehicle in which application was made, complete a very valuable volume.

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[1] See *Lancet*, 1951, i, 33.

THE LANCET

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Nurses in the Making

GIRLS in their 'teens are often afflicted with an urge to do good; and if some irresponsible power compelled them to carry out their secret projects we might be flooded to the point of inconvenience with saints, nuns, missionaries, and self-immolating heroines by land, sea, and air. Fortunately many of them change their minds and take to less exacting courses.

Nursing can appeal both to the romantic imagination of the 15-year-old and the practical desire to do a useful job natural to the girl reaching maturity. Headmistresses often deplore that girls who leave school at 15 or 16 burning to nurse are lost to the profession because no-one fosters the flame until they are old enough to begin training; and in an attempt to keep that interest alive many cadet schemes have been started in our hospitals. Now that the minimum age for entry to training has been fixed at 18[1] protests about the gap between school and hospital are likely to multiply; and it may be necessary to remind ourselves that in some, at any rate, of these young people the fire will burn itself out as the endocrine upheaval subsides. Time is a good test of earnestness; and if the later age of entry loses us some recruits who looked promising as school-leavers, it may also deter in good time many who might contribute to a high wastage in the first few months of training. At the moment recruitment is higher than it has ever been: the report just issued by the King's Fund[2] mentions that the numbers of student nurses in our hospitals have risen from 46,655 in 1947 to 58,270 in 1951, and there has been a small further rise since then. For the first time in many years, in fact, we are in a position to consider the quality, as well as the quantity, of the new entry.

Nevertheless the higher age of admission is bound to affect recruitment, even if only for a time, in those hospitals which have been accustomed to take girls aged 17½ or less. From an inquiry made by the *Times*[3] it appears that some hospitals—among them a few provincial teaching hospitals and some provincial and Metropolitan non-teaching hospitals with nurse training schools, as well as many children's hospitals—think they will be seriously hampered. They may be taking too dark a view, for in cases of real hardship the General Nursing Council has power to relax the rule until the situation adjusts itself; and in any case those girls under 18 who have already started training are to be allowed to continue. Difficulty should not be acute after the coming six months, at the end of which the current 17½-year-olds will have matured to the right age. A few may be lost to other occupations in the interval, but it is hard to believe that the keener ones will be defeated by the setback. For those who are not, an added six months of growth, particularly if it is coupled with further education, can hardly fail to be an advantage. It means that, on the average, the girl's resistance to childish ailments will be greater, her bones and muscles stronger for lifting, and her endocrine balance—and hence her emotional fortitude—six months nearer maturity. We can hardly, in these days, urge Miss NIGHTINGALE's view that a nurse entering training should be 25, but we can at least give hearty support to the ruling that she should not be less than 18, even if it means some staffing difficulties at the outset.

It may not be generally understood, however, that, for the purposes of this regulation, "training" means training for the general State register or one of the supplementary registers (of nurses holding a certificate in sick children's nursing, infectious-diseases nursing, mental nursing, or the nursing of mental defectives). Orthopædic and eye hospitals, and (very unfortunately) tuberculosis sanatoria, thus fall outside the regulation: as they do not train nurses for any State certificate they are at liberty to take them below the age of 18. This matters less, perhaps, in orthopædic and eye hospitals than in sanatoria, which often have difficulty in getting enough staff. The position has been eased in many of the larger sanatoria by the secondment of nursing staff from general hospitals—a practice which, as the King's Fund points out, is largely responsible for the reopening of 3723 more beds by sanatoria during 1950–51. But some of the smaller sanatoria have been known in the past to accept 16-year-olds, and even 15-year-olds, some of whom, as Dr. ESTHER CARLING[4] notes, acquired tuberculosis. In addition there are many non-training hospitals and nursing-homes which can still employ girls under 18.

For the prospective nurse, the extra six months' delay is likely to create financial problems. The G.N.C., the Ministry of Health, and the Ministry of Labour urge girls to stay on at school, if possible, until they are old enough to enter hospital—or at any rate until they are 17. Some, of course, cannot afford to do this; and the question then arises how can they best fill the gap? Should they take a pre-nursing course, join a hospital cadet scheme, enter a hospital as a "juvenile worker," or go into some stopgap job? This question is not easy to answer in a word. Where the local authority offers a pre-nursing course the girl who has left school at 16 or 17 probably cannot do better than take it. She will be given further education as well as instruction in the subjects for the preliminary State examination, and she can usually get a grant from the local authority to carry her through. A good second choice is a job in a nursery school, if there is one to be had. Girls who leave school at 15 may not be old enough even to be accepted for a pre-nursing course. Many hospitals seek to attract these into cadet schemes, some of which are good, some not so good. The young people wear a simple uniform, have some class work, and spend the rest of their time acting as messengers and helpers in the various departments of the hospital other than the wards; and they are paid a small wage. A good cadet course, such as that described by Mr. S. HODKINSON,[5] keeps up their interest in nursing, and prepares them to enter the wards with a sound idea of what a hospital does and how it does it. But not all schemes are so well organised: sometimes the young girls are used far too freely as extra pairs of hands, and even find themselves in the wards helping in nursing duties, such as the serving of meals. Moreover the wage, though small, can be a dangerous attraction; girls have been known to leave pre-nursing courses, and even to leave school early, to go and work as juveniles in hospitals. They can hardly be blamed: the combination of drama with remuneration would be almost irresistible to almost any young person. Nor do these schemes of juvenile employment always fulfil their intended purpose; both the matron of Addenbrooke's Hospital [6] and a sister tutor [7] have pointed out the weaknesses. The girl who has been pottering about a hospital for three years before she starts her training has sometimes lost much of her initial zest, and may give up the whole idea from boredom. Moreover if she completes her training she has led an unusually regimented life from childhood on: she has not had much chance to grow into a fully mature person. There are good arguments for the view that whatever a girl does between leaving school and starting her nursing training, at least she should keep clear of hospitals: let her work in a nursery school, a shop, an office, a hairdresser's, or a circus—anywhere where she will meet people as they live, anywhere but in the laundered setting of her future profession. Nursing training, like a training in medicine, can be dangerously narrowing. It is true that, unless caught young, some girls will inevitably find their way into other careers; but while recruitment is at its present pitch we can face that: the keener ones will keep to their purpose, and the others might in any case have fallen out. A more important objection is that the alternatives open to the school-leaver of 15 may not be such as to help her to mature; they may even be actively damaging. Certainly it may be doubted whether work in a chain store, or as a cinema usherette, is likely to fit her for nursing better than a well-planned cadet course. Clearly the best way of filling the gap varies in different localities and for different people. Fortunately the King's Fund Nursing Recruitment Centre is able to give informed advice, and is now commonly approached for guidance by headmistresses who have candidates for nursing among their leavers.

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[1] *Lancet*, Aug. 2, 1952, p. 251.

[2] Fifty-fifth annual report of King Edward's Hospital Fund for London, 10, Old Jewry, E.C.2. Pp. 89.

[3] *Times*, July 28, 1952.

[4] *Lancet*, 1952, i, 874.

[5] *Lancet*, *Ibid*, p. 1113.

Pharmacology of Isoniazid

BECAUSE such promising, and at times startling, results have been obtained with isonicotinic acid hydrazide (isoniazid) in the treatment of tuberculosis, and because, to quote the statement of the American Trudeau Society,[8] "preliminary observations in man indicate that there is little significant or serious toxicity," comparatively little consideration has yet been given to the pharmacological behaviour of this drug or its derivatives. But more information on this subject is certainly required; for unexplained side-effects often appear during treatment, and the many new derivatives that are being prepared in the world's laboratories will soon lead, despite some official control, to the extensive use of these compounds in clinical medicine.

Chemically, isoniazid is a pure synthetic substance of relatively simple molecular structure, obtained in almost colourless crystals and readily soluble in water. Laboratory assay may be performed by an iodometric method,[9] but estimation in body-fluids is more difficult. Photometric, colorimetric,[10-12] and biological[13] techniques have been devised, but to what extent they are specific or even accurate remains to be seen. For the moment, then, the available data about the distribution and fate of the drug in the body must be accepted with reserve. After giving isoniazid by mouth to mice and dogs, RUBIN and his associates [14] found that it was rapidly absorbed. ELMENDOFF et al.[15] confirmed this observation in man, and showed that after a single oral dose of 3 mg. per kg. body-weight, plasma concentrations of 1·3–3·0 µg. per ml. were reached between one and six hours later, the level remaining at or above 0·40 µg. per ml. for from six to twenty-four hours in all. A similar picture is given by RUBIN and his team [12]; their curves of plasma level against time suggest that a peak is reached in a matter of a half to two hours, that the level falls quickly in the next six to eight hours, and that no significant amount is detectable after twenty-four hours. There is, moreover, no evidence of accumulation after repeated doses. In patients with meningitis appreciable quantities of the drug were present in the cerebrospinal fluid within three hours of an oral dose of 2–3 mg. per kg., and the plasma levels were in fact much higher than those known to inhibit sensitive strains of the tubercle bacillus in vitro. Incidentally, the administration of 5 ml. of a 2% solution of isoniazid—i.e., 100 mg.—has been safely accomplished by the intrathecal route. A large proportion—from 50 to 70%—of an oral dose has been shown to appear in the urine within twenty-four hours; and a small amount is also voided in the fæces. Whether isoniazid remains extracellular or penetrates the cell membranes is not yet established; but it is significant that SUTER [16] has shown by the Mackaness technique that the minimal concentration of the new drug which causes complete inhibition of the tubercle bacillus within the phagocyte is identical with that which has a similar effect on organisms suspended freely in 'Tween-albumin' medium. The inference is that isoniazid (unlike streptomycin) readily finds its way into the phagocytes, and, by the same token, may enter other cells as well.

BENSON and his colleagues [17] remark on the paucity of pharmacodynamic effects with the isoniazid compounds. Therapeutic doses given to animals did littl to alter intestinal activity; they did not suppres salivation or lacrimation; they had no antipyreti action (a relevant point because the fever of tuber culous patients very often subsides after givin

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6. *Ibid*, p. 821.
7. *Ibid*, p. 1166.
8. *Amer. Rev. Tuberc.* 1952, 65, 649.

9. Canbäck, T. *J. Pharm. Pharmacol.* 1952, 4, 407.
10. Kelly, J. M., Poet, R. B. *Amer. Rev. Tuberc.* 1952, 65, 484.
11. Ballard, C. W., Scott, P. G. W. *Chem. & Ind.* 1952, p. 71
12. Rubin, S. H., Drekter, L., Scheiner, J., de Ritter, E. *Dis. Ches* 1952, 21, 439.
13. Klee, P. *Dtsch. med. Wschr.* 1952, 77, 578.
14. Rubin, B., Hassert, G. L. jun., Thomas, B. G. H., Burke, J. *Amer. Rev. Tuberc.* 1952, 65, 392.
15. Elmendoff, D. F., Cawthon, W. V., Muschenheim, C., McDermot W. *Ibid*, p. 429.
16. Suter, E. *Ibid*, p. 775.
17. Benson, W. M., Stefko, B. L., Roe, M. S. *Ibid*, p. 376.

isoniazid); and they produced no significant change in the blood-pressure. Only high concentrations of isoniazid inhibited the activity of isolated intestine—again an interesting observation, for constipation may occur in treated patients. With the exception of a definite bronchiolytic action by the isopropyl derivative on cholinergically induced bronchial spasm in the guineapig, there was little evidence of parasympathetic activity. Investigating acute toxicity, RUBIN et al.[14] showed that for mice and dogs the therapeutic ratio was generously wide. The animals succumbed, after excitement and convulsions, to death by respiratory failure. It seems more than likely that this was the result of a direct stimulation of the central nervous system, especially now that P'AN et al.[18] have demonstrated that barbiturates give protection against these toxic effects. The changes which may follow long-continued treatment are possibly of greater importance. Animals so treated lose appetite and weight, become ataxic, and have convulsions; jaundice, with fatty degeneration of the liver and kidneys, has also developed. But these alarming results have followed doses higher than those generally given therapeutically, though the margin is not great. More encouragingly, they are reversible in most cases as soon as the drug is withdrawn. In man the side-effects recorded include constipation, difficulty in starting micturition, twitching of the extremities, exaggerated reflexes, headache, vertigo, drowsiness, dryness of the mouth, eosinophilia, and slight anæmia. These have seldom been of serious consequence, but, as there now seems to be a tendency to give larger doses of the drug, and as further derivatives are coming into use, an even closer watch must be kept for these danger-signals. When they are observed, details should be sent to the Committee on Therapy of the American Trudeau Society, as requested by Dr. D. T. Carr in a letter in our last issue.

Bacteriophage and Epidemiology

MANY years ago, when TWORT described a transmissible agent which attacked staphylococci,[19] and D'HÉRELLE extended the study of *Bacteriophagum intestinale*, the hope arose that a virus of this kind might be used against bacterial infections. In treating patients, it was thought, bacteriophage might eliminate the invading bacteria, and in preventive medicine it might, for example, get rid of the cholera vibrios in a contaminated well. But these hopes were frustrated. In the first place bacteriophages were found to be highly specific and to attack only closely related strains; which meant that an extremely large number of bacteriophages would be needed to cope with the variety of pathogens encountered in Nature. Secondly, it was discovered that bacteriophage added to a culture does not lyse all the bacteria present: a few resistant organisms survive and multiply, and the new culture which grows out consists of organisms resistant to the bacteriophage. For these reasons bacteriophage never proved itself as a therapeutic or preventive agent, and its use has been confined mainly to the laboratory, where the specificity of its action has been a great asset. As bacteriophages will attack only closely related strains, they are widely used for typing Bacteria responsible for infections.

Meanwhile the place of bacteriophage in Nature has remained rather obscure. What are the origins of specific bacteriophages? Why should almost every serological type of bacterium apparently have a corresponding specific bacteriophage waiting to attack it? Has bacteriophage any function at all in the natural history of bacteria? Elsewhere in our present issue Dr. L. F. HEWITT proposes answers to these questions. It is, as he says, a common observation that bacteriophages which are specific to one serological type of organism can often be adapted to lyse organisms of a different type, on which at first they have no effect. But now he reports that bacteriophages can be adapted to attack not only a different serological type but also a different species: for he has found that staphylococcus bacteriophage can be made to act on diphtheria bacilli. If this interaction between different species turns out to be a general phenomenon, the problem of the origin of a variety of specific bacteriophages will disappear; for we need postulate only the existence of a single bacteriophage, or small group of bacteriophages, to understand how by adaptation the whole multitude of specific bacteriophages may be evolved. From this Dr. HEWITT goes on to suggest that bacteriophages play an important part in Nature in controlling the evolution of bacteria and their virulence, and hence the spread of epidemics. A specific bacteriophage, by lysing all the organisms in a susceptible culture except the few mutants which are resistant, exerts a potent, selective action. The resistant mutants often have quite different characters from the parent strain, and in a single subculture the properties of a strain may therefore be entirely altered: for example, a completely avirulent diphtheria strain can become virulent and toxigenic. The intervention of the bacteriophage may thus be said to speed up, very greatly, the slow processes of natural selection.

Quite a high proportion of bacteria usually carry a latent bacteriophage, which does not seem to do them any harm but is capable of lysing other strains with which it comes in contact. Thus cultivation together of a phage-carrying strain and a susceptible strain can result in modification of the susceptible strain through selection of the resistant mutants which survive the action of the phage. This has been demonstrated in mixed cultures in the laboratory, and a similar process might presumably occur in infected patients. As it must be comparatively rare for a patient to be infected with two strains of the same bacterial species—one carrying phage and the other susceptible to its action—the possible modification of strains in this way has not seemed very important. But if, as Dr. HEWITT claims, staphylococcus bacteriophages can be readily adapted to lyse diphtheria bacilli, a new significance will be attached to the coincident infection of a patient with two different species of bacteria. The bacteriophage from one species, if it is adapted during the infective process to attack the other, could modify its properties by the selection of resistant mutants. The infective agent passed on to the next patient would then be different from the primary infection, and, if the resistant mutant selected happened to differ considerably, the change in the nature of the infection might be dramatic. The plagues which have in the past suddenly flared up and devastated large populations may have originated in some such selective process; and bacteriophage, instead of being regarded as a mere academic toy, must be suspected of possibly very sinister activities in epidemiology. Such speculation apart, Dr. HEWITT's evidence suggests that it has had, and still has, an important rôle in bacterial evolution.

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[18] P'an, S. Y., Markarogla, L., Reilly, J. *Ibid*, 66, 106.
[19] Twort, F. W. *Lancet*, 1915, ii, 1241.

Annotations

OVERCROWDING IN PRISON

THERE can be worse things in prison than iron bars, and sleeping three to a cell is probably one of them. In its seventh report the Select Committee on Estimates[1] deplores that 4500 men in our prisons are sleeping in this overcrowded way. The reason is not far to seek, for the prison population has now risen to over 25,000 men and women—twice as many as before the war. It is ironical that this increase is in part due to the Criminal Justice Act of 1948, which, with the aim of reforming people and not merely deterring them from crime, permits longer sentences. The additional responsibilities which the Act imposes have unfortunately fallen on the prison organisation at a time when it still has not made good war-time deficiencies in accommodation and staff, and the problems of overcrowding are aggravated by those of understaffing. Not only are there too many prisoners but there are too few warders. As a result the prisoners spend long hours of boredom and near idleness in their cells while the warders habitually put in overtime. The committee dislikes both the short working week of the prisoners—sometimes as short as 22 hours—and the long working week of the warders; it thinks that overtime in the long run is neither economical nor efficient. Much of the indiscipline, everyone agrees, is due to a comparatively small group of prisoners. The worst prisoners are not usually the worst criminals, and the committee urges the Prison Commissioners to give high priority to building a separate prison or prisons where these psychopathic trouble-makers could be not only segregated but also studied and treated.

Overcrowding brings problems of health as well as discipline, and the committee is especially concerned at the increased risk of infection, particularly of tuberculosis. Some arrangements have been made to examine prisoners by mass-radiography units; but the initiative is left to the senior medical officer in each prison, and the committee recommends that the Director of Prison Medical Services should approach the Ministry of Health to ensure that prisoners get their fair share of the services of these units. The prison medical service, like the other branches, is understaffed. Instead of 52 full-time doctors, it has only 42; and few recruits come forward, for the salaries are unattractive. The committee particularly regrets that it is no longer possible to produce a medical and psychiatric report of each boy and girl who passes through the borstal allocation centre, and urges an early return to this pre-war custom.

MYXOMATOSIS AND RABBITS

IN the past fifteen months an artificially induced epizoötic has killed many millions of rabbits in Australia, thus demonstrating for the first time that a pathogenic agent can be successfully put to work against a mammalian pest.[2] Myxoma virus, which may be related to the pox group of viruses, has a species of Brazilian "rabbit" as its natural host, and it was first recognised in laboratory animals by Dr. H. B. Aragão, who also suggested its use in biological control. The work started by Sir Charles Martin in 1933 at Cambridge showed that the disease was highly pathogenic for wild and domestic rabbits, but was harmless for all domestic animals and for most of the native fauna of Australia, as well as for the imported European hare. Fears that the virus might be the cause of serious infections in man have also proved unfounded. Myxoma virus thus combines extreme virulence for one animal pest with almost complete avirulence for most other creatures, and it was therefore an ideal pathogen to use in attempts at biological control.

Field trials carried out before the late war in semi-arid pastoral areas were inconclusive, but they did show that the virus was transmitted among rabbits by the stickfast flea, whose limited mobility made it a poor vector. Some of the many ecological difficulties were soon encountered; for example, it was impossible to establish and spread the disease where foxes were lying in wait to pick off the first generations of lazy infected rabbits. After the war the Commonwealth Scientific and Industrial Research Organisation decided to re-examine the possibilities of controlling the increasingly serious rabbit menace with myxoma virus, and between May and November, 1950, the virus was released seven times in the Murray valley. The immediate results were [illegible]: the disease had no appreciable eff[illegible] of rabbits. In December, however, the disease suddenly flared up at one of the infected places, and soon reports came from many other areas, including a place on the Darling river nearly 400 miles from the nearest known point of infection. The wide dispersal of the virus and the intense local spread produced a remarkable epizoötic within the next two or three months, and it was thought that mosquitoes, moving under their own power or carried by high-level winds, were responsible. Nothing else could explain the isolated outbreaks along the southern margins of the epidemic area in Victoria and in South Australia, nor an isolated outbreak almost in the centre of the continent. In the new year the epizoötic gained momentum, and by February, 1951, an area of 1000 square miles was involved. The disease spread at remarkable speed through the rabbit population and killed 90% of them. River courses, creeks, and swamps were most heavily involved, suggesting once again that water-breeding vectors were essential to spread. In such a large area, however, geographical conditions varied enormously; in the Murray valley, for example, only those rabbits within a few hundred yards of the water's edge were killed, whereas in south-east Queensland the disease was unbounded, and it was possible to drive for a day or more through country that had previously been swarming with rabbits and see only a few isolated survivors.

When the trials began it was known that myxoma virus could be transmitted by two species of flea and by several species of mosquito, but little was known about their performance in the field. It was found that transmission was almost certainly mechanical and that any blood-sucking arthropod was a potential vector. The epidemiology of the disease, and hence its practical value in biological control, is largely influenced by the ecology and habits of vectors, the strength of their preference for rabbit blood, and the length of time for which they are about in great numbers. In such a vast and varied area it was likely that different vectors would have local predominance; in the Murray valley, for example, *Culex annulirostris* was a principal vector, whereas on the Victorian coast and the off-shore islands *Aedes camptorhynchus* was the most important. During the winter months of 1951 the disease continued to smoulder, and ectoparasites may have ensured the persistence which was necessary to the success of the scheme. In the summer of 1951–52 a closer study was made of the various vectors, and *Anopheles annulipes*, which spends the day in the rabbit warrens, was found to have played a predominant part. This third phase of the epizoötic has developed mainly in areas not involved before, and attacks were most intense where suitable anopheles breeding-grounds were plentiful. In the Murray valley during 1951–52 this mosquito forestalled in time and outstripped in range the culicine vector of 1950, so that, instead of the disease being confined to a narrow strip along the breeding-waters, it now spread for as many miles as it had hundreds of yards during the previous summer. These entomological studies have now covered a full cycle of the seasons, and the broad pattern of the ecology of the mosquito fauna shows a fairly clear succession of species, each becoming dominant as larval and adult habitats change in nature and extent.

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[1] H.M. Stationery Office, 1952. Pp. 216. 9s.

[2] Ratcliffe, F. N., Myers, K., Fennessy, B. V., Calaby, J. H. *Nature, Lond.* 1952, 170, 7.

What of the practical results so far achieved in the control of the rabbit pest in Australia? What is likely to be the ultimate effect of introducing myxomatosis into the country? Ratcliffe and his colleagues[2] approach these questions cautiously, but in one sample area of 100 square miles, where 64,000 acres were classed as heavily infected before the epizoötic, only 640 acres remained so after it. In large parts of South Australia, Victoria, and New South Wales the number of rabbits is now one tenth or less of the 1950 figure. Thousands of farms have had their land cleared of rabbits, with an obvious and immediate increase in pasture growth and stock-carrying capacity. When the epizoötic took place, rabbits were very numerous, even for Australia, and the seasons were favourable for the virus vectors; in these circumstances the mortality was high and it is probable that tens of millions of rabbits died. It is reasonably certain that myxomatosis is now permanently established in Australia: and it may soon become more uniformly distributed throughout the rabbit population, and thus be able to spread more rapidly under favourable local conditions. But a final judgment is not yet possible. A natural process of adjustment between parasite and host may take place either by the emergence of virus strains of altered virulence or by the development of resistant generations of rabbits, or by both. These possibilities are being examined experimentally and there is already evidence that recovery is commoner in the field than in the laboratory, where a 100% mortality has been the rule.

This interesting experiment is of immense practical importance, and its Australian designers are alive to the many ecological and epidemiological opportunities that it affords.

LARYNGEAL SPASM

THE larynx has been called the watchdog of the respiratory tract. Perhaps it might be better named the watchdog of the patient, because laryngeal closure—probably as a protective response—may follow harmful stimulation of almost any part of the body. The risk of such spasm has always haunted the anæsthetist. While on the one hand it protects patients from inhalation of vomit, on the other it interferes with anæsthesia by making it difficult to introduce irritant vapours such as ether into the lungs, and by rendering many operations more or less impossible under light anæsthesia. Whether the spasm by itself can cause the death of a patient is a question which anæsthetists have long discussed among themselves. It is doubtful whether death from this cause alone ever takes place in ordinary clinical practice; for when the anoxia and carbon dioxide accumulation reaches a certain point the patient gasps once or twice and takes in enough air to get a grip on life again.

The treatment of laryngeal spasm consists primarily in removing the causal stimulus. One of the first lessons learnt by the young anæsthetist is that spasm of this sort during induction of anæsthesia with ether is best treated by weakening the ether vapour inhaled and starting again, rather than by pouring more ether on the mask. Similarly laryngeal spasm in the middle of an abdominal operation is an indication for a pause in the surgical work before, and not after, an attempt to deepen the anæsthesia. The use of muscle relaxants to treat laryngeal spasm in the presence of its causal stimuli can be very dangerous, because the respiratory muscles are paralysed at the same time as the laryngeal spasm relaxes. This method should be adopted only by the most experienced anæsthetists. Artificial respiration by compression of the chest is ineffective against severe laryngeal spasm; for the expiratory muscles are usually in spasm too. Even the worst spasm, however, quickly responds to removal of the ether mask. Then the lungs can be inflated with oxygen from an oxygen-filled bag, which is gently squeezed; or, failing oxygen, air can be used. Very occasionally the larynx may have to be exposed and a small-bore, smooth-tipped, firm catheter gently inserted between the cords—great care being taken to avoid damage to the larynx. Drugs have little, if any, place in the treatment of this condition, which is primarily one of motor reflex activity.

REACTIONS AFTER VITAMIN-B INJECTION

THE vitamins of the B group are the ones most frequently given by injection. Untoward effects after such injections are uncommon, but two fatal reactions have been recorded; in one case[1] thiamine had been given intramuscularly, and in the other[2] intravenously. Other less severe reactions, including circulatory collapse, have occurred not only with thiamine but with other members of the group. Two types of major reaction following the injection of thiamine have been described.[3] In one a condition resembling anaphylactic shock may occur in sensitised persons, usually after a long course of symptomless injections. The other less dramatic type produces symptoms like those of thyroid overdosage—excitement, tremor, palpitation, giddiness, and insomnia. Intradermal tests have shown sensitivity to the vitamin in both types of reaction.[4–6]

Chitwood and Moore[7] have lately reported what they regard as the first case of severe anaphylactic shock after an intravenous injection of vitamin-B complex. Circulatory collapse has also been reported after intravenous nicotinic acid[8 9] and folic acid.[10] But most of the reactions seem to have followed the use of thiamine.[11] Weigand[12] analysed the reports of 143 physicians who gave thiamine by injection and found 179 cases in which there was a reaction, but only 17 were described as serious. The less pronounced reactions might, of course, be easily overlooked. Sensitivity to thiamine and other members of the group can be acquired; in all the reported cases hypersensitivity developed only after repeated symptomless injections, with the notable exception of nicotinic acid which caused circulatory collapse in 2 patients immediately after the first injection.[9 10]

Acute vitamin-B deficiencies are rare in this country, and the risks arising from injection of vitamin B must be taken into account when considering its advantages. Obviously there will be a stronger case in its favour when absorption by mouth is deficient. As a precautionary measure skin tests may be carried out, but it has been said that thiamine is an obligate weal-producing agent[13]

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1. Mills, C. A. *J. Amer. med. Ass.* 1941, 117, 1500.
2. Reingold, I. M., Webb, F. R. *Ibid*, 1946, 130, 491.
3. Leitner, Z. A. *Lancet*, 1943, ii, 474.
4. Laws, C. L. *J. Amer. med. Ass.* 1941, 117, 176.
5. Schiff, L. *Ibid*, p. 609.
6. Eisenstadt, W. S. *Minn. Med.* 1942, 25, 861.
7. Chitwood, W. R., Moore, C. D. *J. Amer. med. Ass.* 1952, 148, 461.
8. Reiner, L. *Ann. intern. Med.* 1947, 26, 299.
9. Powers, B. R. *Ibid*, 1948, 29, 558.
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and if this is so a positive intradermal test would not be conclusive proof of individual sensitivity. In most cases hypersensitiveness develops suddenly during a course of injections; and the best form of prophylaxis at present seems to be to question the patient thoroughly about the effect of previous injections before giving him another one.

FLAGELLA FOR SPIROCHÆTES?

WHEN the name "spirochæte" was first used by Ehrenberg in 1833, it was applied to a large motile organism found in water. Nowadays the term denotes a group of organisms which are motile, spirally twisted, and flexible. Their structure has always aroused interest, and the information amassed about them seems to support the opinion expressed by Dobell[1] forty years ago that the group are most closely allied to bacteria. Thus, while they differ from protozoa in many ways, there is only one respect in which they do not conform to general bacterial characteristics—namely, their motility in the apparent absence of flagella. All the four genera (spirochæta, cristispira, treponema, leptospira) which are generally accepted as spirochætes possess well-defined group features. They contain no colouring matter or nucleus, they divide transversely either by simple or multiple division, and no evidence of any sexual reproductive apparatus has ever been demonstrated. Though they are supposed to have no flagella they can move in a forward or backward direction.

With the coming of the electron microscope this question of spirochætal flagella has been reopened, for some investigators claim to have seen at least some spirochætes with these appendages.[2,3] The latest evidence of the existence of spirochætal flagella includes photographs taken with the electron microscope by the shadow-casting technique using chromium.[4] The organisms studied included cultured strains of Nichol and Reiter's treponemes, and the authors maintain that the flagella are definite structures and not fragments of the spirochætes. Flagella are described as being attached subterminally, but, while the basal granules seen in bacterial flagella have not been demonstrated, a slight enlargement of the body of the organism was noted where the tuft of flagella emerges. Knaysi[5] refers to "flagellum-like extensions," but quotes Dyar as saying in 1947 that in a free-living spirochæte resembling *Spirochæta plicatilis* it was not possible to demonstrate these flagellum-like extensions with either the optical or the electron microscope.

Bradfield and Cater,[6] in an interesting report on a study of leptospira, treponema, and cristispira by electron microscopy at 70 kV, suggest that spirochætes consist of a central protoplasmic core around which is wound a bundle of fibres, the whole resembling a two-strand flex. In some cases a cell membrane envelops this structure, while in others the bundle of fibres lies outside the membrane. "Chemical dissection" of the organisms by trypsin digestion partially or completely removes the cell membrane, while the bundle of fibres is either left intact or falls apart into its components; the central protoplasmic core remains unaffected. In the experience of these workers when spirochætes are intact or undamaged by preparative techniques, they *never* possess flagella. There is indirect evidence that the fibres are contractile, and Bradfield and Cater suggest that these structures do not have a skeletal function. If this is the case it could account for the changes in shape and possibly the movements of the organisms.

It is clear that at the moment there is no agreement about the reality or otherwise of spirochætal flagella. Nor, indeed, have we yet heard of any final settlement of the larger question whether flagella really supply the motive power of the types of organism which everybody has recognised as flagellate. Working with proteus and salmonella, Pijper has satisfied himself that they remain quite mobile when deprived of their flagella; and much has now been written on this fascinating subject.[7]

THE BIOCHEMICAL CONGRESS

THE second International Congress of Biochemistry met in Paris, at the invitation of the Société de Chimie Biologique, from July 21 to 28. The preceding congress of this kind took place in Cambridge in 1949, and the third congress is to be in Brussels in 1955. The Paris congress attracted over 2000 members of more than forty nationalities, including Russians, Poles, and Yugoslavs, and more than 800 papers were read during the week.

The inaugural ceremony, at which the members were welcomed by Prof. Gabriel Bertrand (president d'honneur), Doyen René Fabre (president of the congress), and Prof. Claude Fromageot (president of the executive committee), was held in the great amphitheatre of the Sorbonne, and the various discussions were held in its lecture-theatres—many meetings, of course, being concurrent. The major events included four special lectures given in the great amphitheatre, by Prof. J. N. Davidson (University of Glasgow), A. I. Oparine (Bach Institute of Biochemistry, U.S.S.R.), Prof. S. Ochoa (College of Medicine, New York University), and Prof. R. Linderstrom-Lang (Carlsberg Laboratories, Copenhagen): their respective subjects were nucleoproteins and tissue growth, the changes in enzymic action in plant cells under the influence of external factors, carbon dioxide fixation in plants and animals, and proteins and enzymes. Thirty-one separate sections of the congress considered mineral elements, lipids, amino-acids and proteins, nucleoproteins, pigments, fat-soluble vitamins—and twenty other topics. In addition there were seven symposia devoted to biochemistry of hæmopoiesis, the biogenesis of proteins, the tricarboxylic acid cycle, protein hormones and hormones derived from proteins, the metabolism of micro-organisms, the mode of action of antibiotics, and the biochemistry of sterols. In each symposium there were about ten "reports," occupying about an hour each, and a large number of "communications." The gathering was remarkable in bringing together so many active investigators from so many lands, and if it was a little disappointing in that it did not seem to evoke pronouncements on any new and revolutionary discoveries, it nevertheless demonstrated very clearly the enormous progress made in the last few years in understanding details of biochemical mechanisms. Biochemical knowledge is extending very rapidly deep into the intercellular reactions, and the use of radioisotopes has given biochemists a penetrating tool.

The Société de Chimie Biologique has made a very useful contribution to the advancement of biochemistry by providing such good conditions for the meetings and discussions, formal and informal. The opportunity for such concentrated cross-reference to other fields is invaluable to every specialist.

H.R.H. the DUKE OF EDINBURGH has accepted the honorary fellowship of the Royal College of Physicians of London.

Mr. E. R. GARNETT PASSE, aural surgeon to Wembley Hospital, died in London on Aug. 1.

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Before our Time

RAMÓN y CAJAL

The First Centenary of his Birth *

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ON May 1, 1852, Santiago Ramón y Cajal was born in Petilla of Aragon, the eldest of a modest family from the foot-hills of the Pyrénées in the area whose political and cultural centre was the town of Huesca. His father's family name indicates the Pyrenean roots of his ancestors, Ramón being a local patronymic and the name of many princes in the lands extending from the Garonne to the Ebro rivers. Cajal depicts his grandfather as a fair mountaineer who at 75 was a strong and agile giant. Casasús, the family name of his paternal grandmother, is again typical of the Catalano-Aragonese land. From his mother's side he inherited the name of Cajal, Aragonese adaptation of the Catalano-Provençal *caxal* or molar tooth.

The land from which his family came, and that in which he spent his early life, has forged many strong and resolute men: strength and resolution are in fact the two more outstanding characteristics of the Aragonese race. From the southern side of the Pyrénées, in the area extending from Jaca to the Mediterranean, came the medieval soldiers known as *almogavers* who left such a mark of their passage across the lands of Sicily and Greece in the 13th and 14th centuries. But, side by side with these fighting characteristics, other more precious if less striking qualities form part of the Aragonese nature; I refer to their sincerity and their simple and modest nobility. As will be seen later, all these features are apparent in Cajal.

The two best examples of human activity he saw in his infancy and early childhood were that of his father, a village surgeon later a qualified doctor in medicine, and that of his mother's brother, a home weaver, in whose home in Jaca he lived for some time.

Up to his 15th year Cajal was more of an *almogaver* than a student. In the places where his father successively worked young Cajal became the head of the children's gang which terrorised neighbours and irritated authorities; and on one occasion this landed him in prison for four days. He repeatedly failed in his studies both in Jaca and in Huesca, and his authoritarian father thought to punish him by placing him as apprentice to a shoemaker and later to a barber. During these years his only other activity, alternating with his violent enterprises, was drawing. He had decided to make drawing and painting his profession, and it was only because of his father's iron will and lack of artistic sense that he was not forever lost to the world of science. Even as a scientist he never forgot his early inclination for designing, and the fidelity of his pen is evident in the drawings illustrating his early histological works.

In contrast with this rapid physical and artistic development, his intellectual awakening was very slow. Latin was to him an obstacle much harder to surmount than the highest stone wall or the more inaccessible mountain. In his own phrase, he regarded Latin as "a profuse shower of rules desauthorised by infinite numbers of exceptions." But if reading his school books on Latin, algebra, and physics bored him terribly, he soon developed an insatiable hunger for the literature of adventure, which (as he tells us in his autobiography) agreed with his desire to be known and famous and with his decision to strengthen his will by controlling his emotions. At 12 he read a Spanish translation of *Robinson Crusoe*, and because it hints at some of the reasons for his later passion for research I shall reproduce in his own words the impression this book made upon him:

> "Robinson Crusoe (which I read again and again with true delight) revealed to me the sovereign power of man confronted with nature. But what impressed me most was the noble pride of him who, owing to his own efforts discovers a wild isle full of traps and dangers capable of becoming, thanks to the miracles of will power and intelligent efforts, a delightful paradise. What a magnificent triumph it must be to explore virgin land with the landscape animated with strange flora and fauna as if it had been expressly created as a prize to the extreme heroism of its discoverer."

An associate of Cajal's in his early days, Dr. R. Solillás, wrote that the boy was so convinced of the reality of his dreams that he organised an expedition to an island on a neighbouring river and managed to make his friends believe that the wild animals and all the rest of his fantasy were real. In considering his later work we should not forget this powerful imagination, which made his scientific contributions so revolutionary, and so personal, while his cold realism made them so reliable. He was in fact one of those Spaniards who are endowed with this strange combination of realism and imagination—who fuse in themselves the opposite natures of Don Quixote and Sancho Panza. Perhaps the purpose of Cervantes in portraying the heroes of his immortal novel was to split into two the human features that he considered indescribable when woven together into a single human nature. Goya, the Aragonese painter, shows equally this apparent contradiction. The realism of such men is saved from crudity or hardness not only by their creative imagination but often also by a kind of poetic halo.

THE YOUNG DOCTOR

Having finished his preliminary studies, he entered the Medical School of Zaragoza where his father had been appointed prosector in anatomy. With his father's help he mastered the complexity of descriptive and topographic anatomy, and his ability to design anatomical preparations made him popular with some of his teachers.

Qualification was followed by service into the army as a medical lieutenant, and soon he was sent to Cuba where the nationalist guerrillas, and particularly the yellow fever and malaria, were causing havoc among the Spanish troops. Full of patriotic enthusiasm, he joined an expeditionary force which landed in La Habana, and was immediately sent to an advanced medical post where the two previous medical officers had died of malaria. Soon he became extremely ill, and after remaining in this post for several months he was repatriated an emaciated and defeated man suffering from jaundice and anæmia. It is understandable that he complained of the way in which the war had been conducted; he thought that the war could have been prevented by following the example of England—"the indisputable master in the arts of politics, always attentive to learn from reality."

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* Paper read to the Osler Club on May 9, 1952.

As soon as he had recovered sufficiently he went back to Zaragoza as assistant in the department of anatomy, with an annual salary of 1000 pesetas (about £30 at that time).

After this Cuban adventure his health was precarious, and two or three years later he suffered two severe hæmoptyses while sitting in a café in Zaragoza. It was then found that in Cuba he had contracted tuberculosis as well as malaria. Fortunately for Cajal, and for science, his strong nature reacted favourably while among the forests of the Pyrenees, and after about a year he was back at his work in anatomy in Zaragoza. He married shortly afterwards a beautiful girl, with large green eyes, who was to be his life companion. Meanwhile he was preparing himself to enter the academic life.

ACQUIRING A CHAIR

Here a word is necessary about the strange procedure traditionally followed in Spain to fill the professorial chairs.

The competitors go through a series of oral, written, and technical exercises and tests of their ability, *not unlike those* undertaken in England by candidates for the F.R.C.S. or M.R.C.P. What is unusual, however, is the direct competition among the candidates, who are invited to criticise the clinical and scientific exercises of their opponents and to demonstrate any weakness these may have shown. This method of investigation is no doubt based on the old procedures for inquiry into religious matters.

The competition ends, in theory at least, in the most brilliant among the candidates being elected to the post. But unfortunately a technique that may be valuable for assessing the basic knowledge of a doctor of 30, whose experience and wisdom lie in the future, is nearly disastrous to a man of 50 or more, whose experience and wisdom have been *long acquired. The effect of the Spanish method of selection* is that in Spain the ambitious and capable young man may begin competing for professorial posts a few years after qualifying, and with good luck he can become professor in a medical school at 30 or 32. If, instead, he spends his time in acquiring sound medical knowledge, or in research requiring much reading and thought, his name may be respected and even famous at 50; but by that time he will hardly dare to compete for a chair against youngsters saturated with bibliographical references, who have nothing to lose, not even reputation.

Cajal's first attempt to become a professor was in 1879 when he was only 27; he competed for the chair of Zaragoza and he failed. During his short visit to Madrid he saw some histological preparations by Maestre de San Juan, the earliest histologist in Spain, and he became so enthusiastic about this method of observation that he bought himself a Verick microscope and several books on micro-techniques and histology. He also subscribed to the *Quarterly Journal of Microscopical Science* and to a French journal.

Having carefully analysed the weak spots responsible for his failure in the competition, he presently competed for the chair of anatomy of Granada; but an "official" candidate was preferred. At his next attempt, this time at Valencia in 1883, he was appointed professor. Thus in his 31st year he finally became free from the limiting compulsion of the "oppositions" and was able to concentrate on microscopy. While still in Zaragoza in 1880 he had published his first paper on the histology of the nervous system, studying the neuromuscular synapse, and later in Valencia prepared for publication his famous book *Manual of Normal Histology and Microscopical Technique.*

BARCELONA AND MADRID

In 1887 the new chairs of histology in Barcelona and Zaragoza were to be filled, this time by selecting an applicant professor from another university, and Cajal was appointed to Barcelona. There he organised his laboratory in the old Hospital de la Santa Creu; it was the same place where Antoni de Gimbernat devised his operation for hernia before coming to London to discuss the merits of his methods with John Hunter in 1776. In this hospital I learned to become a surgeon more than thirty years after the appointment of the great histologist.

In 1888 he entered what later he called the greatest year of his life. The International Exhibition of Barcelona was stimulating the growing activities of the Barcelonians, of whom he was one of the more illustrious. He presented his micro-preparations in the exhibition and was awarded a gold medal. He had been told of the silver method used by Camilo Golgi since 1875 to dye nervous structures and he began using and adapting this method to explore the unknown worlds of the cerebellum and then the cerebrum. The Barcelona *Gaceta Médica Catalana* appeared with several of the greatest contributions by Cajal; in 1888 he put forward the main facts supporting the anatomico-physiological laws of the nervous cells of the grey matter. He also described the "fine axons" and published his earliest work on the retina. From now on works appeared in an uninterrupted flow. His name became known abroad and his collaboration was sought first in Germany and soon in other countries. In 1892 the chair of histology in the University of Madrid became vacant and Cajal was appointed professor, after going through a new competition. In Madrid he was able to begin the second part of his life-work and that by which his stature as a teacher must be measured. This was the creation of his school of microscopical anatomy.

DAYS OF HONOUR

Cajal endured from early times the pleasant but disturbing interferences brought about by distinction and fame. In February, 1894, the Royal Society of London invited him to deliver a Croonian lecture and on March 8 he read his paper on the Fine Structure of the Nervous Centres which appeared in the *Proceedings of the Royal Society.* Sherrington gave him hospitality in his home, and Cambridge gave him a SC.D. hon. causa. In 1899, one year after the defeat of Spain by the United States, he lectured in the victorious country and was made a D.SC. hon. causa of Clark University, Worcester. In 1900 he was awarded the International Prize at the International Congress of Medicine in Paris. In 1904 the Helmhoth gold medal was presented to him by the Royal Academy of Sciences in Berlin, and in 1906 he and Golgi received the Nobel Prize. From then until he died in 1934 Cajal was honoured by universities, academies, and medical societies as few people had ever been. In 1922, having reached his 70th anniversary, he retired from his chair but continued the direction of the Institute that had been created in 1898. At his retirement a book was published in his honour.

On Oct. 17, 1934, Cajal died in his 82nd year, surrounded by his sons and by his pupils and friends Tello, Illera, Carro, Yagüe, and Hernando. The social and political disorders of the days immediately following the abortive revolution of the "6th of October" caused the funeral of this great man to pass unnoticed by the authorities, but he was accompanied to his resting-place by the sympathy, and in many cases the love, of all in Spain who cared for the progress of science.

THE TAUGHT AND THE TEACHING

There is no better way of judging the merits of a master than to consider the work of his pupils, and I must refer at least to some of those who owed Cajal their histological education and have been known abroad, particularly in the Anglo-Saxon world.

J. F. Tello was considered by Cajal a personal friend apart from being his senior pupil. P. Del Rio Hortega after leaving Madrid in 1936, worked for three years in Oxford before moving to Buenos Aires, where he died a few years ago. Lorente de No established himself in New York for many years. F. de Castro is still in Madrid and I understand is now only partially working in research. G. R. Lafora is back in Madrid after teaching in Mexico for several years. N. Achúcarro died years ago.

If ever a civil war can bring anything but sorrow, perhaps we may detect, after fifteen years, some benefit in the Spanish war having disseminated throughout the world some of the pupils whom Cajal moulded by his example and daily teaching. They sowed in fertile soils the seeds he had put in their hands.

Even to index Cajal's histological works is a strenuous task. For nearly fifty years he worked with a passion difficult to parallel. Ten books in Spanish, four in German, two in French, and two in English, with 263 monographs and papers, constitute a volume hardly ever equalled by any scientist in any field. To analyse the nature of his work would be yet harder, and here it must suffice to say that from his early paper published in Barcelona in 1888 his contributions were continuous. In that paper he had described for the first time the arborisation of the endings of the cylindro-axons. The structure of the cerebellum was likewise described in 1888 in the *Gaceta Médica Catalana* where for the first time he formulated the theory of the neurons which forms the anatomo-physiological code of the nervous system. In the same journal and in the same year we find his accounts of the structure of the spinal cord and of the method of the double silver impregnation. In 1891 he produced his work on the retina and his description of the neuroglia of the sympathetic ganglia. In 1905 came his early work on the degeneration and regeneration of the peripheral nerves.

It is, I think, impressive that so many of Cajal's works have resisted, and are still resisting, the assaults of modern research. He removed the unfounded theories of Gerlach and Golgi on the transmission of the nerve impulse, and what he put in their place is still standing after 70 years. That is the measure of his calibre as an accurate investigator.

INFLUENCE ON CONTEMPORARY SPANISH THOUGHT

The awakening of interest in the three laboratory branches of biology (bacteriology, physiology, and histology) took place in Spain almost at the same time. The requisite circumstances arose about the last quarter of the 19th century.

Fortunately for Spain three notable men decided almost simultaneously to explore the three different fields. Jaume Ferran took bacteriology and immunity as his province and from his institute in Barcelona he introduced active immunisation against cholera in 1885, when Cajal was professor in Valencia. Ferran's method was tested for the first time during the epidemic at Valencia, after Cajal had advised the authorities to try the new method; but economic difficulties and lack of official support, among other causes, prevented consolidation of his work. Ramón Turró, like Pasteur a veterinarian, was responsible for creating the Institute of Biology at Barcelona, mainly devoted to the study of physiology; like Cajal's, his school came to have pupils scattered throughout the world. But after so many labours, of these three schools only that of Cajal has survived the civil war.

Cajal, Ferran, and Turró appeared during the twenty-five years preceding the Spanish-American war of 1898. A long period of internal peace gave the conditions necessary for developing scientific research—those conditions that are basic to the England whose example Cajal so much admired. It also tended towards acceptance of the English method of building a Cambridge in front of every Oxford, to reduce the risks of exclusiveness —another of the essentials for modern science. In this respect Cajal also had a clear view of what was desirable.

At the end of his days he could look back with satisfaction to the many unknown islands he had explored for the first time with the help of a microscope. He must have been happy in seeing the dream of his youth fulfilled; that of becoming an explorer and a hero—a Robinson Crusoe of modern science.

Special Articles

CLINICAL RESEARCH IN THE UNITED STATES

THE following summaries of some of the papers read at three meetings in Atlantic City this summer will give readers a picture of some of the clinical research being done in the U.S.A.

American Federation for Clinical Research

Antagonisms between Heparin and Adrenocortical Eosinopenia in vitro and in vivo.—R. C. MUEHRCKE, J. L. LEWIS, J. PETERS, and R. M. KARK (Chicago) showed that cortisone and other 17-hydroxy compounds will produce lysis of eosinophils in sterile defibrinated blood in the test-tube. This effect is blocked by heparin, oxalate, or resins that remove calcium from the blood. Large doses of heparin injected at the same time as A.C.T.H. (in vivo) also block eosinolysis. In test-tube blood, after eosinolysis, they noted many degenerate eosinophils on smeared slides. In vivo, they believe, these cells are sequestrated and removed by the lungs. The confirmatory evidence is the different eosinophil levels in pulmonary-artery blood (taken by catheter) and in arterial blood. They demonstrated that adrenaline acts not via the pituitary but peripherally in the presence of cortical hormones; and they showed in five patients who had undergone complete bilateral adrenalectomy that injections of adrenaline caused the eosinophils to disappear from the blood. These do not seem to be direct effects on the eosinophils, for in vitro adrenaline does not potentiate the eosinolytic action of cortisone.

Deuterium Oxide and Total Body-water in Œdematous Subjects.—W. W. HURST and F. R. SCHEMM (Great Falls, Montana) found that in the estimation of total body-water oral administration of deuterium oxide gave much the same result as intravenous injection. In 7 œdematous patients they found that the distribution of deuterium oxide in œdema, pleural, and ascitic fluid was complete at 15 hours. Total body-water was calculated after correction for urinary loss of deuterium. After diuresis, the patients' total body-water was again measured and a very close correlation was noted between the calculated loss of body-water and the measured urinary output. The conclusion reached was that the oral method is reliable provided a long enough time is allowed for distribution of the deuterium oxide and a correction is made for urinary loss of deuterium.

Absorption of Radioactive Iron in Normal, Anæmic, and Hæmochromatotic Subjects.—R. B. CHODUS and J. F. ROSS (Boston, Mass.) gave radioactive iron (Fe^{59}) to healthy people and to patients with iron-deficiency anæmia and with hæmochromatosis. They measured the fæcal excretion (taken as representing unabsorbed iron) and the radio-iron incorporated into hæmoglobin, assuming that the remainder was deposited in the body's iron stores. The percentage partition of ingested iron was found to be as follows:

	Fæces (%)	*Hæmoglobin* (%)	*Stored* (%)
In healthy people ..	66–90	1–10	1–25
In iron-deficiency anæmia	40–60	40–60	4–7
In hæmochromatosis ..	84–98	0·5–11	0–5

Chodus and Ross interpreted these data as indicating that the absorption of iron is greater than normal in iron deficiency, whereas in well-developed hæmochromatosis it is less than normal. Their conclusion regarding hæmochromatosis was based on long-established cases and could only be accepted if the same findings were obtained in early hæmochromatosis.

Treatment of Barbiturate Poisoning by Hæmodialysis.—W. P. WALSH, L. H. KYLE, P. D. DOOLAN, and H. JAGHERS (Washington, D.C.) showed that in experimental barbiturate intoxication 20–30 times as much barbiturate as the normal kidney excreted could be removed from the body by dialysis with an artificial kidney. They reported 2 severe cases successfully treated by hæmodialysis, and suggested that this is the best treatment to adopt for such patients.

Ascorbic-acid Deficiency in Pernicious Anæmia.—R. O. WALLERSTEIN, J. W. HARRIS, and G. T. GABUZDA, jun. (Boston, Mass.), estimated the vitamin-C levels in peripheral blood or bone-marrow buffy coats from 21 patients with untreated pernicious anæmia and 2 with nutritional macrocytic anæmia. No vitamin C was found in 20 of the 23 patients. None of the patients had any clinical evidence of scurvy. Six patients were studied intensively. Two were given 1 mg. of vitamin C daily for 11 days; in one the reticulocytes rose to 7·7% but there was no concomitant rise in hæmoglobin or evidence of marrow maturation; in the other there was no hæmatological response. Two patients were given B_{12} without vitamin C, and then vitamin C was added later; 1 had a mild reticulocytosis, followed by a second greater reticulocyte response to the B_{12} but no secondary response on the addition of vitamin C. Finally, 2 patients were given folic acid, producing a mild reticulocyte response, after which they were given vitamin C and there was a second response. The conclusion drawn from these observations was that there is a severe biochemical vitamin-C deficiency in pernicious anæmia, and the Boston team believe that vitamin C may play an adjuvant rôle in hæmopoiesis, probably by enhancing the production of citrovorum factor.

American Society for Clinical Investigation

The Thyroid Hormonal Pool in Man and Dog.—A. STONE FREEDBERG, LEONARD WOLSKY, GEORGE S. KURLAND, and MILTON W. NAMOLSKY (Boston, Mass.) infused thyroid hormone labelled with I^{131}, obtained from the blood of patients who had been treated with I^{131}, into euthyroid, hyperthyroid, and myxœdematous patients. Studies of the turnover rate of the hormone and the size of the diffusable hormonal pool indicated that in thyrotoxicosis the total pool was about three times, and the turnover rate about four times, as great as in the euthyroid state. The myxœdematous patients had a very small pool and a slow turnover of the tagged hormone. In further studies, euthyroid dogs were infused with euthyroid and thyrotoxic tagged hormone, and the turnover rates of the thyrotoxic hormone were about twice those of euthyroid hormone. Dr. Freedberg and his colleagues therefore postulated a basic difference in the hormone elaborated by thyrotoxic and by euthyroid persons.

Disturbance of Inositol Metabolism in Diabetics.—W. H. DAUGHADAY, J. LARNER, and ELIZABETH HOUGHTON (St. Louis, Mo.) established that in normal people inositol excretion was only slightly influenced by wide variations in inositol intake and urine volume. Diabetics, on the other hand, excreted 5–15 times as much inositol. The amount of inositol excreted was related to the degree of control of the diabetes; higher levels of urinary inositol being found in uncontrolled patients. When the glycosuria was controlled the inositol excretion fell towards normal.

A Pituitary Respiratory-quotient-depressing Factor.—LILLIAN RECANT (St. Louis, Mo.) recalled that hypophysectomised rats have an abnormally high respiratory quotient (R.Q.). The animals' R.Q. can be reduced by giving them anterior pituitary extracts. She found that in Warburg vessels the R.Q. of the normal fasted rat diaphragm was 0·68 in a Ringer-phosphate substrate, but in a glucose substrate it increased to 0·83. In vitro the addition of certain anterior pituitary preparations to the glucose substrate depressed the R.Q. to 0·68. "Growth hormone" seemed most potent in lowering the R.Q. The addition of insulin in vitro did not reverse this effect, but adrenaline and dinitrophenol reversed the action of "growth hormone." To determine the level of intermediary metabolism at which this pituitary R.Q.-depressing factor acted, normal fasted rat diaphragms were incubated with glucose, hexose diphosphate, 3-phosphoglyceric acid, pyruvate, and acetate. Any of these substances caused a rise in R.Q. to 0·83. The addition of growth hormone to the different media inhibited the effects of glucose and hexose diphosphate only. Dr. Recant concluded that the R.Q.-depressing factor inhibits the transformation of hexose diphosphate to pyruvate. Further studies indicated that the pituitary R.Q.-depressing factor is similar to, but not identical with, growth hormone, since R.Q.-depressant activity can be lost without any change in growth activity. On the basis of preliminary observations on serum from fasted patients she suggested that the pituitary R.Q.-depressing factor conserves carbohydrate in the presence of carbohydrate depletion.

Spermine and Tubercle Bacilli.—JAMES I. HIRSH (New York) isolated a crystalline substance from the serum of tuberculous patients which is highly bactericidal to tubercle bacilli in vitro and has been identified as spermine phosphate. In-vitro studies of the action of spermine on tubercle bacilli indicate that it acts only in the presence of minute amounts of a plasma activator, apparently an alpha-globulin, which apparently converts it into an active antituberculous substance.

Viræmia in Poliomyelitis after Infection by a Natural Route.—DOROTHY M. HORSTMANN (New York) infected monkeys either by mouth or subcutaneously with one of two strains of poliomyelitis virus. Virus was recovered from the blood on the 4th, 5th, and 6th days after oral, and the 3rd and 4th days after subcutaneous, infection. Virus was recovered only from the animals which developed paralysis, and these were the only ones that developed antibodies. Viræmia persisted for about 3 days, so it is possible that active viral growth occurred outside the nervous system.

Aromatic Diamidine in the Treatment of Systemic Fungal Diseases.—EMANUEL B. SCHOENBACK and JOSEPH M. MILLER treated various fungal infections with stilbamidine in dosages of 150 mg. daily in three courses, to a total of 4·5–6·0 g. It was ineffectual against histoplasmosis and cryptococcus infections, but highly effective in systemic blastomycosis; the single case of actinomycosis treated responded well to the drug. The only toxic reaction encountered was neuritis, which was common.

Effects of Aureomycin in Undernourished Men.—Stimulated by reports that aureomycin enhances growth in children, GEORGE J. GABUZDA, GEORGE G. JACKSON, and MARGARET E. GRIGSBY studied its effects on 3 undernourished men. The patients were given a diet providing 75 g. of protein and 2800 calories daily, and their body-weights, nitrogen balances, and excretions of riboflavine were recorded. During the preliminary control period, all 3 gained weight and were in positive nitrogen balance. Then they received aureomycin in dosages of 2–3 g. daily for 9 days. None of the patients developed diarrhœa, glossitis, or stomatitis, but soon after the aureomycin was started they began to lose weight, their urinary nitrogen rose, and their nitrogen balance became negative. Their fæcal nitrogen was unaltered. The urinary output of riboflavine increased two or three days before the change to a negative nitrogen balance. When aureomycin therapy was stopped, their weight started to rise once more, their nitrogen balance became positive, and their riboflavine excretion dropped to pretreatment levels. When similar studies were performed with non-absorbable antibiotics (polymyxin and bacitracin) no such effects were observed. The suggested explanation was that aureomycin blocks the utilisation of riboflavine in the cells and thus prevents normal deposition of nitrogen.

Experimental Porphyria in Rabbits.—By feeding 'Sedormid' to rabbits, RUDI SCHMID and SAMUEL SCHWARTZ (Minneapolis, Minn.) produced a condition with the essential features of human porphyria (acute, intermittent, and "mixed" porphyria). The rabbits excrete uroporphyrin and porphobilinogen in their urine in amounts even greater than are found in the human disease. The uroporphyrin is of the Waldenstrom type (methyl ester, m.p. 252°C), yielding on decarboxylation about equal amounts of coproporphyrin I and coproporphyrin III. A further resemblance to the human disease is that the increased urinary coproporphyrin is principally isomer type III, and, like the uroporphyrin, it is excreted as the zinc complex. The bile contains enormous concentrations of coproporphyrin and protoporphyrin and gives an intense red fluorescence. The liver also exhibits this red fluorescence and contains large amounts of uro-, copro-, and proto-porphyrin, as well as porphobilinogen, whereas the amounts of porphyrin found in the bone-marrow and erythrocytes are within normal limits. These findings have obvious implications in human porphyria and porphyrin metabolism in general, for they suggest that the production of porphyrins by the liver is not dependent on the porphyrin formation related to hæmoglobin synthesis in the bone-marrow.

Vitamin B_{12} Levels in Pernicious Anæmia.—Using *Euglena gracilis* for bio-assay, JOHN W. HARRIS (Boston, Mass.) studied B_{12} levels in the serum, erythrocytes, and white cells of 12 normal people and 16 patients with untreated pernicious anæmia. The levels of B_{12} were found to be very low in all three elements of blood from the pernicious anæmia patients, as follows:

	Red cells	*Vitamin B_{12} (µµg.)* *Serum*	*White cells*
Normal persons	36	55	786
P.A. patients	0·5	1·0	131

Treatment with 5 µg. of B_{12} daily raised the patients' levels to about half normal, and 15 µg. daily raised them to about three-quarters of normal. Relapse-rates were found to vary inversely with the amounts of B_{12} given in treatment—the higher the dosage the lower the relapse-rate. On a dosage of 15 µg. daily relapses ceased altogether.

Association of American Physicians

Blood-volume in Congestive Heart-failure.—It is assumed that the blood-volume is *increased* in congestive heart-failure, but JOSEPH J. ROSS, ROBERT B. CHODOS, WILLIAM H. BAKER, and EDWARD D. FRESS have revealed fallacies in this view. They estimated the blood-volumes of patients in failure, and during and after treatment, by the method using P^{32}-tagged red cells. They compared the blood-volumes of 35 patients in failure with 57 normals measured by the same technique, and found no significant difference. When 14 patients in failure were studied before and after successful therapy, they found that 5 had a slight increase and 9 a slight decrease in blood-volume, though the changes were not statistically significant. But when the blood-volumes of patients in failure, calculated by the P^{35}-tagged cell technique, were compared with those of the same patients calculated by the Evans-blue dye technique, the dye method was found to give volumes almost twice those obtained with the tagged cells. After treatment, the dye method revealed a big fall in blood-volume, when the tagged-cell technique indicated no significant change. The reason suggested is that, in failure, the dye diffuses into extravascular fluid, to give an artificially high calculated blood-volume.

Clinical Picture of Hypertension associated with Unilateral Renal Disease.—GEORGE A. PERERA and ARTHUR W. HAELIG compared the clinical features of 20 patients who had been relieved of hypertension by unilateral nephrectomy with 20 patients thought to have hypertension associated with unilateral renal disease who were not improved by therapy. The results can be summarised as follows:

	Relieved	*Not improved*
No. of patients	20	20
Hypertension present over 4 yr. before surgery	1	13
Males	12	7
Diastolic pressure over 130 mm. Hg ..	17	5
Headaches and/or convulsions	15	7
Retinopathy	14	0*
Pyelonephritis as cause of unilateral renal disease	11	5

* Of 10.

Perera and Haelig emphasised that hypertension associated with unilateral renal disease is generally a severe, rapidly accelerating process, often associated with infection in the involved kidney. They suggested that its mechanism is different from those of chronic bilateral renal disease and other types of vascular disease.

Distribution of Nephron Activity in Man.—There are two schools of thought regarding nephron activity: (1) *homogeneity of function*, as outlined by Homer Smith, who believes that all functioning nephrons work at the same level of activity; and (2) *heterogeneity of function*, according to which there are wide differences in function in different nephrons. STANLEY E. BRADLEY, JAMES F. NICKEL, and EDGAR LEIFER studied this problem using tagged urea injected intravenously. They noted a wide difference in specific activity between the serum-urea and the urine-urea in the first hour after the injection, and these activities took a long time to reach equilibrium. This they interpreted as evidence for heterogeneity of function. If all the nephrons functioned at the same rate, it would be expected that shortly after injection, differences in urine and serum urea specific activity would become constant as equilibrium was reached. The delay in reaching equilibrium between urine and serum suggests that some nephrons form urine faster than others—that filtration may be fast in some and slow in others.

Epidemiological Differences Between Acute Nephritis and Acute Rheumatic Fever.—CHARLES H. RAMMELKAMP, jun., ROBERT S. WEAVER, and JOHN H. DINGLE noted a fairly constant relationship between the development of rheumatic fever and the prevalence of Lancefield group-A streptococci, about 3% of all cases infected developing rheumatic fever regardless of the type of group A, the locality, or the clinical form of infection. They found that almost all the cases of acute nephritis followed infection with type 12 of group-A streptococci. Other types less frequently involved were 2, 4, 18, and 31. These strains, particularly type 12, therefore appeared to be specifically nephritigenic. Further studies with type 12 indicated that this organism may attack the kidneys directly at the beginning of infection, in that microscopic hæmaturia was noted about 3 days after infection with this organism, though clinical symptoms developed later.

Distribution of Poliomyelitis in the Epidemic Community.—It is now usually accepted that in epidemics of poliomyelitis a large percentage of susceptible individuals are infected, though few develop the clinical disease. Evidence for this view is the increasing resistance with age, presumably from an active immunity acquired through subclinical infections, suggesting that the infection-rate is high. THOMAS FRANCIS, jun., and his colleagues studied large segments of the community in areas of poliomyelitis epidemics, examining stools from most of the children and many of the adults for polio virus. Their results demonstrated a high incidence of infection in persons in the household of children with clinical poliomyelitis, and a moderate incidence in the close contacts of such children. In the remaining population the incidence of infection was extremely low. Judging from these findings, contrary to the general belief, the infection in polio is concentrated in households where clinical cases occur, and the virus is not uniformly distributed in the community.

Isonicotinic Acid Hydrazide in Tuberculosis.—WALSH MCDERMOTT, CARL MUSCHENHEIM, CHARLES M. CLARK, DUMONT F. ELMENDORF, jun., and WILLIAM N. CAUTHON reported on 80 patients treated at New York Hospital and the Arizona Navajo Reservation. They pointed out first that the maximal activity of the drug in vitro is against active growing bacilli, and that there is no effect against resting organisms; that 0·05 µg./ml. will repress growth in vitro, but 80 times this concentration is needed in the serum. The drug is excreted by the kidneys, and diffuses throughout the body-fluids and to a lesser extent into the cerebrospinal fluid. It is active at the low pH range of inflammatory tissue, unlike streptomycin, and is effective against intracellular as well as extracellular forms of the organism. In the patients studied, the usual dosage was 5 mg./kg./day, given in 3 or 4 divided doses. In meningeal or miliary tuberculosis larger doses, up to 10 mg./kg./day, were used for the first week. *No* toxicity was noted at these dosages. The best results were in patients with miliary and/or meningeal tuberculosis where the course and outcome are known and predictable. Of the 9 miliary cases studied, 4 of which had meningitis, 2 began treatment too recently to be reported on; 2 have died, and 5 have recovered. Improvement was observed within 7 days of the start of therapy. X-ray clearing was seen in 2–4 weeks, and defervescence of clinical disease in from 7 days to several weeks. There was definite evidence that the drug possessed a high degree of antituberculous activity. Of 8 cases with meningitis alone, 2 died within the first week of treatment; the other 6 improved, though not so dramatically as the miliary cases. Though 38 pulmonary cases have been studied, only 9 have been observed for 3 months or longer. Most have shown general improvement with improved appetite, gain in weight, fall in temperature, and lessening of cough. No patient has suffered an increase in his disease while under treatment. However, while the evidence supports the view that the drug is highly active in pulmonary tuberculosis (as in miliary and meningeal), the observations have been too short for definite conclusions to be drawn. As to bacterial resistance, this is a much more complicated problem than with streptomycin, since one can find strains resistant to this drug in any patient, whether or not he has been treated with it. The indications are that for the tubercle bacilli to develop a significant degree of resistance will take at least as long as with streptomycin.

Excretion (and Absorption) of Co^{60}-labelled Vitamin B_{12} in Pernicious Anæmia.—After giving vitamin B_{12} labelled with radioactive cobalt, by mouth ROBERT W. HEINLE, ARNOLD D. WELCH, VICTOR SCHARF, GORDON C. MEACHAM, and WILLIAM H. PRUSOFF studied stool excretion of the vitamin in normal subjects and P.A. patients. The normal people were found to absorb most of a small dose (0·5 g.). With larger doses there was less absorption. Adding intrinsic factor (derived from human gastric juice or hog-stomach extract) did not increase absorption. Four P.A. patients, however, were found to excrete 72–96% of orally administered radioactive B_{12} in their stools. When small amounts of intrinsic factor (3–10 mg.) were added, then stool excretion dropped to 25–30%. Larger amounts of intrinsic factor did not lead to any further absorption, though when less intrinsic factor was added absorption decreased. This poor absorption of B_{12} and the improvement with additional intrinsic factor might prove a useful tool in the diagnosis of pernicious anæmia, particularly in patients who have been treated before a reliable diagnosis has been made.

CHIEF CHARACTERISTICS OF NERVE GAS

WITH NOTES ON FIRST-AID TREATMENT *

"Nerve gases" are liquids with boiling-points varying from 150° to 250°C (approx.). They are therefore roughly comparable in volatility to kerosene. They are fairly soluble in water and are slowly destroyed by hydrolysis. Alkalis such as solutions of caustic soda or washing-soda will decompose them more quickly. They are almost odourless and the vapour is invisible. They have no immediate irritant properties either to the eyes, skin, or respiratory tract. No warning of their presence is therefore given to the subject exposed to them.

MODE OF ACTION

Their very dangerous and insidious qualities are primarily due to the fact that their action is that of cholinesterase inhibition—i.e., they prevent the action of the enzyme which, under normal conditions, continuously destroys acetylcholine in the body as it is produced. This leads to the accumulation of acetylcholine and hence all neuromuscular mechanisms are upset. Voluntary muscle, including the muscles of respiration, ultimately becomes paralysed and smooth muscle passes into a state of spasm. In effect there is a generalised parasympathetic stimulant action.

The total amount of cholinesterase in the body is small and nerve gases inhibit this enzyme for a prolonged period. Therefore, these gases are highly toxic and may be lethal in minute concentrations. They are rapidly absorbed either by inhalation of the vapour, absorption of the liquid through the skin and mucous membrane, or by the ingestion of contaminated food or water. A drop of liquid in the eye or the inhalation of a high concentration of vapour for a few seconds may cause incapacity or death within a few minutes. Liquid on the bare skin penetrates somewhat less rapidly, but two or three drops may kill within half an hour. Ordinary clothing cannot be relied on for protection as it is quickly penetrated.

The inhibition of cholinesterase activity may persist for many weeks so that repeated exposures to very low concentrations may have a cumulative effect.

SIGNS AND SYMPTOMS OF POISONING

These can be divided into primary and secondary.

Primary due to direct action of the nerve gas.—There is copious salivation, slowing of the heart, constriction of the pupils, headache, nausea, diarrhœa, vomiting, muscular weakness, and sometimes generalised muscular fibrillation. The muscles of respiration are weakened or paralysed, the diaphragm being affected most. The bronchial musculature may be in spasm.

Secondary due to the anoxia brought about by respiratory paralysis.—This will produce cyanosis, venous congestion, low blood-pressure, convulsions, and possibly pulmonary œdema.

Death occurs suddenly from the effects of the anoxia.

CLINICAL FEATURES

Since comparatively few cases of poisoning have occurred, the clinical picture is as yet imperfectly known. The following summarises the features which have been recognised.

A severe case of nerve-gas poisoning will present itself as one of acute asphyxia. The subject may be unconscious from anoxia with cyanosis, sweating, and pallor. Breathing will be laboured and wheezing in character, similar to that of an acute asthmatic attack. While conscious, the subject will be anxious and suffering from air-hunger, there may be restlessness and lack of coöperation due to the effects of the anoxia.

In mild cases the main respiratory symptom will be tightness of the chest and throat. There will be intense headache, constriction of the pupils, and difficulty of near vision. There may be nausea, vomiting, dizziness, abdominal pain, and diarrhœa. These symptoms may commence several hours after exposure and may persist for days if untreated.

POST MORTEM

No specific changes other than those due to anoxia are found. The accumulation of acetylcholine causes death by an interference with function and not by destruction of tissue. There is cyanosis of the viscera and blood and congestion of the brain and conjunctivæ. There may be a dilation of the heart. The speed of post-mortem autolysis will be increased.

TREATMENT

To be of use this must be immediate, because of the danger from anoxia. Atropine is the antidote to the nerve gases. If there is severe respiratory distress and cyanosis, artificial respiration must be started at once and maintained until adequate respiration returns of its own accord.

Antidote.—Subjects suffering from nerve-gas poisoning tolerate large doses of atropine. An initial dose of 2 mg. (gr. $^{1}/_{32}$) should be given intramuscularly. This dose should then be repeated—by either the intravenous or intramuscular route—until such time as the symptoms of poisoning disappear. A useful sign of the degree of atropinisation achieved is the pulse-rate, and the dose of atropine should be repeated so as to maintain a pulse-rate of 110–120 beats/minute. (The

Fig. 1.

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* A memorandum from the Ministry of Supply.

signs of atropine poisoning are largely psychotic, with mania, extreme excitement, and restlessness. The latter must not be confused with the restlessness that occurs following anoxia. As much as 12 mg. atropine sulphate in 16 hours has been given in nerve gas intoxication.)

Artificial respiration.—The method recommended is a small hand bellows which will ventilate the lungs in spite of the bronchial constriction. When using the hand bellows the patient should be supine and the attendant should kneel to the right of the head. His left hand should encircle the face and hold the face-piece firmly in position (fig. 1); the face-piece must fit under the chin. The attendant's other hand should work the bellows so that the main force is exerted at an angle of 30° to the horizontal (fig. 2). This is to ensure that the lower jaw and tongue do not fall back and obstruct the air-passages. The pressure used should not exceed 20 cm. of water, since with higher pressures the lung and stomach may be overinflated. The resuscitator illustrated has a safety valve on the face-piece which blows off at 20 cm. Ventilation should be carried out at a rate of 20 to 30 times a minute and should be continued until the subject is capable of breathing adequately himself. This will probably occur within 30 minutes, but it must be remembered that respiration may fail again due to excessive elimination of carbon dioxide during the artificial ventilatory period; hence the subject should be kept under observation. During artificial ventilation the stomach will be inflated with air by the resuscitator. This will cause some respiratory embarrassment when normal respiration is re-established. It can be minimised, however, by firm pressure over the stomach, applied intermittently to force the air up the œsophagus. During this manœuvre the patient's head and shoulders should be raised, so as to ensure that it is air and not the liquid contents of the stomach which is forced into the œsophagus. While artificial ventilation is being carried out, there will be excessive salivation and, if practicable, this should be allowed to drain away by periodically tilting the subject's head down. If no form of positive pressure ventilatory apparatus is available then manual artificial respiration should be performed. Oxygen, if available, should be used in conjunction with this.

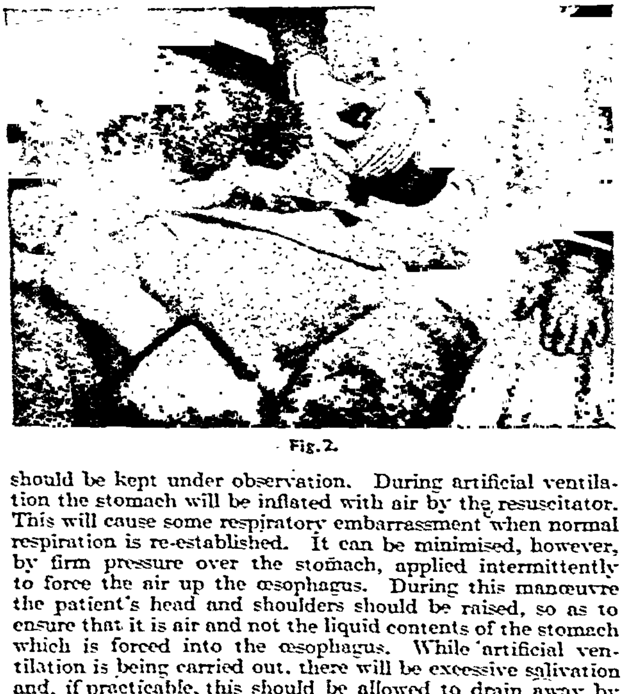

Fig. 2.

In mild cases of nerve-gas poisoning the eye symptom and headache are best treated by the instillation of atropine drops or ointment in the eye. This should be used as an adjunct to parenteral atropine therapy if necessary.

DECONTAMINATION

In the event of toxic liquid being splashed on the skin it should be washed off immediately with plenty of water. As soon as this has been done, ordinary anti-gas ointment should be applied as the subject will be unable, at this stage, to know whether the liquid is nerve or mustard gas.

If the clothing is contaminated, the outer clothing should be removed at once and the skin washed as soon as possible.

The above first-aid treatment should be within the competence of trained non-medical personnel and, in certain emergencies, will have to be carried out by them to save life.

In England Now

A Running Commentary by Peripatetic Correspondents

THE subject is wastage in beddage—horticultural, domiciliary, and institutional.

Crawling over a neglected flower-bed, I began to wonder why we laboriously collect the decayed greenery, transfer it to the compost-heap, turn it, secundem more or less artem, into compost—which would be done by Nature and Time if it were left in situ—only to transfer the result back to the original beds in due course. No doubt a neglected bed is a better medium for insects and other pests; but mere tidiness, the gardener's Old Man of the Sea, plays a big part. A welcome transition brought me to my Morphean couch; and here again I spent time and effort removing the bedspread, the eiderdown, and most of the blankets, which are unnecessary in summer but which feminine tidiness replaces—without, usually, the excuse of pest harbourage—every morning in a hundred thousand homes.

Next day, brooding over some statistics which seemed to show extraordinary variations between the turnover per bed in comparable hospitals and departments, I began to wonder whether the same factor might not be at work. How Sister's heart must rejoice at the incomparable tidiness of a well-made empty bed compared to the amorphous and unattractive spectacle of a bed with a patient in it! To those immediately concerned, a high turnover brings more work—and nothing much else. Yet if an empty bed always called for an explanation our waitage might show shrinkage.

* * *

Pending the arrival of atomic energy as the everyday means of supplying most of our material needs we ought, I feel, to be making more widespread use of interim measures. Think, for example, of all the energy expended and at present running to waste in the whole field of sport. If we could but harness all the work done in all the football matches throughout the season we should be well on the way to providing ourselves with all the electricity we need. And think of the ergs that go down the drain, so to speak, in any given cricket season, Grand National, Henley, or Wimbledon—to say nothing of Olympic Games. Nor should we neglect those unnamed heroes and heroines who bicycle madly about the country at weekends, nor those who pad around on dance floors for hours on end.

To chaps who understand these things erg-collecting on this grand scale should present but a trifling problem in applied science.

* * *

Others have remarked—perhaps even in these columns—that the world seems to shrink every year, and at an increasing rate. No sooner has one adjusted one's ideas to rounding the world in 80 days than somebody does it in a week, 3 days, 2 days, and so on. It didn't seem natural to me that I could spend 13 days on holiday in Newfoundland and be back again before Billy Bloggs was free of infection from the chickenpox I diagnosed on the day I set out. But so it was.

Prestwick to Gander was a 10½ hours' trip, and the tilt-back chairs, with barley-sugar and blankets thrown in, made the journey less trying than a long railway journey. Gander was dark, cold, and uninteresting; but Newfoundland itself, with its forests, lakes, and rivers, is a grand place for holidays of the heartier kind. Unexpectedly the mosquitoes did not bite—presumably they could find better fare than a British-fed G.P. We swam, we boated, we sunbathed, and we ate. We drove the 180-odd miles to Corner Brook to attend some medical lectures and inspect the newly opened hospital and sanatorium, which incidentally compare favourably with their opposite numbers in Britain. We went to Grand Falls and explored the paper mill. We visited Botwood and its hospital, and took a boat down the river. At Bishops Falls I swam in the Exploit, ate a week's ration of meat at a sitting, saw the local robins which are as big as our thrushes, and was chased by a bittern. I sat through a baseball match, sampled hamburgers and "spare ribs," and listened to "Laura," the Newfoundland equivalent of Mrs. Dale, on the radio. For 13 days I forgot all about telephone calls and night bells.

Back at Gander I was told that my B.O.A.C. plane was held up with "mechanical trouble" in New York; but the ever-helpful airport officials found me a seat on a Pan-American plane, and in 12 hours I was in London, after a holiday that was "completely different" and one of the best ever.

* * *

Complaints of over-specialisation in the profession and fears for the status—or the continued survival—of the G.P. are no new thing. In 1500 B.C. the citizens of Thebes were lamenting the lack of good family physicians of the old school, for Herodotus later reported: "The practice of medicine is so divided among them that each physician is a healer of one disease and no more. All the country is full of physicians, some of the eye, some of the teeth, some of what pertains to the belly."

It seems strange that the ancient Greeks did not have a word for each and every specialty, but perhaps they had more respect for their language, from which we moderns fashion such monstrous hybridisms.

* * *

A letter we have had from our regional hospital board begins with this sentence:

> "Under a suggestion made by the Department of Health for Scotland, the *Regional Hospital Board has been considering* the possibility of the establishment of some periodically-functioning machinery through the agency of which the effects of changing circumstances upon the individual time-factor of medical staff contracts may be ascertained."

It left most of us "like one that hath been stunned and is of sense forlorn."

* * *

I have never been able to understand the intricacies of sight-testing, with its cylinders and sphericals and axes and dioptres, and when I visited an optician lately for a check-up on my friendly but failing glasses, I was greatly impressed by the latest contraptions for accurate measurement. I was duly impressed, too, when, after a succession of flicks and clicks, I was able to read the smallest letters at the prescribed distance and see transverse and horizontal lines in the uniform black of corrected astigmatism. In a week or two I got my new glasses, splendid things that gave me a fine feeling of dignity and importance.

A few days later when I was shaving, and more than usually interested in my face, I noticed that the hinges of my new spectacles were not bilaterally in alignment with my external canthi—one hinge being above and one below. Greatly worried lest I might be wearing out my eyes by making them look through cockeyed lenses I called on the optician. He was gracious; he smiled at my complaint; he asked me to look at the bridge of his nose. I noticed that his glasses were very neat. I felt confident. "You see," he said, "your glasses appear to be just a fraction of a millimeter out of the level when judged by the corners of your eyes; but that's your fault—your eyes aren't exactly level, nor, for that matter, your ears." "So that's it, is it?" I said. I know that one of my shoulders droops, because I've been told repeatedly by my various tailors; but I have my full share of vanity when my face is the subject of conversation. So I did not follow up the pros and cons of my asymmetry. After all, I thought, I might easily be told I wasn't level-headed.

* * *

There has been a good deal of discussion lately about the free use made of human volunteers in experimental work. Some of them seem to be very willing and very tough, judging by a description in the *Proc. Soc. exp. Biol. Med.* (1952, 79, 296) of the treatment given to a pharmaceutical graduate. Some of the details of his, or her, experiences are unfortunately left to the imagination, but, "the filter candle" we read "was placed in a pharmaceutical graduate with a narrow bottom . . . the filterable material was then removed through the filter by suction. . . ." Then there is a reference to "the non-filterable residue on . . . the bottom of the graduate." We are also told that "all these procedures were carried out at about 0°C." I think I should have found the technique easier to follow if the article had been illustrated.

Letters to the Editor

MALARIA IN EX-SERVICEMEN

SIR,—The letters from Professor Macdonald and from Dr. Adams and Dr. Seaton in your issue of July 5 emphasise once more the importance of thinking of malaria when a Serviceman, or ex-Serviceman, presents with an unexplained fever.

Since February, 1952, no fewer than 52 cases of malaria have been treated in the Military Hospital, Tidworth. 31 of these patients have served in Korea, 15 in Malaya, and 6 in Hong-Kong. Without exception the patients had been on a suppressive dose of 100 mg. of proguanil ('Paludrine') daily while overseas; the drug was stopped either on embarking at the overseas port, during the voyage home, or just before disembarking in this country. Most of the cases were experiencing their first attack and it is noteworthy that, in the majority, symptoms did not begin until six months after stopping suppressive proguanil.

In all the cases the parasite was *Plasmodium vivax*, which causes the "benign tertian" fever. Some showed the typical high fever preceded by a rigor and followed by an afebrile phase; others complained merely of vague generalised body pains and headaches, and these were often accompanied by a low irregular fever. On the whole the illness has not been severe and in many of the cases the spleen was not palpable. Recovery, on specific treatment, has been rapid and so far only 1 case has had a relapse.

Military Hospital, Delhi Barracks,
Tidworth, Hants.

R. G. MACFARLANE.

*** It will be useful to many readers to have particulars of the methods of malaria treatment now used in the Army, and we are glad to be able to publish here some extracts from notes put at our disposal by the Director-General of Army Medical Services.—ED. L.

From time to time general practitioners in this country are called upon to treat malarial attacks in ex-Service personnel who have recently returned from overseas, or in Service personnel on leave. Relapses of benign tertian infections are most frequently met with; but it should be remembered that the initial clinical attack may occur in the United Kingdom although the actual infection took place months previously. Less commonly, malignant malaria may occur for the first time in a patient recently returned from the tropics.

Delay in diagnosis may have disastrous consequences, especially in virulent or heavy falciparum infections, when cerebral symptoms or collapse may occur with dramatic suddenness. The key to the diagnosis is the finding of malarial parasites in the blood, and in all suspected cases blood films should be taken at once and steps should be taken to have these examined without delay.

In the treatment of benign tertian malaria, quinine and pamaquin, or 'Chloroquine' ('Nivaquine' is the British equivalent) and pamaquin, should be used. The following course is the most likely to cure the condition and lessen the chance of relapse:

> Quinine bihydrochloride gr. 10 t.d.s. for 14 days in conjunction with pamaquin 0·01 g. t.d.s. for 14 days.

If the patient has had a previous attack the length of the quinine-pamaquin course may be extended to 21 days.

As an alternative chloroquine (nivaquine) may be given as follows:

1st day: 0·9 g. base (6 tablets).
2nd day: 0·6 g. base (4 tablets).
3rd to 5th day: 0·3 g. base (2 tablets). Total: 16 tablets

with pamaquin in the same dosage as before. During this treatment the patient should not be allowed to go about and is best treated in bed.

Malignant tertian malaria without pernicious manifestations can be treated with the course of chloroquine given above. Pamaquin is not required, for there is little tendency to relapse. However, it is best to have such cases admitted to hospital, because severe or pernicious symptoms necessitate the immediate administration of intravenous quinine. Mepacrine is still used in the routine treatment of uncomplicated malignant tertian malaria and as an alternative to quinine or chloroquine. The recommended course is:

1st day: 0·3 g. (3 tablets) t.d.s.
2nd and 3rd days: 0·2 g. (2 tablets) t.d.s.
4th to 7th day: 0·1 g. (1 tablet) t.d.s.

Proguanil ('Paludrine') is not used in the treatment of malaria in the Army, although it is extensively used for suppression and has almost completely replaced mepacrine for this purpose.

SKIN BANKS

SIR,—The institution of "skin banks"—i.e., stores of human skin that might be drawn on for certain acute surgical emergencies—is known to be technically feasible.[1] On the other hand, it is almost universally agreed that skin homografts can never be used for permanent repair, so that apparently such banks could at best be of only very minor value. My purpose here is to show that the expectation that skin homografts will always fail is needlessly pessimistic.

It is not known with certainty how many distinct antigenic factors there are which, present in the homograft but absent from the recipient, will cause a homograft to break down. From what is known of skin grafting in rabbits[2] and the transplantation of tumours in mice,[3] it may be said that 20 is a fair guess, in which case the number of possible antigenic compositions is over a million.

If A and B are two individuals selected at random from the population, then the probability that B's skin would form a permanent graft upon A may be as high as 1/300. Thus a bank containing the skin of a few thousand individuals may have a high probability of containing skin acceptable by a random individual in need of a graft. (The bank would differ from a blood bank in that there would be no certainty.) The bank could, of course, consist merely of a card index, provided that the donors themselves were readily accessible. All this depends on the ultimate possibility of being able to analyse antigenic composition, and researches which may lead to successful antigenic analysis are thus of more than academic interest. An individual who had volunteered as a donor would have the advantage that if he became a casualty his composition would be known without delay.

Among the thousands of skin-homografting operations that have been tried in a speculative spirit by surgeons, just a few between unrelated individuals may well have succeeded. In 1943 Medawar[4] said: "It is certainly possible that isolated genuine claims for the persistence of homografts have been overridden by our now almost comprehensive scepticism," but he informs me that he did not really think it was at all likely. Any alleged claims of success should be supported by the fullest documentary evidence, since the prior chance of success on any given random occasion is small, even if larger than has often been supposed.

A curious fact is that a knowledge that B's skin is tolerated by A decreases the chance that A's skin is tolerated by B, assuming that A and B are not relations. (This result can be completely proved if no set of antigens are determined by multiple allelic genes other than diallelic ones.) It follows that when testing two individuals for being identical twins rather than being unrelated it is important that grafting should be done in both directions, as in a recent example.[5]

A skin antigen has (by definition) the property that if it is present in B but not in A, then B's skin is not acceptable by A. The condition for the acceptance of B's skin by A is, then, that A should "antigenically include" B—i.e., that A should have every skin antigen that B has.

Let the possible human skin antigens be $a_1, a_2, \ldots, a_n$ and assume for the present that no group of these is determined by allelic genes. Let the probability that an individual has antigen a_i be p_i and write $\pi_i = 2p_i - 1$. The probability that A does not have a_i while B does is $(1-p_i)p_i = (1-\pi_i^2)/4$. The probability that a_i is harmless when B is the donor is therefore $1-(1-p_i)p_i = (3+\pi_i^2)/4$. Assuming independence, the probability that A "antigenically includes" B is

$$p = \prod_{i=1}^{n} \frac{3+\pi_i^2}{4} \cdot \qquad (1)$$

If there is linkage the probability will be even higher. Now it may be optimistic to take $n = 20$ but it would be pessimistic to take all the π_i's equal to zero. So it may not be far from the truth to say that

$$p \simeq \left(\tfrac{3}{4}\right)^{20} \simeq \frac{1}{300} \qquad (2)$$

The probability that A's antigens include B's and vice versa—i.e., that A and B are antigenically the same—is

$$q = \prod_{i=1}^{n} \{p_i^2 + (1-p_i)^2\} = \prod_{i=1}^{n} \frac{1+\pi_i^2}{2} \cdot \qquad (3)$$

It is easily seen that $p^2 > q$ since

$$\left(\frac{3+x^2}{4}\right)^2 \geqslant \frac{1+x^2}{2},$$

equality occurring only if $x = \pm 1$. The inequality $p^2 > q$ implies the "curious fact," mentioned above, for the case where no two antigens are determined by allelic genes.

A slight modification is required corresponding to diallelic pairs, a_i, b_i (analogous to the blood factors M, N in man). The probabilities of the compositions a_ia_i, a_ib_i, and b_ib_i are p_i^2, $2p_iq_i$, and q_i^2 where $q_i = 1 - p_i = \frac{1}{2}(1-\pi_i)$. The factor $(3+\pi_i^2)/4$ in (1) should then be replaced by $p_i^4 + 2p_iq_i + q_i^4 = (5 + 2\pi_i^2 + \pi_i)/8$. This is slightly greater than $\left(\frac{3+\pi_i^2)}{4}\right)^2$ so we are slightly better off when two antigens are found to correspond to diallelic genes. (This result does not generalise to the triallelic case.) For example, if $n = 20$ and if the antigens correspond to ten pairs of diallelic genes and if all $\pi_i = 0$, then p is $(5/8)^{10} \simeq 0{\cdot}01$.

The probability that A and B are antigenically the same with respect to a diallelic pair is $p_i^4 + 4p_i^2q_i^2 + q_i^4 = (3 + 2\pi_i^2 + 3\pi_i^4)/8$. The "curious fact" is now implied by the inequality

$$\left(\frac{5+2\pi_i^2+\pi_i^4}{8}\right)^2 \geqslant \frac{3+2\pi_i^2+3\pi_i^4}{8}.$$

This fact also does not apply to the triallelic case in complete generality.

I am much indebted to Prof. P. B. Medawar, F.R.S., for encouragement and useful suggestions.

London, N.W.2. I. J. GOOD.

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[1] Billingham, R. E., Medawar, P. B. *J. exp. Biol.* (In the press).
[2] Medawar, P. B. *J. Anat., Lond.* 1945, 78, 176.
[3] See Little, C. C. *In* The Biology of the Laboratory Mouse. Philadelphia, 1911; chapter 7.
[4] Medawar, P. B. *Bull. War Med.* 1943, 4, 1.
[5] Franceschetti, A., Bamatter, F., Klein, D. *Bull. Acad. suisse Sci. méd.* 1948, 4, 133.

MILIARY TUBERCULOSIS DURING CORTISONE THERAPY

SIR,—I have recently seen a similar occurrence to that described by Dr. Harris-Jones and Dr. Pein in their article of July 19 (p. 115).

My patient, a woman of 25, was first seen in May, 1950, with typical subacute systemic lupus erythematosus; she had a characteristic rash, arthritis, and fever with the usual biochemical and hæmatological findings. With one or two remissions she survived until March, 1951, when she was admitted to hospital in an acute phase; at this time Hargraves's cells were numerous, the direct Coombs's test was positive, and cold agglutinins were present in the blood to a titre of 1/128 at 18°C (there was even some agglutination at 37°C). The initial response to cortisone in doses of 200 mg. a day was dramatic. However, this was not maintained and the symptoms started to "escape" after two weeks of treatment. At the end of a month she had received 3500 mg. of cortisone, and it is interesting to note that during this period the striking hyperglobulinæmia (albumin 2·0 g., globulin 5·4 g. per 100 ml.) never varied. By the time cortisone had been stopped she had developed deafness, and other symptoms of tuberculous meningitis soon became apparent; this was confirmed by lumbar puncture, and she died a meningitic death. At necropsy the meningeal changes were typical, and the focus from which tuberculosis had disseminated was a soft but partly calcified paratracheal gland; there was no active lesion in the lungs. A further interesting observation was that during cortisone treatment she developed a whitlow which had failed to heal after five weeks. It was felt that this delayed healing was comparable to the breakdown of a previously well-scarred tuberculous focus.

I feel that the lighting up or reactivation of a latent tuberculous focus during the administration of cortisone is directly comparable to the behaviour of the whitlow in my patient. I have little doubt that tuberculosis is sometimes an important factor in the pathogenesis of both discoid and systemic lupus erythematosus, but it is not invariably so, and the evidence produced by these two patients does not specifically incriminate tuberculosis as the cause. Streptococcal infections are as frequently culpable, as are many other infective processes, drug reactions, and more obscure phenomena. Lupus erythematosus should not be classified (as it is in many textbooks) with tuberculous diseases of the skin, but rather with erythema induratum and erythema nodosum, which are morphological reactions stimulated by many processes, of which tuberculosis is only one.

St. George's Hospital,
London, S.W.1.

STEPHEN GOLD.

HOSPITAL HYGIENE

SIR,—Recently I returned as a patient to my old teaching hospital, one of the largest in the country. Whilst my treatment was exceptionally good in every way, I was astonished at the primitive method of washing crockery on the wards.

I wonder how many hospitals have heard of the researches of Dr. Betty Hobbs and her colleagues on this matter, and whether any hospital practises the two-sink method. So long as hospitals are backward in this respect it is difficult for the medical profession to exert strong pressure on the café proprietor. Possibly some useful work might be done by hospital bacteriological laboratories.

M.O.H.

EXTENDING BATTLE'S INCISION

SIR,—Battle's incision has many advocates and detractors, each group with strong feelings on one or more of the drawbacks or advantages of its use. While preferring the crease incision wherever possible, and the paramedian if there is any real doubt as to diagnosis, I have often used Battle's incision. From time to time when using this incision I have, on opening the peritoneum, found conditions (e.g., intestinal, ovarian, or uterine) which could not be handled within the safe limits of extension of this incision. On these occasions I have found the following manœuvre simple and effective.

The small opening in the peritoneum is usually made vertically, behind the nerves, if necessary, and, on deciding that much more room is required, the wound is allowed to fall back into its natural layers. The skin incision, just external to the middle of rectus muscle is freely extended in this line. The incision in the anterior sheath is now also extended, but passes more medially as it goes till it is on the medial side of the middle line of the rectus. The muscle, with its vessels and nerves is now displaced laterally, till we meet our original incision in the peritoneum, and this can be enlarged as much as required—as in the paramedian incision which, indeed, it now is.

I have not seen or heard of this method in use, and feel it may be of interest to others faced with a similar problem.

Senior Surgical Registrar,
Wolverhampton Group of Hospitals.

HENRY B. YOUNG.

SUCCINYLCHOLINE

SIR,—I was interested to read the letter by Dr. Kay (July 26) on the use of succinylcholine in 30 appendicectomies. I have been using this drug recently, usually in conjunction with the thiopentone–nitrous oxide/oxygen–pethidine sequence, to produce muscle relaxation in various operations. My findings agree with those of Dr. Kay. The cases have included appendicectomies, herniorrhaphies, repairs of perforated peptic ulcer, [illegible], several laparotomies, and two subtotal [illegible] appendicectomy and herniorrhaphy a total dosage of 100–150 mg. in divided doses is usually ample.

Succinylcholine has been especially helpful to the surgeon in herniorrhaphies, for it allows relaxation and normal muscle tone to be produced at will, so enabling the surgeon to determine exactly how much to close the internal ring, and how tight to make the 'Nylon' repair.

Dr. Kay writes: "Whether it is possible to retain spontaneous respiration still seems uncertain." In my limited experience it has been possible with a continuous drip to maintain spontaneous respirations of reduced amplitude and yet obtain "spinal-like" relaxation. However, the dose which produces relaxation is so close to that which causes paralytic apnœa that spontaneous respiration may be difficult to maintain with intermittent doses.

A drawback to the use of succinylcholine in major abdominal surgery would appear to be a tendency to increased bleeding associated with a moderate hypertensive effect. I have observed this on several occasions even though the total dosage of the drug was minimal —e.g., 450 mg. over 2 hours and 800 mg. over $2^1/_4$ hours for two subtotal gastrectomies. Possibly some degree of carbon dioxide retention was responsible.

London, N.16.

E. HARVEY FRANKS.

SIR,—I agree with Dr. Foldes (Aug. 2) that a dose of succinylcholine chloride that is less than 1·1 mg. per kg. is sufficient for intubation. In our paper we stated (p. 1226): "These doses (1·1 mg. per kg.) are safe, but smaller ones were often found satisfactory." I believe that the optimum dose lies between 0·55 and 1·1 mg. per kg. In a few patients receiving 0·55 mg. per kg. relaxation was only just adequate.

In my experience with 740 patients, using doses within this range, I have occasionally found slight delay in recovery, but in no patient did apnœa exceed 15 minutes.

Dr. Foldes regards apnœa as an undesirable side-effect of using a muscle relaxant. When using a short-acting relaxant, such as succinylcholine, I do not agree with this. A patient fully paralysed and artificially ventilated provides better operating conditions than one in whom both respiration and relaxation may be inadequate. This difference from Dr. Foldes in viewpoint accounts for why I prefer a higher dose by intravenous infusion for abdominal relaxation.

I agree with Dr. Green (Aug. 2) that I have used by infusion doses which are greater than necessary for complete relaxation, and that with smaller doses delay in recovery is less likely. Nevertheless, contrary to his statement, the doses I gave fell within the range (2 to 15 mg. per minute) which Dr. Green found effective.

Before using succinylcholine for abdominal relaxation it is advisable to test the patient's ability to recover from a standard dose. This test may conveniently be made at the time of intubation by giving a dose that is 1·1 mg. per kg. immediately following thiopentone. The duration of the ensuing paralysis is a guide to subsequent dosage, whether by intermittent injections or by continuous infusion.

London, S.E.1.

J. G. BOURNE.

SORE THROAT AND RHEUMATIC FEVER

SIR,—The letter from Dr. Alice Stewart and Mr. David Hewitt (July 19) reveals what seems to me a tortuous method of reasoning. The value of tonsillectomy in preventing acute rheumatism is assessed on an analysis of a tiny number (70) of children who had suffered from tonsillitis but not developed rheumatism, and a minute number (31) of rheumatic children who have previously suffered from tonsillitis. I am irresistibly reminded of the pottery manufacturer who discovered that not one of 100 users of his pottery had suffered from acute appendicitis, whereas every one of 100 cases of appendicitis had used glass-ware in one form or another. The inference was obvious.

Surely the only sound way to assess the value of tonsillectomy in preventing rheumatic fever is to follow up the history of a few thousand children who have had their tonsils removed for tonsillitis, and a few thousand children who have not had their tonsils removed in spite of tonsillitis, and to find out what proportion of the two groups subsequently developed rheumatic fever. This was done over 20 years ago by Kaiser.[1]

R. N. CURNOW

Truro, Cornwall. County Medical Officer.

INTRA-ARTERIAL TRANSFUSION

SIR,—Prof. D. L. C. Bingham (July 26, p. 157) appears to be unaware of all the experimental and clinical work which has been done in the Soviet Union on resuscitation by intra-arterial centripetal blood-transfusion after the publication of Birillo's article in *Khirurgiya* of 1939. One of the chief aims of such transfusion has been to raise the pressure in the ascending aorta sufficiently to re-establish the circulation in the coronary arteries: the blood-pressure is then maintained, in successful cases, by the force of the resumed cardiac contractions.

London, S.W.16. L. CROME.

SIR,—Professor Bingham has done a service in emphasising the value of intra-arterial transfusion. His conclusion, based on a relatively large number of cases, that this route is far superior to the intravenous one in the prevention and treatment of oligæmic shock, agrees with the clinical and experimental findings of others and indicates the need for all to be familiar with the intra-arterial route if the maximum of lives is to be saved.

Unfortunately, the use of peripheral arteries in this procedure is somewhat hazardous, and Professor Bingham adds one more case of peripheral gangrene to those already reported. In addition, there may be difficulty in entering the lumen of a peripheral artery contracted in severe shock, and vasoconstriction can interfere markedly with the transfusion in the very cases where it is most needed.[2]

These difficulties and dangers are obviated by the intra-aortic route which I have practised for twelve months, with a report on the first 10 cases.[3] The needle used is a stepped one, rather like a Finsterer splanchnic needle, with a stem 16 cm. long by 3 mm. diameter and a terminal section 0·75 cm. long and 1·5 mm. diameter. This is inserted in the left lumbar region much as for paravertebral injection of the sympathetic chain but rather further from the midline. The point can be quickly and easily inserted into the aorta and blood introduced rapidly under pressure. I use a simple apparatus similar to that of Professor Bingham but with a two-way tap at the site of his Y-tube. This allows direct readings of the aortic blood-pressure to be made, and these are interesting and helpful in assessing the response to the transfusion. Cases varying in age from two days to eighty-four years have received transfusions by this route, and my impression is that improvement in the general condition is much more rapid than with intravenous transfusion of similar amounts. For example, 3 patients exsanguinated by repeated gastric hæmorrhages were restored to good general condition with 1½–2 pints of blood in twenty minutes, and came through immediate partial gastrectomy without any trouble.

The aorta is relatively constant in position, contains little muscle tissue and so cannot go into spasm, and is sufficiently wide to preclude any chance of obstructive thrombosis developing. Puncture with a reasonably fine needle is free from complications; large series of punctures for aortography have been reported without mishap, and in those patients of mine who died because of the primary disease post-mortem examination revealed little or no trace of the procedure.

In addition to its suitability for preoperative transfusion, the aorta is accessible in both abdominal and thoracic operations, and direct transfusion with a shorter needle could be easily and quickly carried out. It is now my practice to have a suitable apparatus at hand during the performance of such operations as those for Fallot's tetralogy and aortic coarctation lest the need for rapid transfusion should arise.

Crumpsall Hospital,
Manchester. H. A. HAXTON.

MORE MANURE

SIR,—Your annotation of April 12 refers to an address given to the Royal Society of Arts by Mr. J. C. Wylie, of Dumfries. I should like to add a contribution to what Mr. Wylie said on sewage wastes. With the idea of saving money every farmer seeks to dismiss labour. He regards labour as the greatest item of cost in production. He buys a machine and dismisses a man, with the result, from the nation's standpoint, that labour is transferred from the land to the factories. The consequence of this craze for the dismissal of labour (which is leaving our land in thousands a year) is that every operation has to be mechanised and simplified. The spreading of bulky farmyard muck becomes less possible, and the substituted spreading of artificial fertilisers is so easy. The fact that it costs a lot of money to buy artificials does not seem to weigh with farming intelligence. The husbandman is so determined to reduce wages that he dismisses a man and buys more machines and more artificials. This is leading the country into a serious state of affairs, because diseases of all kinds are beginning to show themselves in both crops and livestock, and they are not yielding to remedial treatment.

With the spread of disease, the problems of the farm are mutiplying; but the farmer continues to dismiss his men and buy more machines. This brings me to the problem underlying Mr. Wylie's recommendation—namely, that of composting sewage wastes and making use of these as fertilisers on the land. These sewage wastes, mixed with farmyard manure and an adequate amount of waste vegetation (the latter is an elementary essential) would make a re-fertilising agent of immense value, but the labour is not available. Although machinery, such as the Rapier Muck-shifter, has been invented to make mechanical compost, these machines are expensive to buy, and they have not met with response in farming circles, because the farmer is now so artificial-fertiliser-minded.

The average agriculturist imagines that, when applying sulphate of ammonia, he is replacing the nitrogen that he may have taken from the land in the previous crop. As to whether one is from an organic source, and the other entirely inorganic; as to the possibilities of the natural organic nitrogen being more desirable for the plant than the inorganic—these problems do not occur to him. If he can produce what appears to him to be a useful crop, he is content. Its quality and its life-sustaining abilities—these are no

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1. Kaiser, A. D. *Acta pædiatr., Stockh.* 1930, 11, 227.
2. Porter, M. R., Sanders, E. K., Lockwood, J. S. *Ann. Surg.* 1948, 128, 865.
3. Haxton, H. A. *Manch. med. Sch. Gaz.* 1952, 31, 21.

concern of his. Unfortunately, quality in foodstuffs[4] is not recognised in the economic market. Good food sells at the same price as food of indifferent quality; and this makes those farmers who are interested in quality despair of the national mind rising to the position of being able to discriminate between good and bad food.

In my books I have told the story of thirty years of organic farming, and in following this principle I have achieved two ends: (1) an exalted standard of health in my crops and livestock; and (2) more profit in the long run. I do not dismiss labour: on the contrary, I am always seeking to build new and more cottages, and to employ more men. I am content to do this in the full knowledge that human labour is more dependable than machines. The machine still needs a competent man to make it useful. When men are driven from the land, it is always the best man who leaves. It may well be that the greatest curse that has come to our land is mechanisation. The capital sunk is beyond belief; and farmers at the present moment, throughout Britain, are indebted to our banks in a sum of money not less than £200 million. Much of this is due to the purchase of mechanical equipment and artificial fertilisers. The more we mechanise, the further we get away from enduring fertility, and the soil—man's greatest heritage—depreciates.

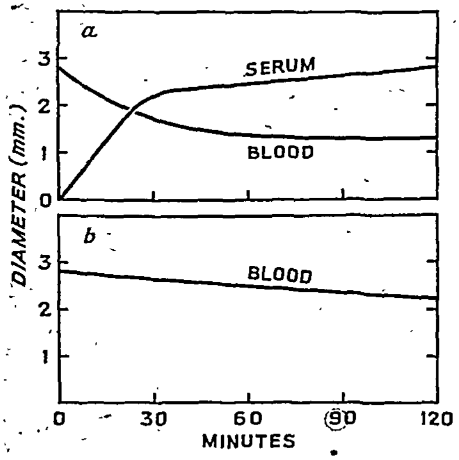
Chute, Andover. FRIEND SYKES.

CLOT RETRACTION

SIR,—Dr. Budtz-Olsen's method of measuring clot retraction, mentioned in your leading article of July 5, is in some ways similar to that recommended in 1948 by Hirschboeck.[1] One of the chief advantages of both methods lies in the fact that retraction is going on in a fluid hydrophobe medium, and so it is not hindered by impurities in badly washed test-tubes, and is not influenced by the varied adsorptive surfaces of different glasses.

The method of Hirschboeck is semiquantitative, establishing only the beginning of clot retraction; that of Budtz-Olsen is superior in this respect, for it measures the quantity of serum extruded in a given period of time. However the Hirschboeck method is a micromethod, needing only one drop of blood—an advantage when dealing with infants and children.

It seems worthwhile therefore to describe briefly a quantitative micro-method which has been evolved along the lines of Hirschboeck and which has been used in our laboratory since 1948. The full details are shortly to be published in the Hungarian journal *Kisérletes Orvostudomány*.



Change in diameter of drop with (*a*) normal blood and (*b*) blood from a patient with thrombocytopenic purpura.

Glass tubes with a flat bottom and a height and diameter of about 1 cm. were selected as containers. 0·02 ml. of blood is slowly blown into these containers on to the surface of some castor oil. The diameter of the blood drop is measured immediately with an ocular micrometer. Taking into consideration the correlation between the enzymatic process of clot retraction and temperature, the container is now placed in a 37°C thermostat, and covered with a cotton-wool cap soaked in water. The diameter of the retracting blood and of the extruded drop of serum are measured after 30, 60, and 120 minutes, and the results are set out graphically.

A typical curve of normal blood with 400,000 platelets per ml. is shown in the figure. After 30 minutes the diameter of the serum drop just exceeds that of the blood. We were able to observe a direct correlation between the number of platelets and clot retraction in the same way as Budtz-Olsen. *A typical curve of a case of thrombocytopenic purpura with* 30,000 platelets per ml. is shown in the figure; here only a very weak retraction occurred during the time of observation, and no serum was squeezed out.

The method is simple and easily reproducible. Knowing the large deviations of platelet-counting methods, we are always checking, in our daily routine examinations, the platelet-counts with clot-retraction measurement. A pathological fall in the platelet-count can be excluded if clot retraction is normal. This method has proved to be extremely useful in classifying the different hæmorrhagic diseases.

Department of Pathology,
Szombathely Hospital,
Hungary.
B. SOLYMOSS.

CHARGES FOR PAY-BEDS

SIR,—Your leading article last week rightly draws attention to the extravagant charges now made for pay-beds, but I think it omits one important point. The cost of a public bed includes the cost of all medical services, none of which the private patient is using, because normally he pays extra for doctors, X rays, pathological investigations, and even the use of the theatre. By basing his charge on that of a public bed, he pays for these things twice over.

All he really gets for his money is a "hotel" service and the cost of nursing. This hotel service does not have to include many of the amenities, such as dining-rooms, lounges, cocktail bars, and even golf-courses, provided by hotels, and should therefore cost much less than a commercial price in a hotel. Six guineas a week ought to cover it. Add to this a fair proportion of nursing costs, and we should have a reasonable figure which many people would be glad to pay.

Ashtead, Surrey. W. EDWARDS.

FEEDING DISORDERS IN INFANTS

SIR,—I was very interested to read Professor Vining's instructive article (July 19). His submission that "Nature would never have provided an infant with a digestive system so delicately balanced that overfeeding or risk of death from harm or illness produced by the food itself could be a possibility" is, I feel sure, very true. That "starvation and underfeeding in any degree are the dangers most to be avoided" may be equally true.

Is it not possible, then, for scientific knowledge of artificial feeding to be so sound and satisfactory that either of these conditions practically never occurs? The child-welfare clinics and maternity wards are the obvious places to teach mothers in this. Perhaps, too, makers of dried milks might give better-balanced recipes.

I believe that if Dr. Truby King's "fantastic formulæ" were studied, his basic principles would be recognised as true, simple, and uncomplicated. He believed to some degree in "percentage feeding."

It is generally recognised that the healthy underfed baby (if underfeeding is not too prolonged) can be put right much more speedily than the baby whose digestion has been strained and upset by wrong feeding or overfeeding. In the former, there is no digestive disturbance (or "dyspepsia"?) to correct. Generous feeding should be introduced gradually, and if the balance is sound and the ingredients are easy to digest, the baby *will respond well.*

I should never call a mild degree of either underfeeding or overfeeding "dangerous," or even apply the word to wrongly balanced feeding. But if the infant is given no opportunity to recover from any of these faults, his physique may finally be so undermined that he may be in grave danger of catching serious infection.

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[1] Hirschboeck, J. S. *J. Lab. Clin. Med.* 1948, 33, 347.

The overfed breast-fed baby will generally regulate his feeds himself if allowed to do so, as will the underfed one if he is permitted to feed more often. But the baby on the bottle is much more handicapped.

Whatever name may be given to digestive disorder in artificially fed infants, the cause is practically always the same—a wrongly balanced mixture. It is seldom due merely to underfeeding or overfeeding.

If a baby on a well-proportioned feed, suited to his condition and age as well as weight, and supplying the requisite calories, is obviously hungry, what is more simple and satisfactory than to increase each feed as needed, still keeping the balance correct? Or it may be slightly strengthened for some babies, for their individual needs should be respected. Such a baby does not develop dyspepsia. It is the pathetic infant having over-concentrated feeds (of necessity with too little fluid) who seems to be dissatisfied when the small feed is finished, and, all too often, will later cry with colic and wind, and be generally restless. If his feeding is corrected quickly the normal baby will practically always settle down well, but if his unhappiness is allowed to continue for long it is harder to put right. Fortunately, in most cases where the trouble is ignored, the child will finally settle, but often only after months of misery for both mother and baby.

The fact that a few babies seem to tolerate exceedingly concentrated feeding without wind or colic is not a sound reason for asking them to do so, or for other babies being expected to.

If, unfortunately, breast-feeding should fail, correct bottle-feeding will go a long way to compensate the baby and ensure peaceful and satisfactory progress. Such feeding must be understood and not be experimental.

London, E.C.4. E. MORRISON.

RADIOGRAPHY FOR THE ACUTE ABDOMEN

SIR,—In your annotation (July 5) you say that possibly further study might bring to light additional radiographic signs of intestinal obstruction.

Such a study is at present being carried out at Adeoyo Hospital, University College, Ibadan, Nigeria, where idiopathic cæco-colonic intussusception in young adults is common and presents diagnostic difficulties owing to its resemblance to the dysenteries.

In the cases so far radiographed preoperatively there has been the expected complete absence of colonic gas shadows from the base to the apex of the intussusception, thus producing a uniformly opaque right side of the abdomen, with the distal colon and rectum, if not yet affected, well shown by its gas pattern.

University College,
Ibadan, Nigeria. P. KONSTAM.

BUTAZOLIDINE

SIR,—I wish to add my support of the findings of Dr. Currie and your other correspondents in regard to the use of this substance in the treatment of rheumatoid arthritis.

Therapeutic trial of this chemical in over 40 cases of severe rheumatoid arthritis has been carried out at my hospital clinics at Coventry and Leamington Spa during the past three months, and the results have been most encouraging. Except for one rather severe gluteal abscess in the area of the injection, no unpleasant results have been encountered.

Much smaller doses have been found to be effective than those mentioned by Dr. Currie. Butazolidine 1·0 g. injected intramuscularly twice weekly is the maximum dosage in my series, and in view of the cost of this preparation this smaller dosage may be an important consideration.

The use of butazolidine in rheumatoid arthritis should not prevent us from considering the efficiency of the parent preparation, 'Irgapyrin.' During the past six months over a hundred severe rheumatoid arthritis cases attending my hospital clinics have had treatment with this preparation. In view of the danger of agranulocytosis, blood-counts are made before treatment and after every second injection. The usual course of treatment has been one ampoule of irgapyrin injected once weekly. The sedimentation-rates (Westergren) in severe cases may drop fairly quickly (one patient with Westergren of 96 dropped to Westergren 22 after two injections). Joint swellings and pains are quickly relieved, but there is a tendency to relapse at the end of the course of treatment. For such relapses I use butazolidine and find it very effective.

I have not yet had time to analyse the small proportion of patients who have failed to respond to this combination of drugs, but it may be that for such cases a larger dosage would be effective.

Using irgapyrin to suppress the severity of rheumatoid arthritis and using butazolidine for maintenance purposes, I am convinced that these two drugs can play a most important part in the treatment of this disease.

I am indebted to Pharmaceutical Laboratories Geigy Ltd. for their kindness in giving me supplies of irgapyrin and butazolidine for clinical trial.

JOHN SHULMAN.

Coventry and Warwickshire Hospital, Coventry.
Warneford Hospital, Leamington Spa.

CALCIFEROL IN PULMONARY TUBERCULOSIS

SIR,—Your correspondents, Dr. Randolph White (June 28) and Dr. J. Fielding (July 26), suggest that six weeks of combined calciferol and streptomycin and P.A.S. therapy is too short a course on which to judge fairly the effects of the treatment. I agree that for the sake of completeness it would have been better had a longer course been given. There were, however, good reasons why we did not feel justified in carrying out such a long trial, the most weighty being the risk to the patient of developing streptomycin-resistant strains of tubercle bacilli and thus prejudicing the chances of successful surgical resection at a later date. As reported, 3 of our cases were given a three-month course of 'Sterogyl' (600,000 units weekly), streptomycin, and P.A.S. These cases had extensive bilateral disease where the development of streptomycin resistance would be of no consequence. They showed no unusual response to the extended course of treatment.

Dr. Fielding is not consistent in some of his statements and hypotheses. He holds that the results in the treatment of lupus vulgaris should be a guide to the treatment of pulmonary tuberculous disease, and yet he discontinues his treatment after only four to six months, whereas lupus vulgaris is generally treated for a year or more. Again regarding the histology of lupus lesions treated with calciferol, Dr. Fielding says: "It was this first phase of vascular and exudative reaction which suggested itself as a method of bringing streptomycin to the site of tuberculous lesions otherwise inaccessible."[1] It is known that the phase referred to occurs well within the six weeks' period following the start of calciferol therapy; indeed, careful perusal of Dr. Fielding's cases 1, 3, 5, and 6 (i.e., 4 of the 6 successful results he published) suggests that the dramatic improvement occurred within the first six weeks of treatment. He did refer to the "possibility" of a second healing phase, but apparently the odds have shortened since then.

In empirical methods of treatment of this sort, hypotheses are of little value unless they can be substantiated. If Dr. Fielding is convinced that four to six months of calciferol treatment is of definite value, I hope he will publish the results of an adequate trial with control cases. Our experience at Clare Hall does not encourage us to pursue the matter further.

Clare Hall Hospital,
South Mimms, Barnet. S. L. O. JACKSON.

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1. Fielding, J., Maloney, J. J. *Lancet*, 1951, ii, 614.

EXTENSIVE RESECTION OF THE SMALL BOWEL

SIR,—In connection with Mr. Johnston's interesting article (April 19), I should like to report the following case.

A girl, aged 10, was admitted to the surgical ward of the Jewish Hospital on Feb. 10, 1951, with vague abdominal symptoms. White blood-cells 7600 per c.mm. (neutrophils 55%); erythrocyte-sedimentation rate (E.S.R.) 5 mm. in first hour (Westergren); fæces negative for parasites. The patient was observed in hospital for five days.

On March 2 the patient was readmitted. She now had an acute abdominal condition, with vomiting and greater tenderness in the upper abdomen. White blood-cells 23,850 per c.mm. (neutrophils 90%); E.S.R. 17 mm. in first hour.

A median laparotomy, performed without delay, yielded turbid fluid from the peritoneal cavity. A large portion of the small intestine was found to be gangrenous, owing to invagination; and the mesentery was extremely œdematous. Complete disinvagination proved impossible; and 90 in. of the small bowel was resected, with end-to-end anastomosis. The invagination was found to be due to a large papilloma.

After the critical first three days, the patient's condition gradually improved and she made an uninterrupted recovery. She left hospital on April 7, apparently none the worse for the extensive operation. She was passing two stools per day, the fat-content of which was not increased; and there were no indications of any physical after-effects, weight and growth being apparently unaffected.

According to Rolssen the small bowel in a child of 10 is about 160 in. long. The absence of disturbance after the operation is no doubt explained by Flint's[1] observation (cited by Mr. Johnston) that in dogs submitted to enterectomy the remaining bowel increased in diameter to about twice the normal, and the absorbing surface increased by 400%.

Cairo, Egypt. H. PICARD.

Medicine and the Law

Appeal from the G.M.C.

THE first of the appeals from the Medical Disciplinary Committee to the Privy Council has now been disposed of, and we have as yet (unless the judgment contained much more than has hitherto been reported) no strong impression of the difference that the new statutory right of appeal will make.

The name of Dr. Daly, who appeared in person, was to be erased, under section 29 of the Medical Act, on the ground of his misconduct with a woman who was his patient. His explanation of how he came to fall in love with her could not greatly help him. He contended that the determination of the Medical Disciplinary Committee was influenced by the admission of evidence of his previous career. It was pointed out to him that the committee was not informed of the previous history until it had come to its conclusion on the facts of the case. It was then proper for the committee to have the information before it decided upon the nature of the penalty. As Lord Tucker observed, if the previous history of a practitioner has been entirely blameless, it would be important and advantageous for the committee to know the position. The Privy Council dismissed his appeal.

Does the concession of a right of appeal to Her Majesty in Council under section 20 of the 1950 Act really make any difference at all? When the Act of 1858 was passed, the courts refused to go into the merits of the doctor's case. They have been ready to intervene if the domestic tribunal acted without the "due inquiry" which the 1858 statute required, if there was no evidence on which the tribunal could erase a name from the register, if the decision was corrupt, or if some member of the tribunal sat when disqualified. These grounds for intervention have seldom been established; they are even less likely to exist today. The General Medical Council (now replaced by the Medical Disciplinary Committee) was declared in Ex parte la Mert (1863) to be the judge whether the medical practitioner on the register had been guilty of infamous conduct. It was not, said the judges in Leeson's case in 1889, a question for the court whether the council arrived at the right conclusion. "We have not," said the court in Allinson's case in 1894, "to say whether the Council were right or wrong in the inference which they draw." Must not the new appellate tribunal follow the same line?

Long-range Shock

The law-courts have long recognised that mental shock without physical impact was a form of injury for which a defendant, if found at fault, may have to pay damages. "It is now settled," said Lord Thankerton in Bourhill *v.* Young (1942), "that such injury includes injury by shock although no direct physical impact or lesion occurs." "The distinction between mental shock and bodily shock," said Lord Macmillan in the same case, "was never a scientific one." One of the earliest decisions for this purpose was the award of damages against a practical joker who frightened a woman with false information that her husband had met with a serious accident. Lately, in King *v.* Phillips,[1] it has been established afresh that there is a geographical radius within which the cause of the shock must arise. Mrs. King, looking out of her upstairs window, heard a scream from the end of the road. She recognised it as the cry of her 5-year-old son, and she saw a taxicab backing on to his tricycle. She saw the tricycle under the cab, but could not see the boy. Eventually she met him running home. Mr. Justice McNair awarded £5 for the not very serious harm to the boy and £10 for the value of the destroyed tricycle. But he found himself unable to award damages to the mother who had subsequently suffered from nervous shock and trembling fits. Like any normal mother, he said, she was anxious for the safety of her child, but she had no special susceptibility to shock. The driver of the cab was not liable for shock unless the injury was within what he ought to have reasonably contemplated as the area of potential danger arising from his negligence. The mother was 70 to 80 yards away from the scene of the accident, "wholly outside the area or range of reasonable anticipation." The learned judge declared it was contrary to common sense to say that a taxi-driver, backing his cab without looking where he was going, ought reasonably to have contemplated *that* he might cause injury by shock to a woman in a house so far away up a side street.

The high-water mark of successful claims in this type of case was Owens *v.* Liverpool Corporation (1939), where the corporation's tramcar collided with and damaged a hearse and overturned the coffin. Mourners following in the funeral procession were held entitled to damages for mental shock. But in the Bourhill case, already cited, the House of Lords rejected that kind of claim. There a motor-cyclist, riding at an excessive speed, collided with a motor-car and was killed. A woman 45 feet away (on the other side of a tramcar) heard the noise but did not see the accident. She suffered fright, but admittedly not from any fear of danger to herself. She was 8 months pregnant and her child was stillborn. Their Lordships asked what ought the motor-cyclist to have contemplated, as a reasonable man, as the area of potential danger arising from his negligent riding. The woman on the other side of a tramcar, they held, was not within that area. The law, it seems, is obliged to attribute even to careless persons a degree of cool ratiocination which they are scarcely likely to have reached. The geographical limitation may furnish as good a test as anything else; but, if he really does apply his mind to such speculative calculation, where, in these days of television, is the too speedy motor-cyclist to draw the line?

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[1] Flint, J. M. *Bull. Johns Hopk. Hosp.* 1912, 23, 127.

[1] *Times*, July 17, 1952.

Cost of Burying Hospital Patient

In Scotland a county council has been held liable to pay for the burial of a patient who died in hospital and whose relatives could not be traced.[2] Apparently the county council was asked to bury him but refused. Burial was then carried out on the instructions of the Secretary of State for Scotland, who sued the county council for the funeral expenses. In the sheriff court the judge found himself obliged to conclude that, whereas the State provided for the health of the living, not only during life but before birth, its obligation ceased on the death-bed. It may have been material that county councils, being bodies corporate, are specifically barred from claiming death grants under the National Insurance Act.

Public Health

Poliomyelitis

POLIOMYELITIS notifications in the week ended July 26 (the 30th week of the year) were (previous week in parentheses): paralytic, 157 (104); non-paralytic, 96 (59): total, 253 (163).

The following table compares this year (up to and including the 30th week) with the preceding five years.

Year	*Total cases up to and including 30th week*	*Cases in 30th week*
1947	1141	336
1948	830	39
1949	1016	169
1950	2226	306
1951	1282	121
1952	1430	253

Up to and including the week ended July 26 the over-all notification-rate for England and Wales was 3·26 per 100,000 population.

The districts which have notified 10 or more cases up to July 26, with incidence per 100,000 population, are:

District or borough	*Total cases*	*Incidence*
Gateshead	63	54·9
Felling	26	103·2
Whickham	13	61·0
Southend-on-Sea	10	6·6
Liverpool	26	3·3
Manchester	24	3·4
Fulham	10	8·2
Wandsworth	15	4·5
Woolwich	20	13·3
Ealing	14	7·5
Harrow	13	5·9
Newcastle upon Tyne	43	14·7
Yeovil	18	102·9
Blyth (Suffolk)	13	50·0
Birmingham	47	4·2
Coventry	11	4·3
Malvern	10	51·1
Leeds	48	9·5
Sheffield	14	2·7
Cardiff	16	6·6

The regional notification-rates and incidence per 100,000 population (up to and including week ended July 26, 1952) are:

Region	*Paralytic*	*Non-paralytic*	*Total cases*	*Incidence*
Northern	133	128	261	8·3
East and West Ridings ..	124	23	147	3·6
North-western	88	28	116	1·8
North Midland	22	34	56	1·7
Midland	85	42	127	2·9
Southern	61	27	88	3·3
South-western	58	42	100	3·3
Eastern	69	47	116	3·8
London and South-east ..	255	91	346	3·1
Wales	53	19	72	2·8

Tuberculosis Figures for Manchester

In his report for 1951 Dr. C. Metcalfe Brown, medical officer of health for Manchester, draws attention to an increase in pulmonary tuberculosis in children under the age of five. In the past five years there have been 2½ times as many notifications in this age-group as in the preceding five years, and nearly 4 times as many as in the five years before the outbreak of the late war. The reason, he thinks, can only be that, though the waiting period for institutional treatment has been considerably reduced, the delay is still too long, and young children with poor immunity continue to be exposed to infectious people. But the notification-rate for non-pulmonary tuberculosis in this age-group in Manchester has again declined; and the mortality of both pulmonary and non-pulmonary tuberculosis in the whole population has also decreased since 1950. The death-rate from respiratory disease was 0·45 per 1000 population (0·58 in 1950), and for non-respiratory disease 0·06 per 1000 population (0·07 in 1950).

The infant-mortality rate in 1951 was the lowest ever recorded in Manchester—35·3 per 1000 live births. The corresponding figure for 1950 was 37·9.

Parliament

Foot-and-mouth Disease

REPLYING to a debate in the House of Commons on the adjournment for the summer recess on Aug. 1, Sir THOMAS DUGDALE, Minister of Agriculture, said the departmental committee, which the Government were setting up to review policy for foot-and-mouth disease, would start work in the autumn under the chairmanship of Sir Ernest Gowers.

There were, he continued, 22 outbreaks in the second half of July compared with 29, 43, and 63 in the previous half-monthly periods. Since Nov. 14 last year, when the first outbreak of the present series occurred, there had been 548 outbreaks. This had entailed the slaughter of just over 36,000 cattle, 37,000 sheep, and 11,500 pigs. In Western Europe, the position had also improved since the winter and spring. In the Scandinavian countries and in Holland and Belgium there had been relatively few outbreaks since the beginning of June. The one exception to the general improvement—and it was serious—was France, where the position was still deteriorating. Fortunately for this country, the infection now appeared to be moving away from those parts of France nearest to our coasts, and there was no evidence that fresh infection had been introduced into this country from France since the end of June. Although his veterinary advisers would like a little longer experience before advising a change, he hoped that the controlled area in Southern England might be removed in the fairly near future.

Closed Shop Dispute

In answer to a question, Sir WALTER MONCKTON, Minister of Labour, said that he had now received the award of the board of arbitration appointed to determine the difference between the Durham County Council and the Joint Emergency Committee of the professions. He said that differences between the county council and some of their professional employees had persisted for a considerable time. The present difference arose over the county council's regulation that applications for extended sick-pay must be made by or through a trade union or other appropriate organisation. At the request of the parties he appointed a board of arbitration and the parties undertook in advance to accept and implement any award made by the board. Both parties accepted that as far as certain professions were concerned membership of a trade union or professional organisation should not be imposed as a condition of employment. The agreed terms of reference accordingly included the question whether the present regulations of the council governing the making of applications for extended sick-pay were in conflict with the principle of voluntary membership of a trade union or professional organisation and should therefore be withdrawn. The board's award was that in so far as the regulations required such applications to be made through a trade union or other appropriate organisation they were in conflict with that principle and should be withdrawn.

Hypnotism Act

On Aug. 1, in the House of Lords, the Royal Assent was given by Commission to the Hypnotism Act.

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[2] *Scotsman*, July 12, 1952.

QUESTION TIME

Pasteurisation of Milk

Replying to a question, Dr. CHARLES HILL, parliamentary secretary to the Ministry of Health, said that 82% of all milk sold in the liquid market in England and Wales and 73% in Scotland was already pasteurised or sterilised, and that these percentages would gradually be improved. None of this milk was mixed with other milks before sale.

Prescription Forms

Mr. V. F. YATES asked the Minister of Health if he was aware that there was considerable discrepancy in the practice of doctors as to the number of prescriptions they put on one form; and if he would alter doctors' terms of service to ensure that greater conformity was reached in this respect.—Mr. IAIN MACLEOD replied: The need may vary in different cases. I am not clear that it would be an advantage to import further requirements into doctors' terms of service.

Hospital Waiting-lists

In answer to a question Mr. MACLEOD stated that the waiting-list for hospital patients was 503,584 on Dec. 31, 1951.

Bone-conduction Hearing-aids

In answer to a question Mr. MACLEOD stated the Electro-Acoustics Committee of the Medical Research Council had now assessed the results of clinical trials of an experimental bone-conduction aid produced for the National Health Service. The committee had recommended this aid for issue to patients for whom a bone-conduction aid is more suitable than an air-conduction aid and he was arranging for large-scale production as soon as possible.

Spectators at Operations

Mr. E. W. SHORT asked the Minister why an American music hall artiste was recently allowed to be present at an operation at the Royal Victoria Infirmary, Newcastle upon Tyne.—Mr. MACLEOD replied: The incident is shortly to be considered by the board of governors.

Mr. SHORT: Has the Minister taken adequate steps to see that this method of entertaining music hall comedians does not spread to other cities?—Mr. MACLEOD: It is a little unfair to leave it at that. The responsibility for admission will, of course, be decided and reported to me, but the person in question—Mr. Danny Kaye, as the hon. member knows—was properly masked and properly gowned, as one would expect.

Mr. M. A. LINDSAY: Is there any reason why any person, irrespective of nationality or sex, should not watch an operation if invited to do so by the surgeon?

Mr. G. R. CHETWYND: As the facilities were given to Mr. Kaye to see the opening of the patient, were any facilities given to the patient to see the opening performance of Mr. Danny Kaye?—Mr. MACLEOD: The patient, in any case, has recovered.

Appointments

BRUNNEN, P. L., M.B. Aberd., F.R.C.S.: *consultant thoracic surgeon*, North Eastern Regional Thoracic Surgery Unit, Scotland.

* LECKIE, F. H., M.C., L.R.C.P.E., M.R.C.O.G.: asst. obstetrician, East District Hospital and Glasgow Royal Infirmary.

LEWIS, W. J., M.R.C.S., D.A.: consultant anæsthetist, Mid-Glamorgan H.M.C.

SINCLAIR, W. W., M.B. Glasg., D.P.H.: senior school M.O., County of Fife.

WISE, LIONEL, M.B., B.SC. Manc.: whole-time consultant pathologist, Wrexham H.M.C.

Colonial Service:

ARMSTRONG, R. F., L.R.C.P.E.: M.O., Tanganyika.
CLARK, J. S., M.B. Durh.: M.O., Nyasaland.
EDDY, T. P., M.R.C.S., D.P.H.: A.D.M.S., Sierra Leone.
GROSS, R. D., M.D. Lond., D.P.H.: D.D.M.S., Federation of Malaya.
HADMAN, D. F., D.S.C., M.B.: resident M.O., Kenya.
HAYNES, W. S., M.D. Camb.: tuberculosis officer, Kenya.
HOLMES, A., M.B.: M.O., Nyasaland.
JOHNSON, A. J., M.B. Camb., D.T.M. & H.: D.D.M.S., Sierra Leone.
JONES, S. H. O., M.B. Manc., D.T.M. & H.:
LINSELL, C. A., M.B.: resident M.O., Kil
Kenya.
MACPHERSON, J. J., F.R.C.S.E.: M.O., Federation of Malaya.
PRICE, P. B. W., M.B. Calcutta: M.O., Seychelles.
ROBSON, J. R. K., M.B. Durh.: M.O., Tanganyika.
WARMANN, J. St. G., M.R.C.S., D.P.H.: M.O.H., Nigeria.

* Amended notice.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Obituary

GEORGE CARMICHAEL LOW

M.A. St. And., M.D. Edin., F.R.C.P.

Dr. Carmichael Low, formerly director of the division of clinical tropical medicine at the London School of Hygiene and Tropical Medicine, died at his home in London on July 31. He was in his 80th year, and he had lived through a fruitful and revolutionary period of medical progress, to which, through his work in tropical medicine, he had substantially contributed.

He was born at Monifieth, Forfarshire, and from Madras College, St. Andrews, he went to Edinburgh University, where he graduated M.B. with first-class honours in 1897. Soon after he had done his house-jobs at the Edinburgh Royal Infirmary the fame of Manson, who was then creating his school of tropical medicine, drew him to London. Manson soon settled his career for him by sending him to Heidelberg and Vienna to learn, among other things, the new technique of sectioning mosquitoes in celloidin by a sliding microtome. At this time progress in studying the development of parasites in mosquitoes had been halted by the difficulty in making sections, because paraffin is unsuitable.

[Haines

It so happened that at the time of Low's return Manson had received a collection of alcohol-preserved mosquitoes (*Culex fatigans*), which had been fed on filaria-infected subjects, in Brisbane, Queensland. Low was given the task of sectioning these insects—and he performed it so effectively that almost in the first specimen he was able to demonstrate the filaria passing down the proboscis sheath of the insect and emerging at the tip. His report on this work, published in the *British Medical Journal* in 1900, proved conclusively that the insect conveyed the infection to man in the act of biting—a method which for some reason had never been apparent to Manson before and which pointed the way to the transmission of malaria as well. This important work was soon confirmed independently by S. P. James working in isolation in Travancore, India.

In 1900 Low was sent by Manson to Ostia on the Roman Campagna, where a mosquito-proof hut had been erected in the most malarious spot. There, in company with Dr. L. W. Sambon and the artist, Signor Terzi, he spent the next three months in the epidemic season. Low, who was in command, shepherded his charges into the hut every evening and shut them up behind mosquito-netted windows and doors for the night. All around them Italian peasants and Red Cross workers lay fever-stricken in their huts; but Low and his party remained unscathed. They were visited by Professor Grassi, who was making his historic researches into the transmission of malaria, and at Ostia the mosquitoes were collected which later were injected with malaria parasites in Rome and despatched to London to bite Manson's son (P. T. Manson) who in due course developed malaria.

Low's next assignment was to the West Indies where he was appointed *Cragg's scholar* for the study of filariasis in those islands. By this work he was also able to demonstrate the relation of *Wuchereria bancrofti* to elephantiasis and the part played by *Mansonella demarquayi* and *M. ozzardi* among the Amerinds of British Guiana.

On his return from the Caribbean Low was appointed, at Manson's instigation, to the Royal Society's mission to Uganda (1903) where a severe epidemic of sleeping-sickness had broken out and it was necessary to assess the relation of the recently discovered *Trypanosoma gambiense* to the mysterious "Negro lethargy." Low was especially interested in the Central African filaria, then known as *Filaria perstans* (now *Acanthocheilonema perstans*), and he worked hard to prove its association—which Manson suspected—with sleeping-sickness.

As an outstanding figure in the new science of tropical medicine, Low was the obvious choice when the post of superintendent of the Tropical School in the Albert Dock fell vacant. He proved a good teacher and organiser and held this appointment for the rest of his professional life. He was always ready to spend hours on any necropsy of tropical importance, and that he found much to interest him is shown by the number of papers he wrote. This side of his work led to his appointment as pathologist to the West London Hospital.

To Low belongs the credit of the creation of the Royal Society of Tropical Medicine in 1907 and of housing it in Manson House, its present headquarters, in 1930. It may be claimed that without him there would have been no society, because for many years he carried the burden almost unaided. He was secretary from 1912 to 1920 and president for the unprecedented period of four years from 1929 to 1933. He was most generous to the society and his gifts included the magnificent rostrum which now adorns Manson House.

During the first world war Low, with the rank of major in the I.M.S., was responsible for the treatment of officers from India suffering from tropical disease, and with Wenyon and Clifford Dobell he began to make a special study of amœbiasis. When the Hospital for Tropical Diseases and the London School of Tropical Medicine were moved to the centre of London he became the senior physician to the hospital and director of the clinical division of the newly constituted School of Hygiene and Tropical Medicine in its new quarters. There he continued to lecture and teach till his retirement in 1937.

Low's interests were not bounded by his specialty, and the naturalist latent in him came to the fore in his closing years. He was a good and deeply read ornithologist, and he was one of the group of bird-watchers who at Staines and other reservoirs put London ornithology on the map. He was the official bird-watcher in Kensington Gardens and for many years secretary and treasurer of the British Ornithologists Club. He was also a member of the council of the Zoological Society and he was responsible for the volume on *Aves* at its centenary in 1929. Of late years his was a well-known figure in the bird room at the South Kensington Museum. His chief contribution to ornithology was his bibliography, the *Literature of the Charadriiformes*, which reached a second edition in 1931.

Among many honours Low received the Straits Settlements gold medal from the University of Edinburgh in 1912, and the Mary Kingsley medal in 1929. He was also corresponding member of the Société de Pathologie Exotique of Paris and an honorary member of the Belgian Society of Tropical Medicine. He was elected F.R.C.P. in 1924. He collaborated with Sir Neil Hamilton Fairley, F.R.S., in the tropical section of Price's *Textbook of Medicine* and with Dobell on amœbiasis in Byam and Archibald's *Practice of Medicine in The Tropics*.

P. H. M.-B., to whom we are indebted for this memoir, adds :

> Low had a brand of dry Scottish humour, all the more apparent because it was often unconsciously expressed. For this reason, and for the exposition from time to time of priceless principles which he enunciated for himself, his lectures were always a source of attraction and entertainment. Few will ever forget the sideways glance of his eye, the knowing and ever-recurring head-nod, and his Celtic ejaculation of "Eh-Eh." With all these attainments and characteristics he was a kindly soul who was ever interested in the doings of young people—among whom he would include his professional colleagues—and he was especially attracted to birds, animals, and dogs. I was associated with him for over forty years, and in saying goodbye to an old and valued colleague I feel I am taking farewell of the generation that he represented so well.

Dr. Low married in 1906 Edith, daughter of Mr. Joseph Nash. There were no children of the marriage.

LESLIE CUNNINGHAM

M.A., M.B. Camb., F.R.C.P.

Dr. Leslie Cunningham, physician to the David Lewis Northern Hospital, Liverpool, died on July 30 at the age of 59.

A foundation scholar of Downing College, Cambridge, he took his tripos in 1914. When war broke out he completed his medical studies as quickly as possible, and qualified M.R.C.S. from St. Bartholomew's Hospital two years later. After serving in the R.A.M.C., with the rank of captain, he took his M.B. in 1921 and his M.R.C.P. in 1923. He held several resident appointments at the David Lewis Northern Hospital in Liverpool, and when later he settled in consultant practice in Liverpool he was appointed to its staff. In due course he also joined the staff of the Birkenhead General Hospital and the Ormskirk General Hospital. In 1942 he was elected F.R.C.P.

R. E. writes : "Cunningham belonged to the ever-dwindling clan of general physicians, and his wide medical interests and sound judgment helped to make him one of the most sought-after consultants on Merseyside. Small of stature and rotund of figure, he was calm and unhurried, and entirely free from airs and graces and frills, with an endearing chuckle that could become a paroxysm of mirth. Like most rather silent men, he was not easy to know, and I think it is true to say that no-one ever knew what L. C. was really thinking. This capacity for silence made him a rather terrifying figure to his juniors, and certainly his nursing staffs were always very much on their toes at his outpatients and ward rounds. But he was beloved and respected, and the large gathering at his funeral service was testimony to his universal popularity. Cunningham was always a popular teacher with students ; there were no fireworks, but a dignified and sound exposition of clinical medicine, leavened with unexpected sly humour.

"Despite his distinctly unathletic build, until recent years Cunningham was no mean player of tennis and golf ; on the tennis-court he was always to be found in the most suitable place to hit a ball, and his golf was of the shortest-path-to-home variety."

Cunningham married rather late in life, but his family life at Prenton was ideally happy, and he was devoted to his young family. He leaves his widow with five children.

Births, Marriages, and Deaths

BIRTHS

DODS.—On Aug. 1, at Bulawayo, Southern Rhodesia, to Noel (née Gilbert), wife of Dr. A. S. Dods—a daughter.

LEWIS.—On Aug. 3, at 106, Stroud Road, Gloucester, to Johanne (née Marcussén), the wife of Dr. Ninian Lewis—a son.

OWEN.—On July 29, to Barbara (née Lewis), wife of Mr. Kenneth Owen, F.R.C.S. of 98, Longmore Avenue, New Barnet—a daughter.

READ.—On July 25, at the Middlesex Hospital, to Ann, wife of Mr. Keith Read, M.R.C.O.G.—a son.

TEMPEST.—On July 26, at St. James's Hospital, Leeds, to Jean Elisabeth (née Turner), wife of Mr. Michael N. Tempest, F.R.C.S.—a daughter.

MARRIAGES

HERDMAN—HOWARTH.—On July 30, in London, Gawin Joseph Seaton Herdman, M.B., to Betty Eileen Howarth, M.R.C.P.

NEWMAN—SANDISON.—On July 26, at Kensington, Graham R. Newman to Joycelyn H. W. Sandison, M.B.

ROGERS—AINSLEY.—On July 30, in London, Lambert Rogers, F.R.C.S., professor of surgery, University of Wales, to Barbara Mary Ainsley.

SOLOMONS—MAITLAND.—On July 29, Michael Solomons, M.B., of Dublin, to Joan Maitland.

DEATHS

ANDERSON.—On Aug. 1, at Greenacres, Wootton Courtenay, Somerset, Kenneth Anderson, M.B. Lond.

BROWNE.—On July 24, in Dublin, O'Donel Thornley Dodwell Browne, M.B. Dubl., F.R.C.P.I., F.R.C.O.G., master, Rotunda Hospital.

CUNNINGHAM.—On July 30, Leslie Cunningham, M.A., M.B. Camb., F.R.C.P., of Rodney Street, Liverpool.

GARNETT PASSE.—On Aug. 1, Edward Roland Garnett Passe, F.R.C.S., F.A.C.S., of Weymouth Street, London, W.1.

HENDERSON.—On July 31, at Coldstream, John Henderson, M.B. Edin.

LOW.—On July 31, at 7, Kent House, Kensington, W.8, George Carmichael Low, M.A. St. And., M.D. Edin., F.R.C.P.

MORRIS.—On Aug. 2, John Morris, M.R.C.S., of Park Avenue, Newport Pagnell, Bucks, aged 71.

News

University of Oxford

On July 19 the following degrees were conferred:

D.M.—J. M. K. Spalding.

B.M.—M. J. A. Davies, P. J. R. Phizackerley, D. R. Oppenheimer, W. D. Hayley, R. T. H. Shepherd, M. A. Smith, M. S. Finn, D. G. H. Patey, R. M. Murray-Leslie, J. M. H. Brooks, A. T. N. Fletcher,
R. A. [illegible] Viscount Suirdale, E. D. R. Campbell,
N. J. [illegible] J. W. P. Bradley, C. W. H. Havard,
J. E. [illegible] Davies, J. C. [illegible]
Mitch[illegible] Wilson, Carm[illegible]
Feldberg, Felicity C. Toussaint, *H. G. Klem.

* In absentia.

Royal College of Physicians of London

At a comitia of the college held on July 31, Sir Russell Brain, the president, announced that H.R.H. the Duke of Edinburgh had accepted the honorary fellowship of the college.

The following fellows were elected officers for the ensuing year:

Censors: Dr. A. H. [illegible]
Lee Lauder, Dr. J. R. H. [illegible]
Registrar: Sir Harold [illegible]
Dodds. *Assistant registra*[illegible]
Prof. J. H. Dible, Dr. F[illegible]
Fox. *Finance committee* [illegible]
Dr. A. D. C. Bell.

The following were elected examiners:

Chemistry: Mr. A. E. Kellie, PH.D., Mr. George King, D.SC. *Physics:* Mr. H. F. Cook, PH.D., Prof. Joseph Rotblat, D.SC. *Materia medica and pharmacology:* Dr. W. N. Mann, Dr. C. J. Gavey, Dr. J. F. Dow, Dr. H. C. Stewart, Prof. J. H. Burn, Prof. J. M. Robson. *Physiology:* Prof. R. J. S. McDowall, Prof. W. R. Spurrell. *Anatomy:* Prof. James Whillis. *Pathology:* Prof. L. P. Garrod, Prof. T. F. Hewer, Dr. Arthur Willcox, Dr. L. C. Martin. *Medical*
anat[illegible] *edicine:* Dr. W. G. Wyllie,
Dr. [illegible] n, Dr. H. K. Goadby, Prof.
S. J. [illegible] Clifford Hoyle, Dr. W. D. W.
Bro[illegible] . V. Neale, Dr. J. F. Stokes,
Dr. [illegible] *diseases peculiar to women:*
Mr. [illegible] Mr. K. V. Bailey, Mr. Ian
Jack[illegible] *: Part I,* Dr. N. M. Good-
man, [illegible] *Tropical Medicine: Clinical*
tropical medicine and medi[illegible] Sir George McRobert;
Tropical hygiene Dr. R. F. [illegible] . A. J. B.
Goldsmith, Mr. L. H. Savi[illegible] *chological*
medicine: Part I, Dr. Henry [illegible] Ironside,
Prof. Alexander Kennedy. *Laryngology and otology:* Mr. C. P. Wilson. *Medical radiology: Part I,* Prof. J. E. Roberts, D.SC.; *D.M.R.D.*, Dr. M. H. Jupe; *D.M.R.T.*, Dr. Gwendolen Hilton. *Anæsthetics: Part I,* Dr. J. H. T. Challis, Dr. R. S. Stacey, Professor Robson, Dr. G. S. W. Organe; *Part II,* Dr. W. G. Oakley, Dr. Frankis Evans. *Child health:* Prof. J. M. Smellie, Dr. Wilfrid Sheldon, Dr. Bernard Schlesinger, Prof. Alan Moncrieff, Dr. Reginald
Lightwood, Dr. Carlyle Potter, Dr. [illegible] *hysical*
medicine: Part I, Dr. K. O. Blac[illegible] D.SC.;
Part II, Dr. H. A. Burt, Dr. Cook [illegible] Prof.
Andrew Topping. *Pathology:* Prof[illegible] *ayling*
Wright. *Panel of examiners for the* [illegible] *: Dr.*
George Ward, Prof. T. L. Hardy, [illegible] rof. J.
Crighton Bramwell, Dr. Donald H[illegible] ttrass,
Dr. J. Forest Smith, Dr. L. B. Cole, Dr. J. L. Livingstone, Dr. C. B. Levick, Dr. Maurice Shaw, Dr. Ernest Lloyd, Dr. Kenneth Harris, Sir Henry Cohen, Dr. J. St. C. Elkington, Dr. A. M. Cooke, Dr. E. R. Boland, Dr. T. C. Hunt, Prof. E. J. Wayne, Dr. Robert Coope, Dr. John Hawksley, Dr. J. G. Scadding, Dr. Horace Joules, Dr. F. Avery Jones.

The following lecturers were appointed:

Dr. George Graha[illegible] Professor Wayne (Brad-
shaw), Dr. E. A. [illegible] Black
[illegible] Clifford
[illegible] berts),
[illegible] all for
[illegible] ewman
(FitzPatrick) for 1954.

The Murchison scholarship was awarded to Dr. C. W. Crane.

The following having satisfied the censors' board were elected to the membership:

J. H. Biggart, C.B.E., M.D. Belf., Uri Birnbaum, M.B. Cape Town, P. S. Brown, B.M. Oxfd, H. M. T. Coles, M.D. Lond., W. M. Dixon, M.B. Lond., Ellis Dresner, M.D. Durh., Donald Emslie-Smith, M.B. Aberd., D. M. D. Evans, M.B. Lond., K. T. Evans, M.B. Birm., S. G. Faris, M.B. N.Z., J. M. Farrar, M.B. Sydney, D. D. Felix-Davies, M.B. Lond., I. T. Gabe, M.B. Lond., C. D. Gettliffe, M.B. Witw'rsrand,
[illegible] .M.C., R. A. K. Harper,
R. R. M. Harman, [illegible] Pathiyil Karthiyayani
M.B. Edin., R. P. [illegible]
Krishnankutti, M[illegible] acFarlane, M.B. Glasg.,
Thomas McKeown, M.D. [illegible] McPherson, M.B. Glasg.,
David Mendel, M.B. Lond., T. G. Milliken, M.D. Belf., Dawood Mustafa, diploma Kitchener School of Medicine, Khartoum, D. G. Neill, M.B. Queensland, Kumaradase Rajasuriya, L.M.S. Ceylon, A. E. A. Read, M.B. Lond., A. C. Ronald, M.B. Cape Town, J. D. Sheehan, M.B. N.U.I., R. G. Shorter, M.B. Lond., J. P. Stanfield, M.B. Lpool, P. G. I. Stoven, M.B. Camb., C. G. A. Thomas, B.M. Oxfd, G. W. Thorpe, M.B. Birm., A. L. Turnbull, B.M. Oxfd, Walter van't Hoff, M.B. Camb., R. H. C. Wells, M.B. Lond., D. M. Williams, M.B. Wales, P. O. Williams, M.B. Camb., M. F. T. Yealland, M.B. Camb.

Licences to practise were conferred upon 129 candidates (104 men and 25 women) who have passed the final examination of the Conjoint Board:

Vincent Ainsworth, A. L. Bass, I. S. Batey, K. B. Bender, Anthony Betts, M. H. H. Bishop, June E. Brett, J. R. Brown, J. W. Brown, C. C. Bull, G. M. B. Bulman, A. R. Butterfield, G. R. C. Campion, Harold Caplan, D. A. Chiswell, J. A. Clappen, B. J. F. Coles, H. A. Collins, Betty R. Corbin, H. J. E. Cox, H. F. Crawford G. T. Crook, R. L. E. Cumberbatch, Bethan Davies, E. P. Denton, J. M. Dolphin, Aileen B. Donnison, A. K. Dowle, Michael Dulake, W. F. Dummer, A. V. Dunlop, B. A. East, T. A. Evans, N. H. Eve, F. W. Fairhead, K. T. Farn, P. M. Forster, J. L. Fraser, A. G. E. Fung-a-Fat, D. R. Gamble, Mary J. Gibbons, Basil Gilbert, I. L. Glaisher, H. W. Goldfarb, J. H. Goode, Kenneth Grainger, Bernadette Gregory, Joan E. Hancock, R. B. Handscombe, N. B. Harris, J. D. Harte, W. D. Hayley, D. A. Heath, E. R. Herst, F. E. Hill, C. B. Hodes, Vera M. C. Hollyhock, Blanche M. Hooper, Shirley E Hoyes, K. R. Hughes, J. P. Hurrell, G. H. Jeavons, R. D. Jones, A. F. Jordan, Leonard Kader, E. E. F. Keal, D. J. Kidd, D. W. G. King, Iris M. Krass, C. G. Lambert, R. J. W. Lambert, Lian Heng Lee, Fred Lees, K. M. M. Lewis, Harry Lindsay, Patricia M. Lumb,
Nancy S. Maguire, George Mangan, R. [illegible]
Marjot, Philippa M. Martin, J. A. Mea[illegible]
Morley, Yusuf Adam Motala, J. H. [illegible]
Kathleen M. Neville, Elizabeth C. [illegible]
W. N. B. Parker, W. P. Pereira, Mary E. R. Perry, R. J. V. Peter, R. A. N. Petrie, E. M. Pilkington, L. J. Posener, L. B. Prescott, M. N. Prichard, Freda E. Prince-White, F. C. Ramsey, G. L. S. Rankin, Shelagh M. Richards, G. G. Robbie, T. E. Roberts, Winifred M. S. Robinson, Vera Rose, Guy Screech, D. B. Shaw, Kenneth Shiffman, D. N. Sinclair, J. J. Slome, Isabel G. Smith, J. L. Stevenson, Mary L. Stewart, J. L. Szentpétery, Elizabeth A. Thomson, G. N. W. Tilsley, David Tingle, G. R. P. A. Vernon, Peter Wallis, A. W. Warltier, P. A. Watt, Joyce D. Waye, E. A. Wilson, P. G. Woolf, J. G. Wotherspoon, S. S. Young.

Diplomas were conferred on those named in the reports of meetings of the Royal College of Surgeons in our issues of June 21 (p. 1265) and July 19 (p. 151). The following diplomas were also conferred:

D.P.H.—Margaret A. M. Howard, F. X. Letellier, R. L. Lindon, J. F. McGovern, Manshanker Laxmishanker Rawal, G. M. Reynolds, Mary M. E. Rutter, Malati Shrinagesh, Irshad Husain Syed.

D.O.—Narindar Singh Batheja, R. D. Calcott, Brojo Mohon Chatterjee, G. V. Cole, P. H. Cowen, Rowland Cowley, C. W. L. Crawford, E. B. Doany, Stella P. Eadie, Margaret Ford, Hamish Fraser, S. D. Gun-Munro, Mohamad Habibulla, James Hughes,
I. G. Johnst[illegible] Joseph, P. J. Mathews, Jean
C. I. Melville [illegible] . N. Ormrod, J. A. E. Primrose,
Anjani Kum[illegible] Sud, J. E. Thomas, Raymond
Traill, C. G. [illegible]

D.I.H.—A[illegible] . W. McConnachie, Sardari Lal Malhotra, Manchsnker Laxmishanker Rawal, J. F. Skone, W. C. Turner, M. D. Warren.

Royal College of Surgeons of England

At a meeting of the council on July 31, with Sir Cecil Wakeley, the president, in the chair, Dr. O. C. Carter and Dr. Bernard Johnson were admitted to the council. Mr. R. C. Davenport and Mr. F. C. W. Capps were elected members of the court of examiners. Prof. F. Wood Jones was appointed to the post of honorary curator of the Hunterian collection of human and comparative anatomy on his retirement from the Sir William Collins professorship of anatomy. The Hallett prize was awarded to Dr. J. K. Ross (Middlesex Hospital).

It was decided that as from Jan. 1, 1954, the period of postgraduate surgical training in recognised posts required of candidates for the final fellowship examination should be increased to two years.

Diplomas of fellowship were granted to D. I. Stirk and G. Westbury.

Diplomas of membership and postgraduate diplomas were granted to the candidates named above in the report of the comitia of the Royal College of Physicians.

Royal Institute of Public Health and Hygiene

The institute holds courses of instruction for the certificate and diploma in public health, and the diploma in industrial health. Further information may be had from the secretary of the institute, 28, Portland Place, London, W.1.

CORRIGENDA: *Salt-retaining Adrenal Hormone.*—In the paper by Mrs. Simpson, Dr. Tait, and Mr. Bush (Aug. 2, p. 226) the first sentence under the heading *Results* should read: "The results of the assay when applied to the extract of monkey adrenal blood are given in table I." The footnote to table I should read: "1 ml. of the adrenal extract employed was equivalent to 140 µg. of deoxycortone acetate." In table II the actual mineral activity found in the corticosterone region (fraction 4) lay between 0 and 15 µg. of deoxycortone acetate.

Paratyphoid-B Fever in Cardiff.—In our note under "Public Health" published on July 19 the infecting organism should have been described as "paratyphoid-B bacillus, Vi-phage type 1."

IMMUNITY TO VIRUSES

A GENERAL DISCUSSION WITH SPECIAL REFERENCE TO THE RÔLE OF ALLERGY[*]

W. I. B. BEVERIDGE
M.A. Camb., D.V.Sc. Sydney
PROFESSOR OF ANIMAL PATHOLOGY IN THE UNIVERSITY OF CAMBRIDGE

THE degree of immunity evoked by viruses varies greatly from one disease to another. It would be useful if we could explain why some diseases are followed by a lifelong immunity whereas others seem to confer no immunity.

In looking for general principles it is often helpful to start by assembling the data and attempting some form of classification. I therefore propose classifying virus diseases according to type of immunity following a natural attack.

In class I I have placed those diseases which evoke what I shall call a first-class immunity, that is, an immunity which is dependable and endures for many years and even for life; recovery is usually accompanied by disappearance of the virus, except perhaps in occasional carriers, and relapses are rare. In class II are those diseases which produce a second-class immunity; repeated attacks of these diseases are common, even at short intervals, but again the virus is usually thrown off on recovery and relapses are unusual. A third-class immunity is the state in which the virus is not thrown off for some months or perhaps never, and in which relapses or persistence of the lesions are common; if the virus is eventually thrown off immunity is not usually solid.

Table I shows the best-known virus diseases of man and domestic animals classified according to these criteria. It is not possible to fit all known virus diseases into one of these three groups, because our knowledge of some of the diseases is too scanty. There is also the difficulty that complex biological phenomena do not lend themselves to rigid classification. But I think some simplification and approximation is justifiable so long as one bears in mind that placing two diseases in the same group does not imply complete identity in the type of immunity each produces.

Let us examine these groups of diseases and attempt to define the factors determining such widely different types of immunological behaviour.

VIRUSES PRODUCING A FIRST-CLASS IMMUNITY

All the class-I diseases are systemic infections running a rapid course. They do not have a chronic phase. Recovery is usually followed by elimination of the virus, or at any rate the virus can no longer be detected. The carrier state is found in only a few of these diseases—notably in infectious laryngotracheitis—and even in this disease only a small proportion of recovered animals continue to harbour the virus and they show no evidence of it. Relapses shortly after the first febrile attack subsides do occur occasionally in some of these diseases but generally are rare. Late relapses (i.e., recrudescences) are never seen, except possibly with varicella: it has been suggested that zoster is a recrudescence of varicella. In some of these diseases a solid lifelong immunity is the rule. Yellow fever is a good example of this. In others, smallpox included, there are sometimes second attacks after a lapse of years. The immunity to sheep-pox, fowl-pox, and contagious ecthyma is said to wane after a few years, but, since the natural host has only a short life, second attacks are not commonly seen. It is, however, characteristic of a first-class immunity that at least for a few years it is solid: second attacks do not occur either naturally or after experimental inoculation.

A significant feature of class-I diseases is that all strains of each of the viruses are antigenically similar—i.e., one cannot distinguish by serological means between strains of virus isolated from different outbreaks of the same disease. (I am regarding the various forms of arthropod-borne encephalitis as distinct diseases.)

All class-I diseases on recovery give rise to antibodies which neutralise the virus—i.e., antibodies in the presence of which the virus cannot infect cells. These antibodies usually persist in the circulation for long periods, commonly for years. Most of these diseases are systemic diseases in which the virus spreads in the blood-stream so as to reach the tissues where the characteristic lesions develop. Thus one would expect immunity to be effective so long as there was any neutralising antibody in the circulation.

A further factor operating in the acute exanthems of man and in mumps, and in some of the other diseases in this group, is that the primary infection takes place in the respiratory tract, and is followed by a long incubation period. This long incubation period would give time for a person with a basic immunity to respond with a rise in antibody before the virus had spread throughout the body. In some of these diseases perhaps what appears to be a permanent solid immunity is only an immunity to the fully developed disease, and repeated unapparent infections of the respiratory tract may take place. Unapparent infections can occur in partly immune animals. On the other hand, we know that, with yellow fever and measles for example, a solid immunity is maintained indefinitely in the absence of further contact with the virus.

TABLE I

Class I	*Class II*
Smallpox	Influenza
Varicella	Poliomyelitis
Measles	Dengue
Rubella	Foot-and-mouth disease
Sheep-pox	African horse-sickness
Fowl-pox	Blue-tongue of sheep and cattle
Contagious ecthyma of sheep	African swine-fever
Mumps	
Canine distemper	
Swine fever	
Cattle plague	
Panleucopenia of cats	
Equine "*influenza*"	
Fowl plague	*Class III*
Newcastle disease	Psittacosis
Infectious laryngotracheitis	Lymphogranuloma
Infectious bronchitis	Trachoma
Yellow fever	Equine infectious anæmia
Rift valley fever	Virus pneumonia of swine
Arthropod-borne encephalitis	Grey-lung disease of mice

VIRUSES PRODUCING A SECOND-CLASS IMMUNITY

Class-II diseases, like those in class I, run a rapid course usually followed by elimination of the virus, except for the very occasional carrier animal. Relapses and recrudescences are unusual. The special feature of these diseases is that second attacks may occur at any time and their severity may be quite uninfluenced by the previous infection. The main reason for this lack of protection is that all these viruses have a variety of antigenic types and/or subtypes. Thus there may be little or no cross-immunity between different strains of the same virus. This has a serological basis in that although all these diseases give rise to neutralising antibodies to the strains of virus causing the attack there is little or no cross-neutralisation between different types, and even subtypes show only partial cross-neutralisation.

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[*] Almroth Wright lecture delivered at St. Mary's Hospital Medical School, on May 13, 1952.

Some at least of these viruses have an interesting characteristic, which is no doubt associated with the fact that each is found occurring naturally in a variety of immunological types: their antigenic character is not fixed but is continually changing. This is well seen in influenza A and one suspects the same applies to foot-and-mouth disease. Presumably a virus found occurring naturally in a variety of serological types has developed those different types through its ability to change its antigenic character; so one would expect it to be still unstable in this way. It is now generally agreed that changes of serological subtypes are continually occurring with influenza A, but there is reason to suspect that even changes from one type of influenza to another may occur. In epidemics of influenza A there are usually a few cases of influenza B and vice versa. Similarly, during the present epidemic of foot-and-mouth in Europe all three main types have been found. These types remain fixed in the laboratory, but it is conceivable that in the field there are occasional mutations from one type to another.

A further reason for the inefficiency of immunity in the case of the influenza viruses (and probably as yet undiscovered viruses of the respiratory tract) may be that the disease develops by the virus spreading over the surface of the mucous membrane without contact with the blood-stream. Similarly poliomyelitis may infect the mucosa of the alimentary canal and establish itself even for considerable periods despite the presence of antibody in the circulation.

Francis (1947) thinks that the surface nature of influenza infection is the main reason for the shortness of immunity in this disease; but I doubt whether this factor is as important as he says. Influenza B seems to confer a considerably longer immunity than does influenza A, because the former recurs in epidemic form at longer intervals than A, and in a recent epidemic in this country the age-incidence was such as to suggest that immunity lasted many years, the disease being largely confined to children. We have no direct information on the duration of immunity to influenza B, but the evidence suggests that it is many years; in fact if we were to regard influenza B as a distinct disease I should feel inclined to include it in class I. Yet influenza B is a surface infection just as much as A is. The latter, however, seems to have a greater range antigenically than B does, and it is this great variability which I regard as far the most important reason why it produces a second-class immunity. Another point in favour of this view is that the prevalent immunological subtype of influenza A seems to change in a major way every few years, suggesting that the community becomes too immune to the older subtypes for them to be able to produce epidemics.

Except possibly for these diseases which are surface infections, immunity to homologous strains of class-II diseases is probably as durable as is immunity to class-I diseases. Second infections with the same type of foot-and-mouth after rather short intervals can probably be explained as being due to differences between subtypes which have only lately been appreciated. Immunity to natural exposure with the same strain of foot-and-mouth lasts about two years. However, foot-and-mouth may be in rather a special category inasmuch as it multiplies extremely rapidly and is probably more infectious than any other known virus.

VIRUSES PRODUCING A THIRD-CLASS IMMUNITY

For the immunological characters of the first two classes, then, fairly satisfying explanations are forthcoming, although there are some points to which we shall refer again presently. Class III presents a very different picture. It includes both systemic and localised diseases, and there are acute and chronic phases. The main feature they have in common is that the infection, and often the lesions, persist for long periods. Relapses are common under adversity and may occur long after the initial infection, so might more appropriately be called recrudescences; these are often severe and even fatal.

Although in these diseases there is not an immunological mechanism capable of rapidly eradicating the virus or of preventing recrudescences under stress, the animal is usually refractory to further inoculation so long as it remains infected. Thus human beings infected with lymphogranuloma resist inoculations of active virus into the skin on a part of the body remote from the lesions. A considerable degree of immunity can be engendered in mice by intraperitoneal inoculation of live psittacosis virus. It is not quite clear how far immunity continues after viruses of the psittacosis-lymphogranuloma group have entirely disappeared from the host, but it seems that at least some degree of resistance persists. This, however, is not so with grey lung or trachoma, or with equine infectious anæmia. If these infections are cleared up, for instance by chemotherapy, the host becomes fully susceptible to reinfection. Repeated inoculations of active grey-lung virus intraperitoneally confers no immunity to intranasal inoculation.

Viruses of the psittacosis group are not neutralised to any significant degree by the sera of convalescent people or animals. It is possible sometimes to demonstrate neutralisation, especially with hyper-immune serum prepared in fowls, but this is of a low order compared with what can be demonstrated with viruses in classes I and II. Similarly, neutralisation by antisera is either absent or feeble with trachoma, virus pneumonia of pigs, and grey lung of mice. With infectious anæmia of horses the virus can be isolated from the blood for long periods; so apparently there is no neutralisation of this virus either.

The common factor in class-III diseases then seems to be lack of any significant degree of neutralisation by antiserum. Several of them are systemic infections and may have an acute febrile phase; so there is nothing about their character that might explain why neutralising antibodies are not formed; indeed we know that complement-fixing antibodies are formed in some of them. Therefore we must regard lack of neutralisation, or weak neutralisation, as a property of the virus and not as due to any character of the disease such as lack of sufficient antigenic stimulus.

One wonders whether the weak neutralisation that can sometimes be shown with the psittacosis group is not more analogous to sensitisation of bacteria with antiserum than to neutralisation as seen with viruses of class I and II—i.e., preparation for phagocytosis rather than prevention of infection of cells. Antiserum affects bacteria in several ways, perhaps the most important of which is to render the bacteria more liable to phagocytosis. Antibodies have similar actions on viruses, but in addition certain antibodies—the neutralising antibodies—are able to prevent the virus infecting the susceptible cell. With some viruses, those of the influenza group for example, the elementary body is prevented from attaching itself to the cell, while in vaccinia the elementary body can attach itself to the cell but antibody seems to interrupt its progress at this stage. This is what I mean by true virus neutralisation.

This lack of neutralisability of class-III viruses may imply that with them the virus-cell relationship is basically different from that with other viruses. A fundamental difference is also suggested by the fact that several of them—psittacosis, lymphogranuloma and other members of this group, trachoma, grey lung, pneumonia of pigs—are susceptible to certain antibiotics. It has been suggested that some of these agents may have a phase of multiplication outside the cell, and indeed microscopic studies have been made which lend support to this view, at least so far as the psittacosis-lymphogranuloma group is concerned (Weiss 1949). It is significant also that all viruses of class III are large, perhaps with the exception of equine infectious anæmia which on not very substantial experimental evidence is said to be not more than 50 µ in diameter. Thus in several respects these viruses occupy a position between the bacteria and more typical viruses, infectious anæmia perhaps being an exception owing to its suspected small size.

SOME ANOMALIES

When we try to arrange biological material into an arbitrary scheme of classification it is often salutary to look at the exceptions that do not fit.

Herpes appears at first sight to belong to class III, since the virus persists and relapses are common. However, there is no persistence of lesions and the relapses are minor and localised—not so serious as the original infection, as the relapses with the other members of class III are. With herpes there is neutralisation with antibody and it has only one serological type. Thus herpes is best regarded as an atypical class-I virus.

Two other odd diseases are lymphocytic choriomeningitis and St. Louis encephalitis infections of mice. There are two anomalies here: (*a*) the viruses often persist even though they are susceptible to being neutralised by antibodies, which however appear very late, and (*b*) recovered mice are immune in the absence of neutralising antibodies—i.e., before they are formed. For some reason that we do not know, neutralising antibodies to lymphocytic choriomeningitis are not formed in any animal for at least several weeks, and in mice, especially those which have become infected in utero, neutralising antibodies may never be formed and the virus may persist in the circulation for many months. These two diseases have been cited by some writers to support the view that neutralising antibody is not the main factor in immunity to viruses. We shall return to this point later. These two viruses must be regarded as intermediates between class I and class III.

The tumour-causing viruses, for instance the Shope papilloma and Rous sarcoma, are known to be susceptible to neutralisation by antibody; yet the tumours persist for a considerable time. The probable explanation is that, as the tumour cells divide, the virus passes to the daughter cells and so need not come in contact with antibody. Most other viruses cause cells to rupture; indeed they have to do so in order to escape and spread to other cells. They risk coming in contact with antibody before getting into the next cell, whereas the tumour viruses stimulate the cells to multiply and do not cause them to rupture. It is well known that all viruses are out of the reach of antibody while they are inside cells.

Some difficulties also arise in trying to fit into this scheme those diseases which have incubation periods running into months—namely, rabies, infectious hepatitis of man, serum hepatitis, and scrapie of sheep. I think rabies would fit satisfactorily into class I but we have not enough data about the other three viruses to attempt a classification.

These anomalies do not invalidate the proposed system of classification because it is common experience in biology to meet intermediates.

CONCLUSIONS FROM THE FOREGOING

In summary, then, the different classes of immunity are not to be explained by the characters of the diseases but by the characters of the viruses. The significant factor seems to be neutralisation of the virus by antibody. The general principle we have been looking for to explain the different classes of immunity may be stated as follows:

> Class-I viruses are neutralisable and each disease has only one antigenic type of virus.
>
> Class-II viruses are neutralisable but have a multiplicity of antigenic types and these may be subject to continual change.
>
> Class-III viruses are not susceptible to neutralisation in the way the others are.

Conversely, if a virus is neutralised by its antiserum and there is no persistence of lesions one can expect a first-class or second-class immunity; but if there is no neutralisation and lesions persist one can expect only a third-class immunity.

Thus in a general way the class of virus immunity can be explained in terms of neutralisation by antisera, and taking a superficial view one might be tempted to end this review here. This, however, is not the whole story. On the one hand, as we have seen, there may be resistance without neutralising antibodies in the class-III diseases and in lymphocytic choriomeningitis and St. Louis in mice. On the other hand the presence of neutralising antibody does not always confer immunity—against influenza or lymphocytic choriomeningitis, for instance.

ARTIFICIAL IMMUNISATION

Let us see if we can get more light on the underlying principles of virus immunity by examining information about artificial immunisation. A glance over the various vaccines available will also serve as an introduction for some ideas I am going to put forward about possible new developments in virus vaccines.

Active Immunity

Active immunity may be produced artificially by inoculation of relatively large amounts of killed virus or inoculation of a small amount of living virus sufficient to set up infection.

Living virus is still used in the fully virulent state for immunisation against some animal diseases. It is either inoculated by an unnatural route or given under cover of antiserum. Usually an immunity follows which is equal to that after a natural attack; but the use of virulent virus has obvious disadvantages, and the most popular and successful methods of vaccination are those employing attenuated strains. Attenuated vaccines are now used against smallpox, fowl-pox, distemper, swine fever, cattle plague, fowl plague, Newcastle disease, yellow fever, Rift valley fever, dengue, African horse-sickness, blue-tongue, and rabies. These attenuated strains set up a mild or an unapparent infection which confers an immunity which is usually not greatly inferior to that following a natural attack. It may be noted in passing that it is not always easy to produce just the right degree of attenuation. There is not only the danger of insufficient attenuation; the process can be carried too far, so that the virus fails to produce immunity.

Killed vaccines against virus diseases are of comparatively recent introduction. It used to be believed that immunity to virus could be produced only by living virus. This was a misconception which originated from our inability to produce virus antigens in sufficient quantity free from excessive amounts of other protein.

Killed vaccines are now available against the following diseases: swine fever, cattle plague, Newcastle disease of fowls, feline panleucopenia and certain forms of arthropod-borne encephalitis, influenza A and B, foot-and-mouth disease, rabies, and abortion of ewes. These vaccines give rise to neutralising antibodies, but the immunity they confer lasts not more than six to twelve months, even though the disease is one in which a first-class immunity follows a natural attack. However, in some diseases, like mumps, a basal immunity may be all that is needed to raise the percentage of unapparent infections from the usual 50 to nearly 100. This is most likely to be achieved in those diseases which have a long incubation period and which normally give rise to a high proportion of unapparent infections. This field has not been explored.

Looking at the data on artificial immunity in the light of our classification we see that, as one would expect, it is against diseases in *class I* that most of the successful vaccines have been prepared. The best of these are attenuated living vaccines, but useful immunity lasting up to a year has been produced by some killed vaccines. In *class II*, whether living or killed vaccines are used, the problem is to include in the vaccine strains producing an immunity to those strains likely to be encountered. This involves constantly examining the antigenic character of the wild strains and adding any new types or major subtypes to the vaccine. *Class-III* diseases would seem, a priori, the most difficult to vaccinate against successfully, and this is what we find. Immunity has been obtained experimentally against psittacosis and lymphogranuloma by repeated inoculation of living virus intramuscularly or intraperitoneally. Killed vaccines against these two agents confer some resistance (Wagner et al. 1946), but it is generally agreed that this is of a low order, and the same applies to feline pneumonitis. Recent reports indicate that satisfactory immunity against the natural disease can be obtained in ewe abortion (a member of psittacosis group) with formalised vaccines (McEwen et al. 1951).

Passive Immunisation

Effective temporary immunity can be conferred against several virus diseases by administration of antisera. It is probably correct to say that this applies to all the diseases in classes I and II provided suitably potent and specific sera are available. Probably no protection against class-III diseases is conferred by antisera.

Summary

Thus the results of artificial immunisation are in general what one would expect from a knowledge of natural immunity. Two points, however, emerge. Firstly, the efficacy of passive immunity provides convincing evidence of the important rôle of humoral factors in immunity to viruses in classes I and II. Secondly all killed vaccines so far put into use produce at best an immunity that is short-lived and inferior to that produced by living vaccines or a natural attack, even though they may produce reasonably good levels of neutralising antibody.

THEORY OF VIRUS IMMUNITY

Any general theory on the mechanisms of immunity to viruses must take into account the following points, among others: (*a*) infection with the virus confers a better immunity than does vaccination with killed virus; (*b*) although immunity and neutralising antibody generally run parallel, with some diseases immunity may be present in the absence of neutralising antibody, and vice versa.

The first point is accounted for by some people by hypothesising that those viruses which confer a long-lasting immunity persist almost indefinitely in the host, even though there is no evidence of their presence: thus there is a continual antigenic stimulus or, alternatively, the presence of the virus may prevent further infection by means of the interference phenomenon. While we know that some viruses do persist for long periods, there is no direct evidence that this is so with most of the class-I diseases. For this reason, and because there is no way of testing the hypothesis, it seems to me more reasonable to look for some other explanation.

The second point, lack of correlation between neutralising antibody and immunity in certain diseases, has led some virus workers to conclude that the principal factor in immunity to viruses is specific cellular immunity and not antibody. However, attempts to demonstrate cellular immunity by tissue culture or grafting experiments have failed; and, indeed, it is difficult to imagine the mechanism of such an immunity, unless possibly it is either in the nature of an interference phenomenon or is due to antibodies attached to the cells; but I doubt if either of these mechanisms is what those who favour cellular immunity have in mind.

It seems to me that we may be able to dispense with the rather obscure concept of specific cellular immunity and with the idea of viruses persisting without being demonstrable. In all these diseases antibodies are produced even if they do not neutralise; a basic immunity is set up—i.e., the ability to produce antibody very rapidly and in high titre on second contact with the virus—and a specific allergy to the virus is produced. It is reasonable to assume that these three factors operate in immunity to all virus diseases, but in addition there is neutralisation in the class-I and class-II diseases, and this, when present, is of overriding importance.

Allergy is usually left out of discussions on immunity to viruses, although it was remarked on by Edward Jenner who first reported that an infection with a virus results in a subsequent heightened reactivity to that virus. He wrote: “It is remarkable that variolous matter, when the system is disposed to reject it, should incite inflammation more speedily than when it produces smallpox.”

By inoculation of killed virus into the skin, allergic reactivity can be shown to be present in persons or animals recovered from, or chronically infected with, vaccinia, lymphogranuloma, psittacosis, trachoma, herpes, mumps, influenza, swine fever, and contagious ecthyma of sheep. The reaction at the site of inoculation reaches a maximum at twenty-four to seventy-two hours. Allergy to the infective agent is seen after recovery in all types of infectious diseases and would probably be found with all virus diseases if looked for. It seems to me most unlikely that such a general phenomenon does not serve a purpose—i.e., has not some survival value for the host.

Although there has for many years been great controversy as to whether allergy in tuberculosis and other bacterial infections is beneficial or harmful, allergy has not attracted much interest from virologists, except as a method of indicating past or present infection. I believe the rôle of specific allergy is to activate and enhance the effectiveness of humoral and cellular defences—i.e., to mobilise the defences at the site of invasion. Thus the three factors—antibody, cellular reaction, and allergy—should be regarded as interdependent and operating together. The outcome of initial infection must be considerably influenced by the vigour of the local reaction to it and also by the speed with which the reaction develops. Speed is perhaps even more important in virus than in bacterial infections because the antibody cannot exert its effect after the virus gets inside the cells.

Thus it seems highly probable that allergy helps the body resist invasion of the epithelial surfaces. Whether or not it is beneficial after the infection has already become established in some internal organ is a different question and may depend on the extent of the infection.

When vaccinia is reinoculated into animals or people who have recently had a previous infection with the virus, there is a rapid and vigorous reaction at the site of inoculation and the infection does not become established. People revaccinated after many years often show a similar “immediate” reaction. Such reactions are apparently due to a persisting allergy to the virus, which, however, may not be associated with the continued presence of neutralising antibody. Repeated reinoculation in such persons produces in a proportion of them a full “primary”-type take. Evidently the allergic barrier, not backed up by antibody, presents a protection which is effective only in a proportion of inoculations, and once the barrier is passed there is nothing to stop a full infection developing.

I think that allergy plays a similar part in immunity to influenza. It is a reasonable assumption that allergic reactivity enables a person to react more rapidly than otherwise to infection with influenza virus and that part of this reaction consists in an outpouring of serum on to the surface of the mucosa. Such a rapid liberation of serum may prevent extensive surface spread of the virus if the serum contains appropriate antibodies. It is well known that with influenza the titre of the antibody is only roughly correlated to resistance to the disease. It may be that resistance is determined by a combination of circulating antibody and specific allergy.

Some years ago Sir Macfarlane Burnet and I produced evidence that an attack of influenza makes a person allergic to the virus (Beveridge and Burnet 1944). The evidence consisted mostly in showing a positive correlation between skin reactions and past contact with the virus as indicated by the presence of antibody, but we also reported some incidental observations suggesting that allergic symptoms may sometimes be elicited by spraying virus up the nose.

Recently indirect evidence supporting the hypothesis that allergy plays an important part in defence has come from quite a different quarter.

PATHOTOPIC POTENTIATION

Fazekas de St. Groth (1951) has found that mice immunised against influenza by intranasal inoculation are much more effectively protected against challenge inoculation than are mice inoculated intraperitoneally, and that this better protection is due to there being more antibody free on the surface of the mucosa in the mice inoculated by the intranasal route. He has further shown that this antibody on the surface of the respiratory tract, and the better protection it affords, is not due to it being formed locally in the respiratory tract, as might be expected, but is accounted for by a phenomenon he calls "pathotopic potentiation." This means that a mild inflammation set up in the respiratory tract by any agent —not necessarily a virus—results in liberation of any antibody present in the serum on to the surface of the mucosa. Thus he was able to show that mice in which antibody had been produced by intraperitoneal inoculation had their resistance greatly enhanced by inoculating into the respiratory tract chemicals causing a mild inflammation. In all such experiments he showed that the effect of the potentiating agent was to liberate antibodies on to the surface of the respiratory tract.

Friedemann (1947) and Fazekas de St. Groth have both stressed the point that as a general principle in immunity it is important for antibody to be present at the site of infection, not merely in the circulation, and they have produced a considerable amount of evidence in support of this view.

What interests me particularly about these findings is that they fit in so well with my views about the rôle of allergy. What better potentiating agent could there be than allergy specific to the infective agent? Specific allergy would seem to be Nature's means of hastening liberation of antibody on mucous surfaces or into intercellular spaces of the skin when an invasion threatens.

EXPERIMENTAL PRODUCTION OF VIRUS ALLERGY

I have carried out some experiments to find whether allergy to influenza could be produced by administration of living or killed vaccines. One group of medical students was inoculated subcutaneously with formalinised virus and another group had attenuated living virus sprayed up the nose.

The living vaccine consisted of a mixture of influenza A and B viruses which had been attenuated by repeated passage in eggs, and it was administered in the form of infected allantoic fluid sprayed up the nose with an ordinary "atomiser." The killed vaccine consisted of formalinised allantoic fluid infected with the same viruses. 1·0 ml. of each strain was inoculated subcutaneously. Skin tests were carried out at the time of inoculation and three weeks later, using a 1 in 5 dilution of virus as allantoic fluid infected with either influenza A or B or, as a control, with the virus of Newcastle disease. 0·1 ml. was inoculated intradermally in the forearm. In reactive persons an area of erythema 5–20 mm. in diameter was produced, reaching its peak in twenty-four to thirty hours. The erythema was often accompanied by slight swelling and sometimes by itching.

TABLE II—INCREASE IN SKIN SENSITIVITY TO INFLUENZA VIRUS AFTER INTRANASAL INOCULATION

Subject	Before			After			Difference		
	A	B	C	A	B	C	A	B	C
a	8	8	4	8	13	3	0	+5	−1
b	5	8	3	12	10	3	+7	+2	0
c	10	5	3	10	10	3	0	+5	0
d	10	4	6	10	14	5	0	+10	−1
e	10	4	3	12	13	3	+2	+11	0
f	5	3	2	14	18	10	+9	+15	+8
g	10	5	0	12	20	0	+2	+15	0
h	6	6	3	17	20	5	+11	+14	+2

A = influenza A. B = influenza B. C = Control. The figures represent the diameter of the reactions in man

Table II shows a few selected results in people who received living virus intranasally. These results are by no means a representative sample, but I have chosen them as illustrating what happens in a proportion of cases.

Table III is a summary of the results with both methods of inoculation. It will be seen that after intranasal inoculation about half the subjects showed an increased sensitivity to each virus, whereas after subcutaneous inoculation there were very few increases. These latter probably represent only normal or chance variations, because about the same proportion of controls also showed an increase.

These results, which have been subjected to statistical analysis, show that killed vaccine in the form of formalinised allantoic fluid does not produce specific allergy, but that spraying living virus up the nose does so in a proportion of cases. I have no controls to exclude the possibility that spraying killed virus up the nose may not also produce allergy, but I think this is unlikely. Antibody titrations were not carried out on these subjects, but we know from past experience with these viruses that they produce an antibody rise in about half of the people sprayed.

THE OUTLOOK

I shall conclude with some speculation on possible future developments in vaccination against virus diseases.

It is now some eight years since Friedewald (1944) showed that killed influenza vaccines inoculated in a water-in-oil emulsion gave an extraordinarily good production of antibody which may be even higher and more sustained than that following infection with the virus. This finding has been amply confirmed, and now that Salk et al. (1951) have overcome the difficulty of finding an effective adjuvant that does not produce an undesirable local reaction it is probable that this type of vaccine will come into wide use for combating virus

TABLE III—INCREASE IN SKIN SENSITIVITY TO INFLUENZA VIRUS

Inoculation	Influenza A	Influenza B	Control
Living virus intranasally . .	23/35	15/29	4/35
Formalinised virus subcutaneously	4/27	4/17	3/27

Numerators = no. showing increase of 0·5 cm. in cutaneous reaction. Denominators = no. of subjects treated.

diseases and supersede other types of killed virus vaccines.

Ten years ago Freund and McDermott (1942) showed that allergy to horse-serum can be produced by inoculating it incorporated in a water-in-oil emulsion along with dead mycobacteria. The sensitisation was such that intradermal inoculation of horse-serum produced a tuberculin type of allergic reaction and this sensitivity lasted at least a year in guineapigs. As far as their investigation went, the presence of dead mycobacteria in the vaccine seemed to be necessary in order to produce the allergic state; therefore probably Friedewald's or Salk's vaccines do not produce allergy. Possibly a more acceptable adjuvant than mycobacteria could be found that would have this effect, and it seems likely that adjuvant, killed virus vaccines could be devised that would produce not only very high and prolonged antibody response but also a specific allergy to the virus. Such a vaccine might well produce just as good an immunity as a living vaccine. Indeed it would have one advantage over a living vaccine in that one could give a recall dose as soon as immunity waned to below a safe level, whereas with living vaccine it is not possible to revaccinate until the person has become susceptible again to the attenuated virus. Perhaps we will eventually be able even to improve on Nature and produce a better immunity than that following a natural attack of the disease.

In suggesting the development of allergenic vaccines against viruses I am assuming firstly that allergy will help in resisting invasion of the epithelial surfaces, and secondly that allergy will not be harmful in those individuals who develop the disease despite vaccination. Many pathologists would contest the second point even if they concede the first. Obviously this is a matter on which we require further information, but at present I see little reason for apprehension about the possible harmful effect of making a person allergic to a virus. If allergy were harmful one would expect to find second attacks of a disease often more severe than first attacks. Generally the opposite is the case, although there are probably exceptions to this rule. After all, the attenuated vaccines we use today produce allergy to the virus. However, a cautious approach is indicated and perhaps we should try allergenic vaccines first in veterinary work.

In a lecture of this sort some indulgence is usually granted in allowing speculation, and I have taken advantage of this. We all know, however, how unreliable even apparently reasonable speculation can be in the field of research.

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"... the public should realise that they have to play their part. If they want hygienic food handling, they should not be afraid of asking for it and of commenting when they see hygienic failures. How many restaurant customers have the moral courage to send back to the kitchen a cup or fork which is placed before them dirty? How many just wipe it on the tablecloth and say nothing? And the spending of a few minutes behind the counter of a snack bar shows forcibly how the public cough or sneeze germs over the food on display or tentatively touch it with fingers far dirtier than any employee would dare to have."—Dr. J. D. KERSHAW, medical officer of health for Colchester, in his annual report for 1951.

EXACT DETERMINATION OF THE CENTRAL VENOUS PRESSURE

BY A SIMPLE CLINICAL METHOD

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THE central venous pressure is the pressure in the veins close to the right atrium of the heart: it is virtually the same as the pressure in the right atrium when this part of the heart is in diastole.

The central venous pressure depends on the quantity of blood returned to the heart in a given time (venous return) and on the ability of the heart to pump it out (competence). There is a reciprocal relation between the central venous pressure and the function of the heart.

The pressure in the atrium can be measured in relation to the atmospheric pressure (actual pressure) or to the intrathoracic pressure round the heart (effective pressure). The effective venous filling pressure is the algebraic difference between the actual pressure and the intrathoracic pressure (Henderson and Barringer 1913, Wiggers 1914).

In the heart-lung preparation the venous pressure regulates the cardiac output (Patterson and Starling 1914, Wiggers and Katz 1922). In the intact healthy body, on the other hand, hormonal and nervous factors exercise a great and sometimes overwhelming influence. When the heart becomes insufficient it behaves more like the heart-lung preparation of Starling, and the dependence of the cardiac output on the venous pressure is then seen quite clearly (Richards 1947). Although it would be more accurate always to measure the effective venous pressure, one must in practice be satisfied with the measurement of the actual pressure.

CLINICAL SIGNIFICANCE OF CENTRAL VENOUS PRESSURE

(1) *A single determination* of the central venous pressure tells us whether the right heart is efficient or not (either at rest or after exertion), and thus whether œdema and ascites are of cardiac, extracardiac, or mixed origin. It can also tell us whether an acute state of shock has a central origin (cardiac infarction or lung embolus) or is due to a decrease in the blood volume or to peripheral vasodilatation. Further, it is a valuable aid in the differential diagnosis of dyspnœa: in the presence of left cardiac insufficiency, with pulmonary congestion, the venous pressure is almost always raised; but, when the dyspnœa is pulmonary in origin, especially in asthma, emphysema, and chronic bronchitis, the venous pressure (during inspiration) tends to be strikingly low, provided there is no concomitant appreciable damage of the right heart.

(2) *Repeated determinations* of the central venous pressure over a period are an excellent measure of spontaneous changes in the state of the heart in cardiac patients and of the effect of rest in bed, salt-free diet, diuretics, digitalis, quinidine, and other therapeutic agents. An increase in venous pressure during intravenous infusion gives warning of overloading of the heart. The influence of the retention of water and sodium chloride on the circulation may easily be determined by following changes in the venous pressure in renal diseases (especially acute glomerulonephritis) and during treatment with adrenal cortical hormones or related compounds.

Any scientific investigation into the control of the circulation is incomplete if the changes in the venous pressure are not followed in detail.

PREVIOUS METHODS OF MEASUREMENT

The method to be used to measure the venous pressure in the above-mentioned types of cases should not be unpleasant for the patient, and the determination should not take too much time. The results obtained by experienced investigators must be accurate to at least 1 cm. of water; for an increase in the diastolic pressure in the right ventricle by 2·5 cm. of water may cause in normal people a rise of 40% in the cardiac output (Cournand et al. 1948). The methods in use hitherto have not fulfilled all these requirements, and this is why the measurement of the venous pressure has not become universal in routine clinical examination or scientific investigation.

Method of Moritz and von Tabora

For measuring the peripheral venous pressure a large needle is inserted into the cubital vein and connected to a manometer filled with sterile sodium citrate (Moritz and von Tabora 1910). The results obtained in normal people by numerous observers have varied very greatly and are 4–12 cm. of water higher than the pressure in the right atrium. The values obtained by the method of Moritz and von Tabora in cases of congestive heart-failure are sometimes improbably high. This is due to the distance between the atrium and the point at which the pressure is determined. As a result the speed of the blood flowing in the vein, and the diameter of the lumen of the vein, which may change by vasoconstriction or dilatation, exert a considerable influence on the value found. The supposition that there is always a linear relation between the peripheral venous pressure and the right atrial pressure cannot be upheld, as has been shown by Moia et al. (1950) and Pedersen (1952). If the vein collapses anywhere between the point where the pressure is determined and the right atrium, the linear relation fails immediately (Ryder et al. 1944). Negative pressures cannot be measured in the peripheral veins (Doupe et al. 1938).

Since the introduction of cardiac catheterisation into clinical methods (Forssmann 1929, Cournand and Ranges 1941, McMichael and Sharpey-Shafer 1944a) it has been possible to determine the mean pressure in the right atrium with a manometer attached to the cardiac catheter. It is clear, however, that this is impracticable as a routine method and especially as a method of following changes in the venous pressure over long periods.

Method of Lewis

Lewis (1930) laid the foundation for the determination of the central venous pressure by using the external jugular vein as a manometer to record pressure changes in the right atrium. He stated that in normal persons the zero (or atmospheric) pressure level of the fluid in the venous system is near the attachment of the second rib to the sternum at the angle of Louis. This would apply for any position of the body, lying, sitting, or standing. Although Lewis used the method of Moritz and von Tabora for *measuring* the venous pressure, he stated:

> "If therefore we can gauge the precise level at which the veins collapse we have a gauge of the filling of the venous reservoir, or to be more exact of right auricular pressure."

McMichael (1938) obtained as good results by Lewis's method as by that of Moritz and von Tabora. We are of the opinion that of the two methods that of Lewis is much to be preferred, provided that the technique is modified and standardised. The distance between the point where the pressure is recorded in the external jugular vein and the right atrium is short, and the lumen of the vein is large; hence pulsations caused by the contraction of the heart and by respiration are little altered. By always making the patient lie so that the vein is partly filled it is possible to measure negative pressures. The pressure in the external jugular vein during atrial diastole is thus almost equal to, and certainly closely related to, the pressure in the right atrium.

THE MODIFIED METHOD OF LEWIS

During the past ten years, investigations have been made in our clinic to develop a standard technique for the measurement of the central venous pressure. The provisional results have already been published by Allen (1948). Like Leishman (1946) we originally used a simple measuring device, which we later modified. Whereas Leishman found the same values as Lewis in normal people, Allen, with the standardised method, obtained results 5 cm. lower than those of either of these observers, and 6–10 cm. lower than those obtained by the method of Moritz and von Tabora for peripheral venous pressure.

Since 1948 we have measured the central venous pressure in a large number of normal persons, and our results are still lower than those reported by Allen, although only slightly so. Great care must be taken to have the patient lying in a good position, and the pressure is measured only when the patient is emotionally and bodily at rest. If attention is paid to these points, the results obtained by two experienced persons generally differ by not more than 0·5 cm.

Since the end of 1947 the measurement of the central venous pressure by the modified method has formed part of the routine examination of all patients, whether admitted to the clinic or attending as outpatients. It has been an indispensable link in our investigations into the relation between the circulation and the excretion of water and electrolytes (Borst 1948, Molhuysen et al. 1950, Blomhert et al. 1951).

Principle of Method

If the external jugular vein is to be used as an atrial manometer, two requirements must be fulfilled:

(1) There must be free communication between the neck veins and the right atrium. We therefore can only measure the pressure when the valves in the veins are open—*i.e.*, during inspiration and falling atrial pressure ("negative" *x* and *y* wave or trough of the venous pulse tracing). During expiration and during atrial systole the central venous pressure rises and the valves of the veins close. *Thus during expiration and atrial systole the filling of the vein does not reflect the atrial pressure; moreover the determination of the highest point to which the vein is filled is more difficult than the determination of the lowest point of complete collapse of the vein.*

(2) There should theoretically be no flow of blood in the vein while the pressure therein is being measured. Therefore *we obstruct the peripheral blood-stream by light pressure* with the finger on the distal end of the vein just below the angle of the mandible. A new potential source of error is introduced by closing the upper end of the manometer, but *this does not prevent the obtaining of a reliable reading, since* the vein is not a rigid tube and does not require any significant pressure to cause it to collapse.

Reference Point

The pressures in the heart are measured in centimetres of water in relation to atmospheric pressure, which is regarded as nil (actual pressure). To eliminate hydrostatic factors the intracardiac pressure must be measured from a horizontal plane through the heart. This plane cannot be determined; therefore a fixed reference point is used on the thorax. The vertical distance from this point to the selected horizontal plane should be as constant as possible. Following Bloomfield et al. (1946) we chose a plane 5 cm. below the angle of Louis with the patient lying horizontal. In theory the plane should pass through the centre of the right atrium, but in practice this is often far from the case. In every person the position of the plane in relation to the reference point is different; moreover it varies with respiration and during the cardiac cycle. Bloomfield et al. measured in normal people the vertical distance from the angle of Louis to the midpoint of a straight line between the anterior tip of the ventricle and the lowest point of the atrium by lateral radiography. They found an average value of

the vein. A mark is made on the skin to indicate the lowest point of collapse, followed by the actual measurement of the pressure.

For the determination of the difference in level between the point of venous collapse and the reference point we use the instrument shown in fig. 5. A small spirit-level is incorporated in the horizontal arm. The method of use is obvious from the figure.

Although it is simple, the determination of central venous pressure, like any clinical method, has to be learnt by experience.

Difficulties in Finding Correct Point of Collapse

(1) The external jugular vein may be kinked at the thoracic inlet if the neck is flexed too far forwards, or if it is too far extended, whereby the muscles of the neck are not relaxed. It is also possible for the head to be insufficiently or excessively rotated. Occasionally no pulsations are seen while the vein is distended. By improving the position of the patient or the rotation of the head, pulsations can usually be brought into view and the vein made to collapse after interruption of the centripetal blood-stream. The vein may be kinked even if pulsations are seen, because the posterior facial vein divides into two parts, of which the posterior helps to form the external jugular vein, and the anterior helps to form the common facial vein, which joins the internal jugular vein. Blood may thus reach the atrium by the alternative path; the intermittent flow causes pulsations, but the external jugular vein will not collapse at the "lowest point." The point of collapse is then usually not sharply defined until the venous occlusion at the thoracic inlet is overcome, and a direct route established for the flow of blood from the external jugular vein to the right atrium.

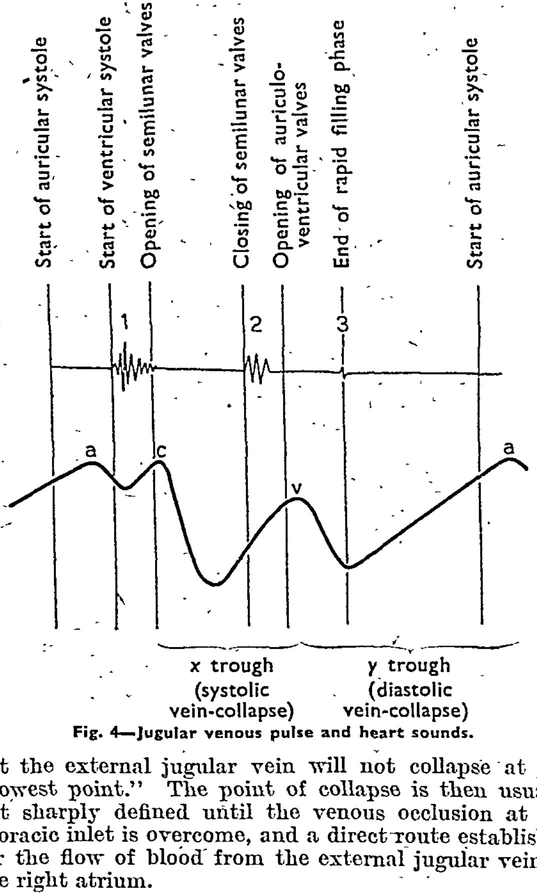
Start of auricular systole
Start of ventricular systole
Opening of semilunar valves
Closing of semilunar valves
Opening of auriculo-ventricular valves
End of rapid filling phase
Start of auricular systole
1
2
3
a
c
v
a
x trough (systolic vein-collapse)
y trough (diastolic vein-collapse)

Fig. 4—Jugular venous pulse and heart sounds.

(2) The measurement of the pressure may be difficult if the external jugular vein is poorly developed and pulsates poorly (in 14% of the patients in our series). In this event sometimes the internal jugular vein should be used.

(3) In severe shock the pulsations in the external jugular vein are small and the vein is contracted. It may be impossible to measure the central venous pressure in such cases.

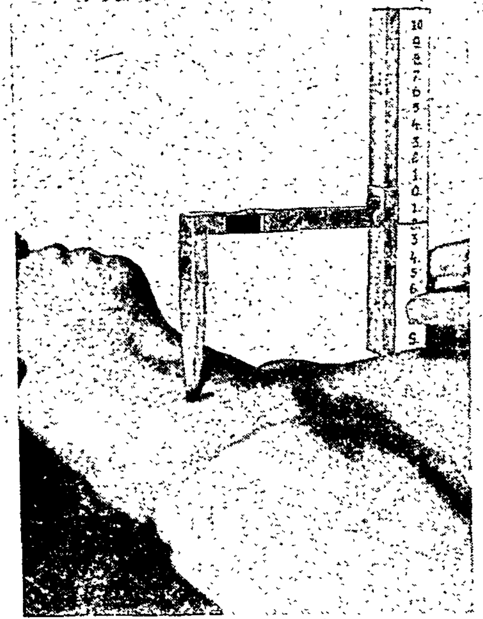

Fig. 5—Method of measuring central venous pressure. A spirit-leve is incorporated in the horizontal arm. Central venous pressure is +3 cm. of water (2 cm. below sternal angle).

(4) Sometimes there are no pulsating or collapsing veins in the neck, as a result of which it may be impossible to measure the venous pressure at all (6% of our cases).

(5) Unilateral or bilateral congested veins without pulsations, even in the sitting position, indicate obstruction to the return of venous blood to the heart, from pressure on the large veins and heart—e.g., mediastinal tumours, enlarged lymph-glands, and aortic aneurysm—or thrombosis of the veins.

RESULTS

Of a series of 400 outpatients:

1. The central venous pressure was determined without difficulty in 321 (80%). The external jugular veins were well developed, pulsated well, and collapsed clearly.
2. The pressure was determined less easily or with difficulty in 55 patients (14%). The external jugular veins were less well developed, pulsated less actively, or collapsed less clearly, and in some cases pressure had to be measured in the internal jugular vein.
3. The pressure could not be measured in 24 patients (6%). There were no visible neck veins or it was impossible, in spite of every attention to the position of the patient, to find a vein which pulsated or collapsed well.

In 332 cases two experienced observers determined the central venous pressure independently. The results showed no difference in 195 (59%); a difference of not more than 0·5 cm. in 104 (31%); and a difference greater than 0·5 cm. in 33 (10%). Thus in 90% of the

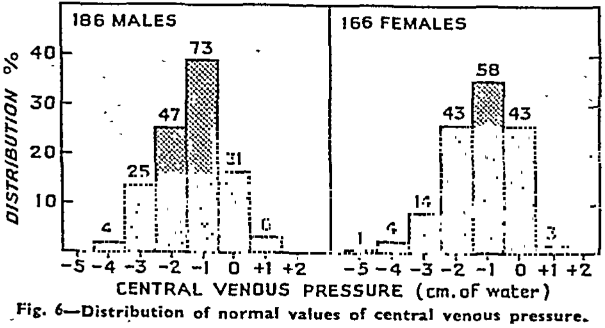

Fig. 6—Distribution of normal values of central venous pressure.

cases investigated the duplicated determinations differed by not more than 0·5 cm.

NORMAL CENTRAL VENOUS PRESSURE

We have taken as normal the results obtained in 352 completely investigated outpatients (186 males and 166 females) who showed no abnormality of the circulatory or respiratory systems, and in whom no definite anæmia or decrease in the plasma-proteins was demonstrable.

Since the error in measurements is generally not more than 0·5 cm., the results are grouped at intervals of 1 cm.: from +1·5 to +0·5 cm., from +0·5 to −0·5 cm., from −0·5 to −1·5 cm.,...from −4·5 to −5·5 cm. The distribution of the normal figures for these males and females is given in fig. 6, which shows that the greatest frequency is found in the interval from −0·5 to −1·5 cm. in both sexes.

The result of the calculation of onesided confidence intervals for the percentages of males and females with a central venous pressure between +0·5 and −3·5 cm. of water is as follows: with a confidence coefficient of 0·005 (0·5%) at least 88% of the males have a central venous pressure between +0·5 and −3·5 cm. of water, whereas with a confidence coefficient of 0·1 (10%) at least 91% lie between +0·5 and −3·5 cm. of water. For the females these figures are 89% and 92% respectively.

In a series of 165 men and 145 women not only was the central venous pressure and the age known, but also the diameter of the thorax at the level of the angle of Louis. The relations between the central venous pressure on the one hand, and the age and the thoracic diameter on the other were statistically investigated. There was found to be a definite relation. To eliminate this factor of dependency of the central venous pressure on age and diameter of the thorax a correction table was compiled from our observations (Molhuysen 1952). New histograms were constructed, but these did not differ materially from the original histograms, and we have given up using them.

Daily Variation

The changes in central venous pressure during the day are fairly large, but seldom more than 1 cm. in normal persons. Patients with a raised central venous pressure often show changes of several centimetres.

RELATION BETWEEN CENTRAL VENOUS PRESSURE AND MEAN PRESSURE IN RIGHT ATRIUM IN NORMAL PERSONS

Several investigators have measured the mean pressure in the right atrium with a manometer attached to a cardiac catheter, with the subjects lying down. In table I we compared their results with the normal values for the central venous pressure determined by our method.

McMichael and Sharpey-Shafer (1944b) took the horizontal plane through the angle of Louis as their zero pressure level. Their figure is therefore increased by 5 cm. to make it comparable with those of other investigators, who, like ourselves, used a horizontal plane 5 cm. below the angle of Louis as zero pressure level.

Because in our method the pressure in the jugular vein is determined when the pressure in the atrium is lowest—i.e., during inspiration and ventricular systole—it is to be expected that our results will be lower than the mean pressure in the atrium. The pressure in the right atrium changes during the cardiac cycle by about 3–4 mm. of mercury (Cournand et al. 1951). Our results, which are slightly lower than those of Allen (1948), agree satisfactorily with those of Bloomfield et al. (1946), account being taken of the above factors.

TABLE II—CENTRAL VENOUS PRESSURE AND MEAN RIGHT ATRIAL PRESSURE MEASURED SIMULTANEOUSLY

Case no.	Sex	Age (yr.)	Diagnosis	Size of catheter	Pressure (cm. of water)	
					Right atrium	Central venous
1	F	23	Coarctation of aorta ..	9	−2·5	−2
2	M	23	Single ventricle ..	9	0	−1
3	F	25	Patent ductus arteriosus	9	0	0
4	F	14	Pulmonary stenosis ..	8	−2	−2
5	F	12	Pulmonary stenosis ..	8	0	−1
6	M	21	Pulmonary stenosis ..	8	+3	−1·5
7	M	33	Pulmonary stenosis ..	9	−1	−1
8	M	12	Pulmonary stenosis ..	8	+3	−1
9	F	33	Mitral stenosis ..	8	−0·5	−1
10	M	29	Atrial septal defect ..	10	+2	+0·5
11	F	15	Patent ductus arteriosus	8	+1·5	0
12	F	20	Patent ductus arteriosus	8	0	−1

SIMULTANEOUS MEASUREMENT OF CENTRAL VENOUS PRESSURE AND MEAN PRESSURE IN RIGHT ATRIUM

In 11 cases of congenital heart-disease and 1 of mitral stenosis we measured the central venous pressure with the patient lying down and at the same time the mean pressure in the right atrium by connecting an intracardiac catheter to a water manometer. The results are given in table II.

Except for 1 patient the pressure in the jugular vein was equal to, or less than, the pressure in the atrium. In 8 cases the difference was 1 cm. or less, in 2 cases 1·5 cm., and in 2 cases 4 and 4·5 cm. One of these latter showed a raised mean pressure in the right ventricle. We could not ascertain whether the systolic pressure in the right atrium was higher than normal in the last 2 cases. In general there was very good agreement between the central venous pressure and the mean right atrial pressure.

FACTORS INFLUENCING CENTRAL VENOUS PRESSURE

In discussing several factors which may exert an influence on the central venous pressure one must distinguish patients with normal cardiac function from those with cardiac insufficiency.

Respiration

During normal respiration the changes resulting from changes in the depth of inspiration are less than 0·5 cm. Although we observed differences of 0·5–2·0 cm. between the pressure measured during inspiration and that measured during expiration, it is questionable, as already stated, whether the pressure during expiration can be measured by our method, since the valves will close immediately, when there is a reversal of direction of blood-flow. This is not a serious objection to the method. If the respiration is normal, the mean difference between the minimum pressure in the right atrium during inspiration and the minimum pressure during expiration is not

TABLE I—NORMAL VALUES OF CENTRAL VENOUS PRESSURE AND MEAN ATRIAL PRESSURE

Reference	Site of measurement	Method	Pressure (cm. of water)	No. of cases
Richards et al. (1942)	R. atrium	Water manometer	From +0·8 to +6	9
McMichael and Sharpey-Shafer (1944b) ..	R. atrium	Water manometer	Av. +1	?
Stead et al. (1945)	R. atrium	Water manometer	Av. +3·1 (from 0 to +8·5)	18
Bloomfield et al. (1946)	R. atrium	Hamilton manometer	From −2·7 to +2·7	9
Allen (1948)	Jugular vein	Lewis-Borst	From −1 to +2 (80%)	55
Present investigation	Jugular vein	Lewis-Borst	From −3·5 to +0·5 (90%)	352
Lagerlof and Werkö (1948)	R. atrium	Hansen manometer	Av. +3·7	13

more than 1·6 cm. of water; though an extreme value of 2·4 cm. of water has been found (Battro et al. 1949).

During forced inspiration the central venous pressure falls several centimetres. The values obtained with our method will then be much lower than those of the mean right atrial pressure. This is seen sometimes in patients with emphysema, bronchial asthma, or chronic bronchitis. If there is severe dyspnœa it is impossible to measure the pressure, because the veins are sucked completely empty in whatever position the patient is placed.

Although the pressure in the atrium falls during inspiration, this change is partly compensated for by the more rapid return of blood to the heart. The effective pressure in the right atrium increases in inspiration and falls in expiration (Lauson et al. 1946).

Posture

So long as the jugular vein collapses between the angle of the mandible and the clavicle, it is possible to determine the central venous pressure by our method. If the central venous pressure is measured first with the patient horizontal, and the body is then elevated to 30° from the horizontal, small changes will be found, usually not more than 0·25–0·50 cm. and never more than 1 cm. (Allen 1948). When the central venous pressure is raised, the patient will have to be more or less sitting, whereby the vertical distance from the centre of the atrium to the reference point alters and the result will differ from that which would be obtained with the patient lying down. When the central venous pressure is much raised, the change in position of the heart will exert relatively little influence on the result. The venous return falls slightly with the patient sitting, and the pressure is found to be slightly lower than with the patient lying down. The reverse obtains for the Trendelenburg position.

Exertion

In 376 outpatients with a normal circulatory system the central venous pressure did not rise after twenty "knees-bends" but remained constant or fell by at the most 0·5 cm. This fall may be explained by the deeper inspiration.

In cardiac patients with a raised central venous pressure a rise of several centimetres was seen after exertion (drawing up of the legs) followed by a slow return during 1–5 minutes to the original level. If the central venous pressure is normal in a patient at rest, one can discover by the effect of exertion whether there is latent cardiac insufficiency.

Pressure on Liver: Hepatojugular Reflux

In the same group of 376 patients with normal cardiac function no rise of the central venous pressure was seen during pressure on the region of the liver, if the patients continued to breathe quietly.

In the presence of latent or manifest cardiac insufficiency the central venous pressure rose several centimetres. Cessation of the pressure was followed by a rapid return of the venous pressure to the initial value. We apply this test in conjunction with the exertion test to diagnose latent cardiac insufficiency.

Emotion

In patients with normal cardiac function no measurable change in central venous pressure due to emotion was observed. In the presence of impaired cardiac function and a raised central venous pressure we often observed a further rise of several centimetres under the influence of emotion.

SUMMARY AND CONCLUSIONS

By a modification of the method of Lewis it is possible to measure the central venous pressure rapidly, accurately, and in a manner not unpleasant for the patient. We successfully measured the pressure in 376 (94%) of 400 outpatients and failed to obtain a reading in only 24 (6%).

In 332 cases with a normal circulatory system the central venous pressure was determined by two experienced observers. In 299 (90%) of these cases the difference between the two readings was 0·5 cm. or less. In 33 (10%) the difference was greater than 0·5 cm.

The central venous pressure was determined in 352 outpatients with normal circulatory and respiratory systems and without anæmia or decreased plasma-proteins, and the results were analysed statistically. In 90% of persons in whom a normal central venous pressure is to be expected the pressure lies between +0·5 and −3·5 cm. of water in relation to a horizontal plane 5 cm. below the angle of Louis.

There was a demonstrable relationship between the central venous pressure, age, and diameter of the thorax. Since the distribution of normal results is little affected by the elimination of these relationships it is unnecessary to take them into consideration in practice.

The normal values for the central venous pressure are lower than those of the mean pressure in the right atrium, since by the modified method of Lewis the pressure is measured when the atrial pressure is at its lowest—i.e., when the end of inspiration coincides with the *x* or *y* trough of the venous pulse. If this fact is taken into consideration, there is seen to be good agreement between the normal values and the values for the mean pressure in the right atrium.

The mean pressure in the right atrium was measured simultaneously with the central venous pressure in patients with congenital heart-disease and mitral stenosis but without evidence of cardiac insufficiency. In 8 cases the difference between the two readings was 1 cm. or less; in 2 there was a difference of 1·5 cm.; and in 2 other patients a difference was found of 4 and 4·5 cm.

Factors which may influence the central venous pressure are discussed.

We are indebted to Prof. D. van Dantzig, Prof. J. Hemelrijk, and Mr. T. J. Terpstra, of the statistical department of the Mathematisch Centrum, Amsterdam, for the statistical analysis of our results, and to Dr. A. P. M. Verheugt, cardiologist of the Onze Lieve Vrouwe Gasthuis, Amsterdam, for permission to compare our method with that of cardiac catheterisation. This work was aided by a grant from the Netherlands Organisation for Pure Research.

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DIAGNOSIS OF MIXED PAROTID TUMOURS

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THE present is a time of change in the treatment of mixed parotid tumours. As a result of the work of Hamilton Bailey (1941, 1947, 1948) in this country and of Redon (1945, 1946), Audouin (1950), and other surgeons in France, enucleation has come under criticism as the standard surgical treatment of mixed parotid tumours, and more radical procedures, such as partial parotidectomy, superficial parotidectomy (i.e., removal of the parotid superficial to the facial nerve), and total parotidectomy, have been advocated, all with identification and preservation of the facial nerve and its branches.

Though some series of cases (Patey 1940) have been published in which the results of enucleation combined with irradiation were not too unsatisfactory, most surgeons agree that recurrence after enucleation is seen too often. Moreover, surgeons with their healthy tradition of removing tumours early and widely have always found it difficult to accept the attitude of conservatism that had grown up towards mixed parotid tumours owing to fear partly of the facial nerve and partly of infiltrative recurrences.

At present, therefore, the potentialities of the more radical operations with preservation of the facial nerve, which have been put on a sound basis technically, are being increasingly explored by surgeons all over the world. In England Kidd (1950, 1951) has published his experiences, and in France total parotidectomy seems almost to have taken the place of other operations for mixed parotid tumour. It is too early to speak of long-term results; in fact it is not yet clear whether, if enucleation is to disappear, the standard procedure to take its place should be partial parotidectomy, superficial parotidectomy, or total parotidectomy, or what are the indications for one or the other of these procedures.

DIAGNOSIS

The present paper deals not with treatment but with a prerequisite to treatment—accurate diagnosis. During the past few years we have been impressed with the inaccuracy of the clinical diagnosis of mixed parotid tumour. This is contrary to what is usually thought and taught, and, for example, candidates in final examinations are usually examined in dogmatic fashion on cases regarded as mixed parotid tumours by their examiners.

The material analysed consists of a series of consecutive cases under the care of one of us in 1940–51 which either a firm diagnosis of mixed parotid tumour was made clinically or this diagnosis was regarded as a strong possibility in the differential diagnosis. A summary of the cases with the confirmed diagnosis, where this was established, is given in the accompanying table.

CASES DIAGNOSED CLINICALLY AS MIXED PAROTID TUMOURS, 1940–51

	No. of cases	
Diagnosis not confirmed (no operation)	7	
Diagnosis confirmed:		
Primary mixed parotid tumour	18	
Recurrent mixed parotid tumour	3	
Adenolymphoma	4	
Cyst	5	
Carcinoma (including one "infiltrating mixed parotid tumour")	4	
Various:		
Chronic parotitis	1	4
Parotid lymph-gland	1	
Angio-endothelioma	1	
Neurinoma	1	
Total	45	

It will be seen that in 7 of the 45 cases the diagnosis was not established, because no operation was done. Of these 7 cases, it is probable from the subsequent course that the diagnosis was wrong in at least 2: in 1 the rapid disappearance of the lump as a result of radiotherapy led to the alteration of the clinical diagnosis to lymphosarcoma, and in the other the subsequent course suggested an uveoparotid syndrome. Of the 38 cases in which the diagnosis was established, in 18 the clinical diagnosis of primary mixed parotid tumour was confirmed, as it was also in the 3 cases of recurrent mixed tumour. But in the remaining 17 the clinical diagnosis was wrong. If we exclude the 3 recurrent cases, in which the correct diagnosis could be presumed from the previous exploration, the proportion of wrong diagnoses (17 out of 35) is approximately 50%.

That the inaccuracy of clinical diagnosis is not just a personal failing is suggested by an examination of the published reports. Thus of Kidd's 9 cases of parotidectomy with preservation of the facial nerve (he does not give his preoperative diagnosis) only 3 proved to be mixed tumours (Kidd 1950). And of Audouin's 38 total conservative parotidectomies (again the preoperative diagnoses are not given), in 12 the findings at operation excluded them from being mixed tumours (Audouin 1950). Redon, who has almost certainly had greater experience of total conservative parotidectomy than any other surgeon, tells us that in his experience the error in the clinical diagnosis of mixed parotid tumour approaches 50%.

An analysis of some of the present cases which were wrongly diagnosed clinically as mixed parotid tumour shows that the three main causes of error were cyst, adenolymphoma, and carcinoma.

Cyst clinically simulates mixed parotid tumour completely. It can be diagnosed by aspiration, but the fluid reaccumulates very quickly and, judging by our experience in the case of a patient who refused operation for eight years, nothing short of excision is curative.

Of the cysts, 2 are of special interest because after removal they were found to have tumour tissue in the wall. In one this tumour tissue was classified as an oncocytoma, and in the other as a mixed parotid tumour. In the latter case the patient, a man aged 30, subsequently migrated to Canada, and eight years later was operated on in Toronto for an infiltrating tumour with secondaries in lymphatic glands.

Adenolymphoma, again, in all our cases completely simulated clinically mixed parotid tumour, though in some cases it may simulate abscess. Contrary to what might be thought from its lymphoid structure, adenolymphoma was in our experience completely insensitive to radiotherapy.

Of the 4 cases of *carcinoma* 1 had at first all the clinical signs of a mixed parotid tumour except that it was growing rather more rapidly, and the diagnosis was only established by exploration and biopsy. In the early months of this case there was no suggestion of facial palsy. Of the other 3 cases, 1 was an extremely fibrosing carcinoma of six years' duration, and 1 an "infiltrating mixed tumour" of eight years' duration in which operation was at first refused. Both had for years no facial palsy. Neither length of history nor absence of facial palsy can be regarded, therefore, as ruling out carcinoma.

Of conditions not figuring in the present series but mimicking mixed parotid tumour tuberculosis is the most important. Redon (1946) comments specially on this fallacy. We have had 3 cases of tuberculosis of the parotid lymph-glands, not included in this series, in which a firm diagnosis of mixed parotid tumour was made clinically and the true diagnosis was not suspected until operation and biopsy. We have also had 1 case of diffuse parotid tuberculosis, but in this case the diagnosis was easily made clinically.

DISCUSSION

Possibly the clinical diagnostic error in mixed tumours of the parotid is exaggerated here by the inclusion of cases in which this diagnosis was only considered in the differential diagnosis and not firmly made. But even the latter group adds up to a considerable proportion of the cases; for example, in all the 5 cysts, all the 4 adenolymphomata, and all the 3 tuberculous lymph-glands (not included in this series) no suspicion of doubt that the condition might not be a mixed parotid tumour crossed the clinician's mind until the exploration revealed his error.

When the standard operation for mixed parotid tumour was enucleation, a false clinical diagnosis was soon rectified at operation; but, if superficial parotidectomy and total conservative parotidectomy are to be adopted as among the standard procedures for mixed parotid tumour, some preliminary diagnostic procedure seems to be indicated to avoid radical procedures for conditions in which such radicalism is not indicated. On the other hand, in carcinoma conservative operations preserving the facial nerve are not sufficiently radical; and again, if there is any doubt, the diagnostic position should be established at the beginning of the operation. The question arises of what diagnostic technique to adopt. Redon (1952) now incises as a routine all parotid tumours as a first stage of the operation and to excise a small piece for microscopy. Alternatively it may be better to do a preliminary enucleation of the tumour, where possible, with immediate microscopy. If, on the other hand, the tumour is so situated that it can be excised with a margin of normal parotid tissue round it, after identification and preservation of the branches of the facial nerve concerned, this tissue might be submitted to immediate biopsy.

We are still exploring these problems and have not yet come to any firm conclusions either on biopsy techniques or on the whole question of the position and type of radicalism indicated in mixed parotid tumours. The only point we wish to raise here is that there is a preliminary diagnostic problem.

SUMMARY

Out of 45 consecutive personal cases in which a diagnosis of mixed tumour of the parotid was made or suspected clinically, a diagnosis was established in 38.

In these 38 established cases the original diagnosis of mixed tumour was wrong in 17.

Cyst, adenolymphoma, and carcinoma were the commonest causes of error in this series. Though not represented in this series, tuberculosis of the parotid lymph-glands is also a common cause.

Adenolymphoma is not radiosensitive.

The establishment of the diagnosis should be the first step in the treatment of suspected cases of mixed tumour of the parotid if radical extirpation is contemplated.

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"... a physician should marry young.... The physician who cannot study in the bosom of his family, and amidst the interruptions produced by domestic duties and professional labours, must neglect either one or the other. Early marriage, before the establishment of fixed habits of secluded study, will, in general, save a professional man from this unfortunate dilemma."—DANIEL DRAKE (1785–1852). *Practical Essays on Medical Education and the Medical Profession in the United States.* Baltimore, 1952; p. 64.

SERUM-ANTITHROMBIN LEVEL IN FIBROCYSTIC DISEASE OF THE PANCREAS

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LABORATORY confirmation of the clinical diagnosis of fibrocystic disease of the pancreas rests mainly on the estimation of the tryptic activity of the duodenal juice. Though this estimation is technically easy, and at present the final diagnostic test, it entails discomfort to the patient and demands great patience from the nurses.

Innerfield et al. (1951), describing the results of estimating the antithrombin content of the plasma in 13 cases of fibrocystic disease, concluded that this test might be "especially useful in early cases." Following their lead, I now record observations on a much larger series at The Hospital for Sick Children, Great Ormond Street.

MATERIAL

The 67 cases investigated were either those attending the hospital for routine assessment of treatment and follow-up examination or those admitted for diagnosis during the period December, 1951, to May, 1952. Their ages varied from three weeks to fourteen years (see table). In every case the clinical diagnosis had been confirmed by examination of the duodenal juice, which failed to digest gelatin at a dilution of 1 : 6 of any specimen examined.

A control group of 200 children of the same age-group was investigated at the same time. These children, suffering from no apparent lesion of the pancreas, were all attending the hospital. 14 of these had cœliac disease.

A third group, numbering 73, consisted of the remaining members of 20 families containing 22 cases of fibrocystic disease of the pancreas included in the table. It comprises 20 mothers, 19 fathers, and 34 siblings of the cases, who had all given abnormal results to the test. With this group 80 further controls were investigated.

METHODS

The method of Innerfield et al. used plasma, obtained from venous blood citrated with 3·2% sodium citrate in the proportion of 9 parts blood to 1 part citrate. This plasma was defibrinated immediately before testing.

Defibrination was obtained by adding to 1·0 ml. plasma 0·14 ml. standardised thrombin solution. To 0·9 ml. standardised thrombin was then added 0·1 ml. defibrinated plasma, and at 1, 3, 5, 10, 15, 20, and 25 minutes a sample of 0·1 ml. of the mixture was transferred to 0·2 ml. citrated normal plasma. The time taken for each sample to produce a fibrin clot in the normal plasma was noted, the entire test being carried out in the water-bath at 37°C. A normal control was run at the same time as, and five minutes after the completion of, each unknown determination. The authors recorded the result of their test plasma as "normal" when the clotting-times of the unknown and control were identical or showed minimal variation. An "elevated" titre was reported when the clotting-times of the unknown were at least twice as great as those of the control: a "low" titre was reported when the clotting-times of the unknown after five and ten minutes' incubation were less than half those of the control.

Two obvious modifications of this original method were first investigated. Firstly, plasma obtained from a finger-prick was compared with that obtained from venepuncture. 10 adults were investigated in this way, and the results showed no significant variation one from the other. When, later, cases of fibrocystic disease were similarly investigated the parallel results were again virtually identical in 5 cases. Venepuncture as a source of blood was therefore abandoned. The second modification towards a simpler technique in children was the use of serum from clotted blood in place of the "defibrinated" plasma. Parallel tests on serum and plasma obtained from the same finger-prick were performed on 28 control children and 5 cases. Once more there were no significant variations between each pair of results, and serum has been used throughout our entire investigation of cases and controls. Experience also showed that little practical value was obtained from the use of the 1-minute sample of the mixture of serum and thrombin, and that any divergence from the normal result was apparent before the 25-minute sample. Both these samples were omitted from the majority of the cases and controls examined, and they have not been recorded in the results given here.

THE RESULTS IN 67 CASES OF FIBROCYSTIC DISEASE OF THE PANCREAS

(The clotting-time of each sample is recorded as a percentage of the mean of the normals investigated the same day)

Case no.	Age (yr.)	Sample time (min.)					Case no.	Age (yr.)	Sample time (min.)				
		3	5	10	15	20			3	5	10	15	20
1	$1^{1}/_{2}$	84	68	46	32	21	35	$8^{1}/_{2}$	70	65	60	60	51
2	1	54	44	38	21	18	36	$^{3}/_{12}$	66	63	63	65	54
3	$^{8}/_{12}$	82	72	70	65	65	37	$7^{1}/_{2}$	61	66	67	60	55
4	$^{3}/_{12}$	59	57	40	41	45	38	$1^{3}/_{12}$	75	65	63	60	31
5	5	64	62	65	72	46	39	$2^{1}/_{2}$	70	78	77	66	49
6	4	67	62	73	52	36	40	$10^{1}/_{2}$	82	70	67	68	60
7	8	73	83	52	54	55	41	$5^{3}/_{12}$	79	70	70	64	57
8	3	83	67	56	44	30	42	$3^{1}/_{2}$	82	77	70	48	46
9	13	83	67	34	24	21	43	$2^{8}/_{12}$	72	72	72	57	41
10	$4^{3}/_{12}$	84	70	59	52	48	44	5	79	76	70	60	47
11	$5^{9}/_{12}$	81	68	50	43	42	45	$^{11}/_{12}$	96	102	105	97	98
12	12	94	71	61	52	46	46	$^{10}/_{12}$	102	98	103	106	102
13	$4^{9}/_{12}$	94	69	64	55	49	47	$5^{1}/_{2}$	63	67	78	64	39
14	$6^{1}/_{2}$	94	67	64	54	53	48	4	76	65	68	60	40
15	$3^{9}/_{12}$	94	57	58	56	53	49	8	71	67	60	65	49
16	$1^{9}/_{12}$	106	60	70	68	63	50	$5^{1}/_{2}$	71	74	54	57	47
17	$4^{9}/_{12}$	77	37	34	34	40	51	$3^{9}/_{12}$	62	63	65	62	62
18	3	82	85	64	68	50	52	$2^{1}/_{2}$	95	98	100	97	94
19	$1^{1}/_{12}$	84	80	49	40	41	53	$^{8}/_{12}$	69	69	55	45	38
20	5	94	87	109	108	113	54	4	95	98	100	102	98
21	8	89	72	64	54	59	55	14	73	72	75	73	62
22	$4^{1}/_{2}$	89	62	61	56	63	56	4	75	67	63	58	60
23	6	81	73	70	49	50	57	$^{7}/_{52}$	70	74	74	74	56
24	9	80	71	75	64	54	58	$1^{1}/_{2}$	77	80	69	67	64
25	$^{11}/_{12}$	104	100	88	50	53	59	14	90	85	82	75	64
26	$2^{1}/_{2}$	104	93	84	75	56	60	6	70	64	70	60	50
27	$^{9}/_{12}$	82	79	75	68	46	61	5	83	88	81	70	59
28	$^{6}/_{12}$	86	76	80	75	51	62	3	72	68	70	52	39
29	$6^{1}/_{2}$	79	78	72	64	60	63	3	83	80	76	70	49
30	$^{10}/_{12}$	61	68	55	57	53	64	$^{3}/_{52}$	76	74	74	56	42
31	$2^{1}/_{2}$	85	86	68	68	51	65	$2^{1}/_{2}$	85	80	76	67	65
32	$1^{9}/_{12}$	75	72	63	61	50	66	$1^{1}/_{12}$	92	92	97	96	104
33	$^{9}/_{12}$	80	80	77	45	50	67	4	97	89	92	95	100
34	2	70	57	53	60	47							

The modified technique employed has therefore been:

Standardisation of the Thrombin Solution

The method of Innerfield et al., a modification of that of Quick (1938), has been followed, using the topical thrombin of Roche.

10 ml. sterile normal saline is injected into the vial containing 1 gramme topical thrombin (5000 international units). This solution can be kept indefinitely at −20°C.

0·5 ml. of this stock solution is diluted with 16·5 ml. normal saline immediately before it is required. To 0·2 ml. normal plasma at 37°C in the water-bath is added 0·1 ml. of this diluted thrombin solution and the time taken for the formation of the fibrin clot is noted. The plasma used for this trial is obtained by venepuncture on the day of test, but stored plasma may be used for periods of up to a fortnight if kept at −60°C. The proportion of blood to 3·2% citrate is 9 : 1. The object is to produce a thrombin solution which will form a fibrin clot in the plasma in 10–15 sec., and to the original dilution of the stock thrombin solution is added saline or thrombin to achieve this end. The standardised thrombin should be made fresh on each day of test, and when not in use should be kept chilled.

Collection of Serum

Blood collected from a finger-prick is allowed to clot at room-temperature and the serum separated by centrifugation. Enough serum for a test can be obtained from 0·5 ml. blood.

Performance of the Test

The entire test is carried out at 37°C in the water-bath. With practice it is easily possible to perform four simultaneous estimations. Each test requires a rack of seven tubes. Into tubes 2, 3, 4, 5, and 6 is pipetted 0·2 ml. normal plasma. Tube 7 contains the serum to be tested. Into tube 1 is pipetted 0·9 ml. standardised thrombin solution, and as soon as possible 0·1 ml. of the test serum is added to it. A stop-watch is started at this addition. After incubation of this serum-thrombin mixture for 3, 5, 10, 15, and 20 minutes, 0·1 ml. samples of it are transferred to the plasma in tubes 2, 3, 4, 5, and 6 respectively, and the times taken for the fibrin clot to form in each is noted.

Recording of Results

For technical reasons there is a slight variation in the results obtained in normal controls examined on any one day and even contained in the same rack. The plasma used, the concentration of the standardised thrombin solution, and the fluctuations in the temperature of the water-bath all produce even wider day-to-day variations. Hence no absolute comparison between the results obtained in one case and those obtained in another is possible, and it has been found that the results are best expressed as the percentage of the mean of the normals tested on the same day, each sample being thus compared. Comparison of cases is then possible.

RESULTS

The table shows the results obtained in the 67 cases investigated, the clotting-times of each sample being expressed as percentages of the mean of the normals examined on the same day. It will be seen that 60 cases showed a definite decrease in the antithrombin content of their serum compared with the normal controls. Fig. 1 shows the scatter of these results, and compares it to the scatter of 200 normal controls. In the latter the variation shown is within experimental error. In the figure the upper and lower limits found at each sample time are shown, while the shaded area in each group shows the variations between which 75% of the sera investigated fell. The lines within each shaded area mark the boundaries of 50% of the sera studied. It will be seen that there is a considerable difference between the results obtained in 75% of the cases and those obtained in the 200 controls, while even the highest reading obtained at the 15-minute and 20-minute samples of the 60 cases is appreciably less than the lowest reading at the same sample time obtained in the

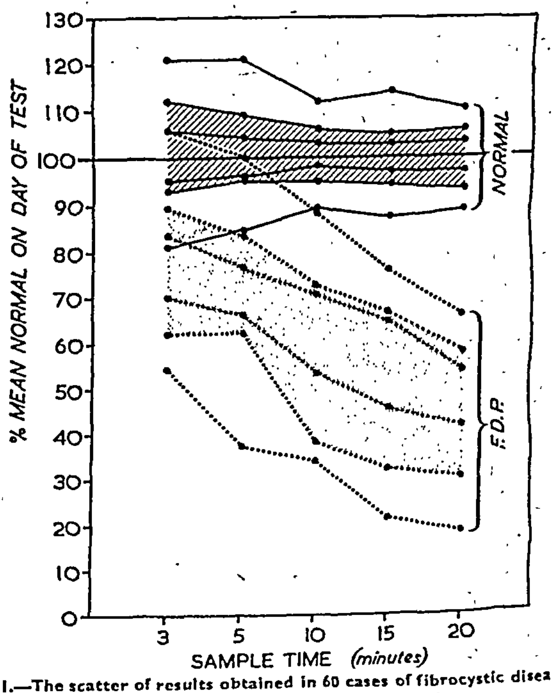

Fig. 1.—The scatter of results obtained in 60 cases of fibrocystic disease of the pancreas and in 200 normal controls.

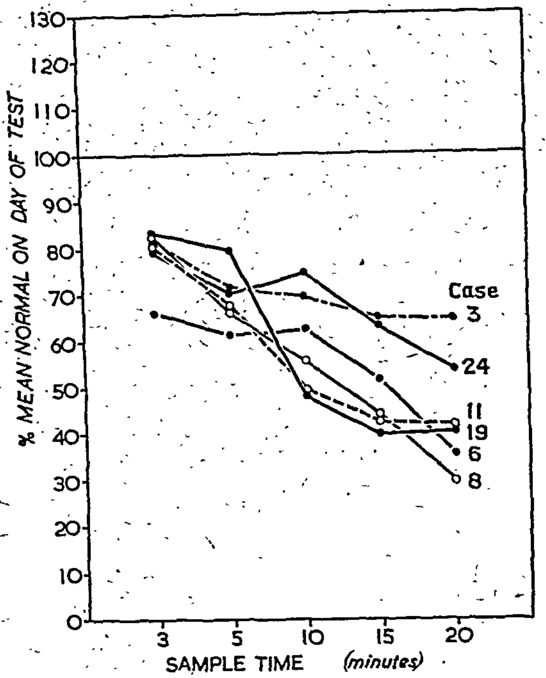

Fig. 2.—The typical results obtained in 6 cases of fibrocystic disease of the pancreas of different ages.

control group. The remaining 7 cases (cases 20, 45, 46, 52, 54, 66, and 67) listed in the table gave results which fell within the limits of those obtained in the control group, as shown in fig. 1. From both the table and fig. 1 it is obvious that the most valuable information can be gained from the 15-minute and 20-minute samples, and for practical purposes it would appear that these samples alone need be studied.

Fig. 2 shows the curves obtained in 6 cases, expressing the sample times as percentages of the mean normal (100%). These curves are typical of the entire series tested, except the 7 cases which gave normal results, and are selected only in that they are the results obtained in 6 children of varying ages.

Investigation of the 20 families containing cases of fibrocystic disease showed no deviation from normal in any of the 73 sera tested, while of a further series of 80 normal controls examined only 1 has given results which are indistinguishable from those found in 90% of the cases.

Experiments have been made into the possibility of storing sera for this test. Sera from 3 cases and from 3 controls were stored for up to a fortnight at room-temperature, in the refrigerator, at —20°C, and at —60°C. The antithrombin content of these sera was estimated frequently during this period and no variation in the results was found at any time, one from the other or in comparison with fresh sera from cases or controls. The findings in children who had been treated with pancreatin and oral antibiotics for a considerable period were similar to those in children admitted for diagnosis whose sera were examined before therapy began. The examination of the serum from one case from week to week has shown very little variation, well within that seen when two cases are compared. This applies equally to the results obtained in another case which has given normal figures over a considerable period.

DISCUSSION

The uniformity of these results is at variance with the findings of Innerfield and his colleagues. These authors reported a decrease in the antithrombin content of the plasma in only 1 of their 13 cases, an infant of three weeks whose diagnosis was confirmed at necropsy shortly afterwards. Raised titres were found in 3 children aged five, seven, and nine months, while the remaining 9 cases, all over three years of age, gave normal results. They postulated that the differences in antithrombin titres coincided with the different stages of the disorder of the pancreas. Stage I, in which the antithrombin content was reduced, was that of pancreatic duct atresia, the histological picture being one of acinar atrophy and fibrosis with hyperplasia of the epithelium of the pancreatic ducts. Stage II represented the transition period of interstitial pancreatitis, and at this stage the antithrombin content of the plasma was elevated, as the same authors had found it to be in acute pancreatitis. Stage III was that of the classical picture of nutritional and respiratory components, the histological picture being one of homogeneous contracted fibrous tissue almost devoid of functioning acini. In this stage the antithrombin content of the plasma was normal. Though their 9 cases over the age of three had all given normal titres, they added the rider that the titre might be influenced by the action of the few isolated acini as yet unaffected by fibrosis and that "it is possible that in total pancreatic fibrosis there would be a concomitant depression in antithrombin titer."

The importance of this rider is obvious from the results of the present series, where 60 of 67 cases showed lowered serum antithrombin titres and only 7 cases gave normal titres. Clinically all the patients showed classical features of nutritional and/or respiratory symptoms. Though 13 of them were under one year of age and a further 15 were less than three years old, none showed the elevation of antithrombin titre suggested by Innerfield et al. as corresponding to stage II of the disease. No confirmation that the antithrombin content reflects the pathology of the pancreas is present in this series.

What is apparent, however, is the great potential value of the test as a confirmation of the clinical diagnosis. In 90% of the cases tested the results have been positive, while in a total of 353 controls there has only been 1 "false" positive. In this case, a girl of eight years, suffering from chronic eczema, has given consistently low antithrombin levels in her serum over a period of three months. She presents no symptoms of fibrocystic disease of the pancreas, and the proteolytic activity of her stool is within normal limits while the tryptic activity of her duodenal juice is at the lower limit of normality (gelatin digested completely at a dilution of 1 : 25). The link between her serum abnormality and that present in cases of fibrocystic disease requires investigation beyond the scope of this paper. Though a series of investigations into the possible rôles of blood trypsin and heparin content are being undertaken, at the moment there is insufficient evidence to implicate either of these factors in the ætiology of abnormal antithrombin contents.

The test appears to offer a very practical, if empirical, method of confirming the clinical diagnosis. It is simple technically, the results are repeatable, and it can be performed on as little as 0·5 ml. blood obtained from a finger-prick. It appears, in our experience, to have a reliability comparable to that of duodenal intubation, and from the viewpoints of the patient and of the nurses much would be gained if it were generally employed to confirm the diagnosis in suspected cases, and if duodenal intubation were resorted to only where the antithrombin content falls within normal limits.

SUMMARY

The serum-antithrombin level was estimated in 67 confirmed cases of fibrocystic disease of the pancreas and in 353 normal controls, 73 of whom were from 20 affected families. Of the 67 cases, 60 (90%) showed a lowered antithrombin level and 7 gave normal results: of the controls only 1 showed an abnormal (depressed) level.

These results are contrasted with those of Innerfield et al. who published the original method.

It is suggested that the test is sufficiently reliable to be used for confirmation of the clinical diagnosis, and that duodenal intubation should be reserved for suspected cases in which the antithrombin content of the serum lies within normal limits.

I am indebted to Dr. I. A. B. Cathie, in whose laboratory this work was performed, for criticism and advice, and to the physicians for access to their cases. I am especially indebted to Dr. A. P. Norman for access to the cases attending the Fibrocystic Clinic, and to Mr. G. W. Cecil for much technical assistance.

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LOCAL USE OF ANTIBIOTICS IN CHRONIC SUPPURATION OF THE MIDDLE EAR AND MASTOID

WITH PARTICULAR REFERENCE TO TERRAMYCIN

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THE purpose of the investigations reported here was to determine the relation between (1) the organisms occurring in chronic suppuration of the middle ear and mastoid and (2) the sensitivity and clinical response of these infections to the various antibiotics. Could one determine the ideal drug in a given case by a knowledge of the sensitivity of the organisms to the antibiotics? And how could one determine the drug of choice when the organisms were sensitive in vitro to more than one?

We treated fifty-four cases of chronic suppuration with four antibiotic powders, each in a sterile lactose base: penicillin, streptomycin, chloramphenicol, and terramycin, limited quantities of the last-named having been made available to us for the investigation.

METHOD

At the initial visit the affected ear was cleaned by dry-mopping with cotton-wool on a Jobson-Horne probe, and a swab was taken for bacteriological examination. The bacteriologist determined in every case the organisms grown on culture and the sensitivity of each organism to the four antibiotics mentioned above. The ear was treated by simple dry-mopping until the report was available and the appropriate drug determined. In most cases, this drug was then applied locally by insufflation in powder form by the method of "frosting" and as often as the patient could attend; in some cases, however, we used a drug to which the organisms were insensitive in vitro. If there was no response to treatment after a reasonable period, a fresh swab was taken and another antibiotic used when the sensitivity was known.

The bacteriological studies were made by Dr. C. W. Morley and Dr. J. R. May, using the method they have already described (May and Morley 1952).

The antibiotics were all prepared in a sterile lactose base in the following concentrations: penicillin 2000 units per g., streptomycin 1%, chloramphenicol 25%, and terramycin 2%.

RESULTS

The follow-up period has varied, but we have not considered any patient to have improved unless a continuously discharging ear had remained dry for at least a month. Many cases were followed up for 2, 3, or 4 months.

Four main groups are distinguished:

Uncomplicated chronic suppurative otitis media.
Chronic suppurative otitis media complicated by granulations.
Discharge following the radical mastoid operation and its modifications.
Discharging fenestration cavities.

For purposes of comparison the results are further divided into three subgroups:

(*a*) Cases treated with terramycin only.
(*b*) Cases treated with penicillin, streptomycin, and chloramphenicol, but not with terramycin.
(*c*) Cases treated with terramycin and other antibiotics.

Uncomplicated Chronic Suppurative Otitis Media

Eighteen cases were treated.

(*a*) Seven of these were treated with terramycin only. Six became dry, after an average of 3·5 insufflations, and have remained dry for 2–3 months. These included one case in which *Proteus vulgaris* sensitive in vitro only to chloramphenicol was grown on culture. The one remaining case was still discharging when last seen, but the patient did not attend for further treatment or follow-up.

(*b*) Five cases were treated with penicillin or chloramphenicol. All of them have remained dry for at least 2 months. In one of them *Bact. coli* sensitive to streptomycin, chloramphenicol, and terramycin but not to penicillin responded rapidly to insufflation of penicillin powder. One case with mixed organisms responded to dry-mopping alone.

(*c*) Six cases were treated with terramycin and other antibiotics. Five of them became dry rapidly with terramycin, after an average of 3·4 insufflations, when treatment with other antibiotic powders over periods ranging from 3 days to 7 weeks had failed, and these have all remained dry for 1–3 months. The one remaining ear became dry with 2 insufflations of chloramphenicol powder after terramycin had failed.

Chronic Suppurative Otitis Media Complicated by Granulations

Seven cases were treated. In each case the granulations were cauterised with fused silver nitrate on a probe before the powder was insufflated.

(*a*) Four cases were treated with terramycin only. All were dry when last seen, although in only one of them was one of the organisms reported as sensitive to terramycin in vitro.

(*b*) Two cases were treated with chloramphenicol. Both have been dry for at least 2 months, and both were sensitive to the drug in vitro.

(*c*) One case was treated with terramycin and chloramphenicol. It responded to 1 insufflation of chloramphenicol, after terramycin insufflated 4 times on alternate days had failed.

Discharging Radical Mastoid Cavities

Seventeen cases were treated.

(*a*) Two cases were treated with terramycin only. Both responded to treatment with terramycin, although in each case organisms insensitive to it in vitro were grown on culture. One has remained dry for 3 months; the other recurred after 1 month but responded to 2 further insufflations of terramycin on alternate days and has remained dry for a further month.

(*b*) Five cases were treated with chloramphenicol. Four of them became dry, after an average of 6·25 insufflations, and have remained dry for 2–3 months. The patient who was not dry when last seen did not return for treatment after 3 attendances. This infection was due to a mixed growth of *Pseudomonas pyocyanea* sensitive only to terramycin and *Pr. vulgaris* insensitive to all the antibiotics.

(*c*) Ten cases were treated with terramycin and other antibiotics. Of this number seven became dry for at least 2 months. Six of them cleared, with an average of 3·4 insufflations of terramycin, after chloramphenicol had failed over periods of 3–16 days. One case responded to chloramphenicol after treatment with terramycin had failed.

Discharging Fenestration Cavities

Twelve cases were treated.

(*a*) Four were treated with terramycin only. All of them became dry after treatment with terramycin, but one recurred. This has received further treatment with terramycin and was dry again after 2 insufflations.

(*b*) One case was treated with streptomycin and chloramphenicol, finally responding to chloramphenicol after earlier failure with this drug and subsequently with streptomycin. The ear has remained dry for 4 months.

(*c*) Seven cases were treated with terramycin and other antibiotics. They all became dry, with an average of 2·7 insufflations of terramycin, after they had failed to respond to treatment with other antibiotics for periods of 3–37 days. Chloramphenicol had been used unsuccessfully in all of them before terramycin was used. In three of the cases, all due to *Ps. pyocyanea*, the organisms were sensitive to terramycin only.

Summary

Fifty-four patients with discharging ears were treated by the local insufflation of four antibiotic powders —penicillin, streptomycin, chloramphenicol, and terramycin. Eighteen were uncomplicated cases of chronic suppurative otitis media, seven were cases of chronic suppurative otitis media complicated by the presence of granulations, seventeen were discharging radical mastoid cavities, and twelve were discharging fenestration cavities.

Three cases have been dry for 4 months, sixteen for 3 months, and twenty-three for 2 months. Complete failure occurred in only two cases, both of which were discharging radical mastoid cavities. One of them had a stenosed external auditory meatus, and the other has not attended for follow-up, but never became dry while he was under observation, and had an infection with *Pr. vulgaris* which was resistant to all the antibiotics used.

BACTERIOLOGY

The incidence of the organisms grown on culture was :

Staphylococcus aureus	19 cases
Pr. vulgaris	16 ,,
Ps. pyocyanea	14 ,,
Bact. coli	9 ,,
Hæmolytic streptococci	3 ,,
Pneumococci	1 ,,

Of the sixteen cases in which *Pr. vulgaris* was grown on culture, three were insensitive to penicillin, streptomycin, chloramphenicol, and terramycin.

Of the fourteen cases in which *Ps. pyocyanea* was grown on culture, thirteen were sensitive to terramycin only.

SUMMARY AND CONCLUSIONS

Fifty-four discharging ears were treated by local insufflation of antibiotic powders. These were cases of chronic suppurative otitis media and discharging radical mastoid and fenestration cavities.

The bacteriology of these infections was studied, and the sensitivity of the organisms to penicillin, streptomycin, chloramphenicol, and terramycin was determined.

There was no constant relation between the sensitivity of the organisms and the clinical response to the drug of bacteriological choice, for in fourteen cases the drug of choice failed to bring about any improvement, and in no fewer than ten cases terramycin was used successfully in treating infections which were insensitive to it in vitro.

This inconsistency may have been due in some cases to changing flora. For example, in one case *Staph. aureus* and *Bact. coli* both sensitive to chloramphenicol in vitro were grown on culture. Application of this drug 7 times, at weekly intervals, did not cure the discharge but after 7 weeks terramycin was applied (after taking a swab) and the ear became dry and has remained dry for 3 months. This final swab, taken before applying the new antibiotic, grew *Ps. pyocyanea* sensitive only to terramycin in vitro.

Further, there was an incompatibility between the concentration of the drugs applied locally in this series and their concentration in the test-plates, for the latter were specifically prepared to approximate to the concentrations revealed in the blood when they were administered systemically. Hence it is possible that some of the organisms reported as insensitive to the antibiotics in the concentrations used in the plates might have been sensitive in vitro to the much higher concentrations that were used locally in our cases.

However, these arguments leave unexplained many of the cases in which there was no apparent relation between the sensitivity of the organisms and their response to the drugs applied.

It therefore seems that one is justified in treating all such cases in the first instance with the particular antibiotic which is found by experience to yield the best results.

Terramycin has undoubtedly given the most satisfactory results in this series ; for, whereas 47% of the twenty-eight cases treated with chloramphenicol became dry, 83% of the forty-one cases treated with terramycin became dry. Further, in a selected group of fourteen cases in which the organisms were sensitive to both chloramphenicol and terramycin, twelve cases responded to terramycin after chloramphenicol had failed, whereas only two cases responded to chloramphenicol after terramycin had failed. Of the twenty-four cases in which terramycin *and* other antibiotics were used eighteen responded to terramycin after other antibiotics had failed.

Definite conclusions are not warranted with so small a series as the present one, and with so short a follow-up period ; but terramycin has given results so much superior to those obtained by any of the other antibiotics that we feel that it is worthy of further extensive trial now that it is becoming more generally available.

This investigation was undertaken at the suggestion of our chief, Mr. J. F. Simpson, to whom we are greatly indebted for his encouragement and advice ; we are grateful also to him and to Mr. I. G. Robin for referring their cases to us. Dr. C. W. Morley and Dr. J. R. May, of the Wright-Fleming Institute of Microbiology, have kindly made all the bacteriological examinations reported here, and to them we extend our sincere thanks.

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"The non-material or internal conditions [of a dwelling] are more difficult to describe and to remedy. By far the most urgent is the relief of overcrowding and the early achievement of the ideal of *one family, one dwelling*. The second condition, which follows hard on the heels of the first, is the intelligent distribution of family life to make the best use of the house as a whole and to give each member a personal 'holding,' however small, within the house. The third condition is the promotion of the family spirit, a sense of independence within each household. . . . In a well-knit family there are interesting jobs for everyone to do ; each member feels that he has a personal stake in the house, and a part to play in making it a home. In present conditions we need to pay more attention to the inward grace of family life."—Prof. J. M. MACKINTOSH, F.R.C.P., *Housing and Family Life*, London, 1952.

THE SITE OF ACTION OF THE TOXIN IN LOCAL TETANUS

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IN a series of papers which have received widespread attention Abel et al. (1935a, b, and c, 1938) have explicitly expressed their view that in local tetanus the toxin acts peripherally at the myoneural junction. This conception of the pathogenesis of tetanus is directly at variance with that proposed by Meyer and Ransom (1903) and widely accepted by other workers. The main thesis of Abel and his Baltimore colleagues is based on their opposition to the earlier belief that in local tetanus the toxin passes centripetally from the focus of infection or depot of injection to the central nervous system by way of regional motor nerve-trunks. Abel reviewed the evidence for this latter view, and after considering seriatim the possible participation in such a process of the various components of nerves—axones, intraneural tissue spaces, and neural lymphatics—concluded that none of these structures could be accepted for such a rôle. Since the issues raised in this problem are wider than the mere mechanism of the intoxication in this disease—for they also concern the possible central transference of other noxious agents by the same route—the pathogenesis of local tetanus has deservedly been the subject of many experimental investigations. The present paper forms one of a series designed to throw further light on these questions; it is specifically directed to clarifying the site of action of tetanus toxin.

The spastic contraction of the affected muscles in the early stages of local tetanus is associated with a pronounced exaggeration of their activity as recorded electromyographically. If the spasticity is only three or four days old, both the contraction and the electrical activity cease promptly on the induction of general anæsthesia. Alone this observation affords no means for discriminating between the two hypotheses of central or peripheral intoxication, for the action of the narcotic might be located either in the central nervous system or at the myoneural junction. But if an experimental procedure is used which, without causing any impediment to the passage of nervous impulses, prevents the access to the affected limb of a generally circulating narcotic, the course of the electromyographic tracing immediately after the administration of an anæsthetic would indicate whether the spasticity depended on a disturbance of a central or a peripheral mechanism. For if the intoxication is peripheral, as Abel and his colleagues believed, the exclusion of the myoneural junctions in the spastic muscles from the action of the narcotic would permit the typical electromyographic activity of the tetanus to continue unabated; whereas, if the toxin acted centrally in the spinal cord, both the contraction and the electrical activity of the spastic muscle should cease for the duration of the anæsthesia. Such a temporary isolation of a limb from the effects of a narcotic injected into the general circulation through a marginal ear vein can readily be effected by the obliteration of its main arteries by the inflation of a sphygmomanometer cuff placed at a site well proximal to the affected muscles whose electrical activities are to be recorded. The brief period of vascular occlusion needed in such experiments has no detrimental effect on the function of the regional nerves; hence, while the limb muscles are shut off from the main circulation, and consequently protected from the action of any drug that may then be introduced into it, they remain in fully functional nervous connection with the spinal cord.

In anticipation of the findings described below it may be stated here that the protection of the myoneural junctions in the affected limb from the circulating anæsthetic does not prevent the termination of both the muscular spasms and the electrical activity. The inference to be drawn from this finding is that in local tetanus the toxin must have a central seat of action, as Meyer and Ransom believed, and not an exclusively peripheral one, as Abel and his associates thought. An important corollary to this finding is that the toxin must have spread to the central nervous system from its depot in the muscles; and, since its hæmic transport can be precluded by the injection of an immunological excess of antitoxin into the blood-stream, this spread can only have taken place by way of the regional motor nerve-trunks. The present experiments thus give support to the belief that tetanus toxin, and possibly other agents too, can pass centrally to the spinal cord by this route.

MATERIALS AND METHODS

Animals.—Adult albino rabbits weighing 2–3 kg. and of either sex were used.

Toxin.—The preparation was the same as that described previously by Wright et al. (1950). A standard dose of 0·1 mg. in 0·2 ml. of 0·9% sodium chloride was injected into the centre of the fleshy belly of the left gastrocnemius muscle with a 1 ml. tuberculin syringe and a no. 20 needle. This sublethal dose gave a local tetanus which appeared in 48–72 hours and showed little or no extension of the intoxication to the opposite side.

Electrodes.—The recording electrodes were small pure silver spheres, 1·5 mm. in diameter, formed by fusing short lengths of wire. These were soldered to fine enamelled copper wires, which were then inserted into thin 'Polythene' tubing, 1·0 mm. in external diameter, so that only the silver spheres were exposed. Two such electrodes were used for each gastrocnemius muscle; one was placed over the centre of the lateral head, and the second 2 cm. lower on the body of the muscle. The electrodes were placed under the skin by first passing a large-bore needle subcutaneously from a site of insertion near the ankle to a point of emergence slightly above the position selected for the electrode head. The insulated electrode lead was passed backwards through the needle, which was then withdrawn to leave the silver head approximately in position between the skin and the epimysium. Its final location was next correctly adjusted, and its head fixed in place with a skin stitch. The leg, together with the emerging polythene-covered leads, was wrapped with gauze bandage made adherent with "plastic skin." An earth lead was formed by an electrode lightly clipped to an area of shaved skin on the back.

Amplifier and recording apparatus.—The pairs of electrodes were connected to a two-channel condenser-coupled amplifier with balanced input stages. Both channels were connected to a Cossor 1049 double-beam oscillograph. A second similar double-beam tube in parallel with the oscillograph was used

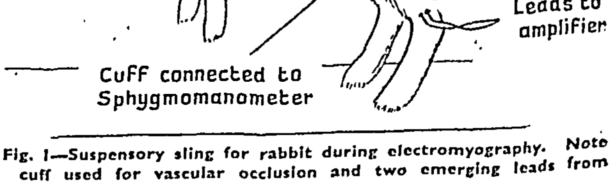

Fig. 1—Suspensory sling for rabbit during electromyography. Note cuff used for vascular occlusion and two emerging leads from recording electrodes.

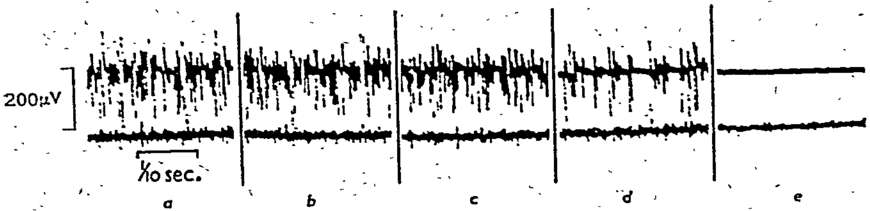

Fig. 2—Electromyographs from tetanus (upper trace) and normal (lower trace) gastrocnemii, showing effect of anæsthesia in terminating action potentials: *a*, at 5 sec. before nembutal injection; *b*, immediately after injection; *c*, *d*, and *e*, at 5, 10, and 15 sec. afterwards respectively. Nembutal injection took about 8 sec.

for photographic recording on a continuous-film camera. The gain of both amplifiers was adjusted to 1·5-cm. per 100 µV screen deflection. A further small oscilloscope tube enabled time and other signals to be photographed simultaneously.

Anæsthesia.—A dose of 'veterinary Nembutal' 25 mg. per kg. of body-weight consistently abolished the electrical activity of both normal and tetanus muscles, and was used in all the experiments. For the insertion of the electrodes this anæsthetic was fortified with open ether.

Suspensory sling for animals.—For electromyography the rabbits were supported in a horizontal position in a sling made of a fold of strong calico with four holes for their legs (fig. 1); the sling was arranged so that the claws of the hind legs just touched the table. The rabbits soon became accustomed to this posture, in which they appeared to be comfortable. In normal rabbits thus slung, action potentials from the gastrocnemius muscles soon ceased.

Vascular occlusion.—To effect the temporary interruption of the circulation through the hind limb a small sphygmomanometer cuff (10 × 5 cm.) was placed round the rabbit's thigh and inflated to a pressure of 200 mm. Hg. The duration of such an occlusion never exceeded two minutes. The efficacy of this procedure in preventing the access of blood to the limb was tested by injecting 30 µC of I^{131} into an ear vein and recording the gamma radiation from the foot during the period of occlusion and shortly after the release of pressure in the cuff. In five successive rabbits the counts obtained during occlusion were never more than 2% of those obtained after free circulation had been restored.

RESULTS

Effect of Anæsthesia on Local Tetanus with Unobstructed Limb Circulation

During the first few days of local tetanus electromyographic records from affected muscles show several distinctive features. A significant sign of impending intoxication is exaggeration and prolongation of the electromyographic activity after such external stimuli as touching or noise. Though the reaction in normal muscles soon subsides after the termination of stimulation, the activity in the affected muscles persists with slow decrement over several seconds. As the limb gradually becomes spastic, electromyographic responses become more and more easily evoked, until eventually they become continuous and apparently spontaneous. It is significant that in this phase of local tetanus, which Ranson (1928) named the "hypertonic stage," both spasticity, which by then has become severe, and action potentials can be promptly terminated by general anæsthesia. The rapid loss of electromyographic activity that follows the intravenous injection of nembutal is shown in fig. 2. Within 10 seconds of the start of the injection the frequency of the action potentials in the affected gastrocnemius has diminished, and by 20 seconds all signs both of spasticity and of electrical activity have ceased. As the rabbit recovers from a moderate dose of the anæsthetic, the exaggerated signs of both mechanical and electrical muscular activity return and, by the end of 2 hours, reach their pre-anæsthesia levels.

Effect of Anæsthesia on Local Tetanus after Occlusion of Limb Circulation

The application, by means of an inflated cuff, of an external pressure of 200 mm. Hg to the hind limb has no detrimental effect on the conduction of impulses down the motor nerve-trunks. Fig. 3 shows an electromyographic record taken from a gastrocnemius muscle in local tetanus immediately before, and at four successive intervals of 15 seconds after, the inflation of a cuff placed proximally on the thigh. The absence of any change in the frequency of the action potentials from the muscle shows that, for a period of a minute at least, this procedure is without significant effect on the local spasticity. Such a finding might be anticipated from the observation of Causey and Palmer (1949) that the application for 20 minutes or more of such pressures directly to the motor nerve to the gastrocnemius muscle in rabbits seldom affects its power of conducting impulses.

When nembutal is injected intravenously into a rabbit with local tetanus, the circulation of whose affected limb has been occluded a few seconds beforehand, the action potentials decrease in frequency and finally cease in the same way as had been seen formerly in similar rabbits whose circulation was unobstructed. The electromyographic records of three rabbits submitted in immediate succession to vascular occlusion and intravenous nembutal anæsthesia are shown in fig. 4. From them it can be seen that the termination of the exaggerated electrical activity of muscles in local tetanus occurs quite independently of whether or not the anæsthetic agent has access to their myoneural junctions.

As the electrical complexes diminish in frequency during the induction of anæsthesia, their individual characteristics usually become discernible. It can be seen from fig. 5 that each diphasic action potential has the character of a single motor-unit response with an amplitude of about 300 µV and occupies some 6 or 7 millisecs. These figures are comparable with those found by Weddell et al. (1944) for single motor-units in man. Our records give no indication that in local tetanus there is any after-discharge at the myoneural junction of the kind described by Harvey (1939) as following a single electrical stimulus to the cut motor nerve, and regarded by him as demonstrating a peripheral action of the toxin. The present findings, however, are in conformity in this respect with those of Göpfert and Schaefer (1940), Acheson et al. (1942), and Perdrup (1946), all of whom after a careful electromyographic study of local tetanus were unable to confirm Harvey's observation and regarded his "after-discharge" as an artefact.

DISCUSSION

The termination of the spasticity and the action potentials of affected muscles in local tetanus by an intravenously injected anæsthetic whose entry into the limb is prevented by arterial occlusion shows that the source

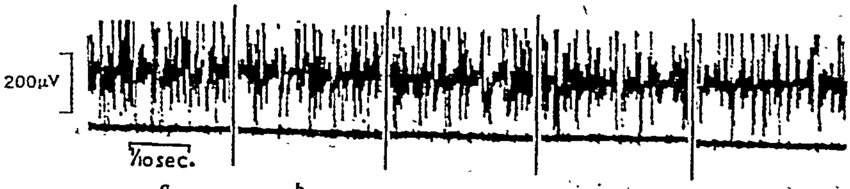

Fig. 3—Electromyographs from tetanus (upper trace) and normal (lower trace) gastrocnemii, showing that inflation of pressure cuff on thigh has no effect on muscle action potentials: *a*, immediately before inflation; *b*, *c*, *d*, and *e*, at 15, 30, 45, and 60 sec. afterwards respectively.

This suppressive action has been found to take place even if the circulating anæsthetic is prevented from reaching the affected muscles by the inflation of a pressure cuff on the thigh.

From this latter observation it is inferred that the source of the exaggerated mechanical and electrical activity in such muscles lies within the central nervous system and not peripherally at the myoneural junctions.

We wish to thank Mr. A. Nightingale, of the physics department, Guy's Hospital Medical School, for his help in designing the recording apparatus.

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POLYARTERITIS NODOSA AFTER THIOURACIL

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SHORTLY after the introduction of thiourea derivatives in the treatment of thyrotoxicosis it became clear that these drugs often produced toxic effects. Fowler (1946), in a review of 1573 patients treated with thiouracil, found such complications in 13·7%, of which the most serious was agranulocytosis, which was responsible for all the 7 deaths. He found no instance of polyarteritis nodosa, and so far there have been few other reports of this complication.

CASE-RECORD

A housewife, aged 44, developed symptoms of thyrotoxicosis in September, 1950. She was given iodine for seven months, at the end of which time she was worse. She was then given thiouracil 100 mg. three times a day and began to improve. In May, 1951, she was referred to the outpatient department with obvious signs of thyrotoxicosis. She was flushed and perspiring and had slight tremor of the hands. There was a little proptosis of the eyes with some lid lag. Her pulse-rate was 120 and blood-pressure 160/85 mm. Hg. Her thyroid gland was uniformly enlarged and vascular. She was advised to continue taking thiouracil.

Early in August,* 1951, on return from holiday, a rash appeared on her legs. Her doctor thought this was severe sunburn and that she also had some phlebitis in the legs, for there was œdema of the feet and ankles. She had some fever, but no other abnormal signs were noted. Thiouracil was discontinued. The patient went to bed and received local treatment, and after ten days, feeling better, she got up and began to take thiouracil again.

About a fortnight later, on Sept. 3, she complained of weakness, malaise, and pain in the legs. She had pyrexia and was put back to bed. Thiouracil was again discontinued. The next day she had cramping pains and pins-and-needles in her calves. Dark-red patches appeared on the dorsum of the feet. On this day her feet became weak, and during the next few days the weakness gradually spread up the legs, being worse on the right. At the same time she lost the use of her hands, and the right arm became weak. She vomited several times during this period. Pyrexia (99°–103°F) continued. Because of this she was given 'Sulphatriad,' about 20 g. in the next five days without any improvement in her condition. Nine days after the onset of the episode she was admitted to hospital.

On admission she was very ill. Her temperature was 101°F, pulse-rate 120, and respirations 35 per minute. Her blood-pressure was 100/60 mm. Hg, but otherwise the cardiovascular system was normal. Her respiratory system and abdomen showed no abnormality. She was confused, and it was difficult to hold her attention, which made subjective testing difficult. There was flaccid paralysis of the arms and legs, with loss of tendon-reflexes. All forms of sensation were lost on the arms distal to the middle of the upper arm and on the legs from the mid-thigh downwards. Sensation appeared to be normal on the trunk. The respiratory movements were fairly good. The cranial nerves were normal, but the right optic fundus showed fullness of the veins and blurring of the disc margin. Over the dorsum of each foot were some dark-purple indurated areas.

Investigations.—The urine contained a little protein and some pus cells but no red cells, casts, or organisms, and no porphyrin derivatives. A white-cell count showed 39,000 per c.mm. (polymorphs 95%). Lumbar puncture produced clear cerebrospinal fluid under a pressure of 180 mm. and containing 135 white cells per c.mm. (polymorphs 68%, lymphocytes 30%), protein 30 mg. per 100 ml., and a normal amount of glucose. Culture of the fluid was sterile, the Wassermann reaction was negative, and the colloidal-gold curve was normal.

Progress.—Next day she was worse and had difficulty in breathing. She was put in a Drinker respirator, where she remained for four days until her death. During this time her condition steadily deteriorated and she became more confused and finally unconscious. Her fever and tachycardia gradually settled, but signs of bronchopneumonia appeared, though penicillin was given to try to prevent chest infection. Another lumbar puncture, the day before death, showed a further increase in the number of white cells and a slight increase in the protein.

Necropsy thirty-eight hours after death showed extensive bronchopneumonia. Macroscopic changes were seen in several organs. There were two patches of discoloration close to the anterior descending branch of the left coronary artery. The kidneys were enlarged and congested, and there was hæmorrhage into their pelves; yellow patches resembling pyelonephritis were seen on the cut surface. No obvious changes were seen in the brain, spinal cord, or posterior-root ganglia. Both sciatic nerves, 15 cm. below the sciatic notch, were swollen, hyperæmic, and hæmorrhagic, and this change extended down the popliteal branches.

Histologically sections of numerous parts of the brain, spinal cord, and posterior-root ganglia showed acute arteritis throughout the small vessels, with necrosis of the wall and abundant fibrin exudate surrounded by polymorphs. No other lesion was observed in the central nervous system. The sciatic and popliteal nerves showed the same lesions to a much greater extent, there being profuse hæmorrhages with gross œdema and widespread arteritis of all the vessels. The two discoloured patches on the anterior descending left coronary artery were similar foci of arteritis. Here again it was the small arteries that were involved, but the main anterior descending branch showed slight inflammation in one place. The lesions in the kidneys were not due to infection but to an acute polyarteritis causing patches of infarction. The chief impact was on the afferent arterioles and the smaller branches of the interlobular arteries, but to a lesser extent similar changes were present in the arcuate arteries. In none of the organs was there any sign of healing of the arteritic lesions. Histological examination of the thyroid showed that there was a uniform hyperplasia of the acini, which were dilated and contained poorly staining colloid; in addition there was a very intense arteritis of all the small arteries. These findings thus established the diagnosis of acute polyarteritis nodosa which appeared to be of brief duration.

DISCUSSION

The first case of this type of complication of thiouracil therapy was recorded by Gibson and Quinlan (1945), who described the case of a woman of 46, treated for thyrotoxicosis with thiourea for thirty-five days, who then developed fever and conjunctivitis followed by a peripheral neuritis. She died in two weeks, and at necropsy evidence of polyarteritis was found. This patient had also been given Lugol's iodine for fourteen days before the onset of symptoms. In view of the report by Rich (1945) of polyarteritis in a woman with thyrotoxicosis treated with iodine, the possibility of iodine as an ætiological factor should perhaps be considered. Barnum et al. (1951) reported on a woman who undoubtedly developed polyarteritis three weeks after restarting treatment for thyrotoxicosis with thiouracil and iodine. Several months before this she had had both these drugs for nine weeks. When the antithyroid therapy was stopped, her polyarteritis gradually settled. McCormick (1950), however, had a case in which the patient died from widespread polyarteritis nodosa which developed six days after the inadvertent restarting of propyl thiouracil for a third course of treatment. She had been shown to be sensitive to the drug some months before, when a test dose was given. This test was made with only 50 mg. and was done because she had shown untoward symptoms on beginning a second course of the drug. Neither this patient nor that of Barnum et al. had any unusual symptoms during the first course of treatment. On the other hand, Foss (1950), reported generalised aches, pains in the legs, swelling of the ankles, and pyrexia in a thyrotoxic woman treated with 2-mercapto-imidazole for forty-seven days uninterruptedly. These symptoms disappeared when the drug was stopped, and twenty-six days later, there being no abnormal signs, the treatment was restarted. Sixteen days later the patient developed pyrexia, polyneuritis, and evidence of renal involvement. Polyarteritis was diagnosed, but never proved histologically, because she recovered and a biopsy specimen was negative. Two days before her illness began she had been switched from 2-mercapto-imidazole to methyl thiouracil because of shortage of the former drug.

In the present case there is strong circumstantial evidence that thiouracil was responsible for the development of the polyarteritis. The patient had been taking the drug for about four and a half months when she developed an unusual rash and swelling of the legs and became febrile and ill. This condition subsided when the thiouracil was stopped, only to recur in a more severe form within fourteen days of resuming treatment. This picture is similar to that of Foss's patient. Barnum's and McCormick's patients became ill only during their subsequent courses of treatment. Thus in 4 out of these 5 cases the frank attack of polyarteritis developed when thiouracil compounds were given for a second or subsequent course. This fact supports the belief that polyarteritis nodosa can be due to sensitisation to various foreign substances.

SUMMARY

A woman with thyrotoxicosis developed polyarteritis nodosa while under treatment with thiouracil. The attack developed during a second course of the drug. This sequence is similar to that in three previous accounts.

I should like to thank Dr. J. E. Cates for permission to report this case and for his advice and criticism, and Prof. T. F. Hewer for the necropsy report and histological details.

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PETROL PNEUMONIA

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Cope (1942) collected 6 published cases of pneumonia due to aspiration of petrol and reported one of his own. Since then few others have been published.

CASE-RECORD

An African male, aged about 22, was admitted to the Salisbury Native Hospital on Oct. 2, 1951. On the day before admission he was coming from Bindura to Salisbury by car, when the car suddenly stopped and he was instructed to blow into the petrol tank. He blew, but then stopped to inhale, and petrol immediately welled up into his mouth and out of his nose. He coughed violently and collapsed. Feeling extreme nausea he put his finger into his mouth and vomited blood mixed with bile. On admission to hospital he had persistent cough and complained of vague pains in his chest.

On examination he was not unduly distressed. His temperature was 100·5°F, he looked well, and there was no cyanosis or pallor. No sputum was produced. On auscultation of the chest tubular breathing with respiratory crepitations was audible in the right base anteriorly. Scattered rhonchi were heard over both lungs. The heart was normal. The blood-pressure was 120/86 mm. Hg.

Radiography showed a large irregular dense shadow over each lower lung field, typical of an aspiration bronchopneumonia (fig. 1).

Examination of the blood showed hæmoglobin 83%, white cells 5100 per c.mm. (neutrophils 57%, lymphocytes 41%, monocytes 2%).

Other Investigations.—The Paul-Bunnell agglutination test for glandular fever was negative. Routine urine and stool tests were negative.

Treatment and Progress.—The patient was given penicillin and sulphathiazole, and recovery was rapid. His cough persisted for two days. His pyrexia continued for about three days and then subsided gradually. Radiography some days later showed that the lung changes were rapidly clearing (fig. 2). He was discharged on Oct. 15, having completely recovered.

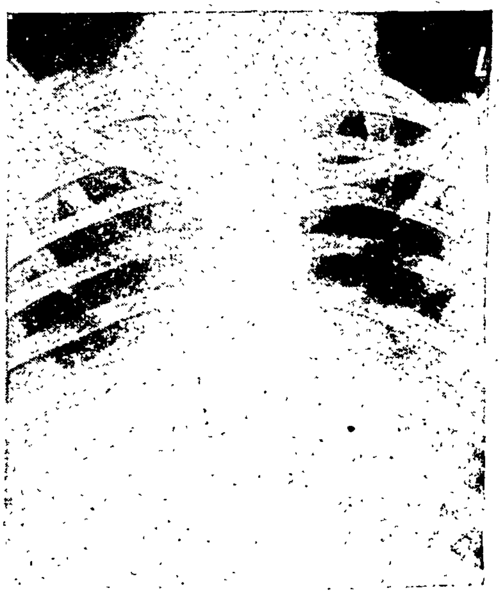

Fig. 1—Extensive bronchopneumonic lesions at both bases two days after inhalation of liquid petrol.

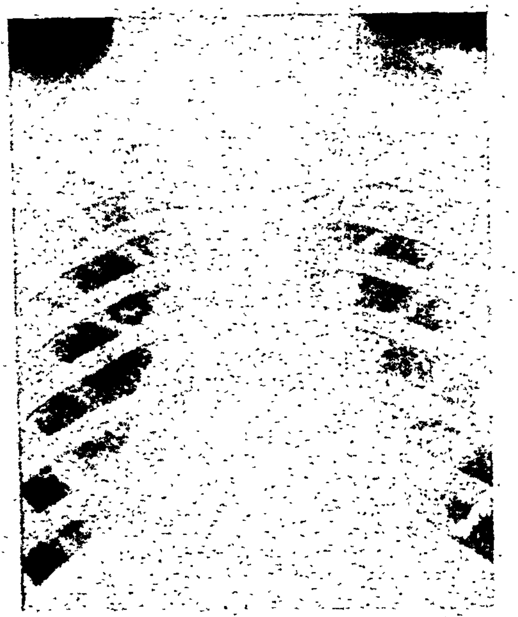

Fig. 2—Same case as fig. 1 four days later, showing rapid improvement.

COMMENTS

The effects of aspiration of liquid petrol are to be distinguished from those of aspiration of petrol vapour—e.g., in the holds of ships. The main effect of vapour seems to have been mental with schizoid and epileptiform disturbances in the foreground. Pneumonia may follow the inhalation of petrol vapour, but it is more common after the inhalation of the liquid (Rudd 1944).

Cope (1942) classifies the effects of aspiration of fluid petrol into immediate, general, and delayed. The immediate effects are due to irritation of the bronchial tree—e.g., burning pain in the œsophagus, nausea, vomiting, collapse, and cyanosis. The general effects are due to absorption of petrol into the blood-stream—e.g., transient exhilaration, drowsiness, cyanosis, and unconsciousness. The delayed effects are wandering pneumonia, hæmorrhagic pneumonia, pneumonitis, and pleural effusion. Cope declares, however, that lung signs are not necessarily proof of aspiration, because petrol in the blood-stream is largely excreted in the expired air and by irritating the lungs may produce bronchitis and coarse crepitations in the chest. He mentions three reported cases in which a pleural effusion followed the aspiration of petrol and one in which there were wandering pneumonic signs for nearly two months after the accident.

We wish to thank Dr. J. D. Addison for the photographs and Dr. R. M. Morris for permission to publish.

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Preliminary Communication

MEPACRINE AND RHEUMATOID ARTHRITIS

Describing the successful use of mepacrine in the treatment of lupus erythematosus, Page[1] said that 2 of his patients also had arthritis, and that this, too, was much improved. It seemed logical therefore to try mepacrine in rheumatoid arthritis. It has now been given to 23 patients, and all but 1 are very much better. The longest period of observation is eight months, and the shortest six weeks.

Patients were selected who had had the disease for more than two years, and who showed active joint inflammation. Periarticular swelling of several joints and tenderness on pressure were present in each case, and were taken to indicate active disease. Symptoms and signs, and results of performance tests, were recorded on a chart at each examination—weekly for inpatients, and every two or three weeks for outpatients. At first no definite scheme of dosage was followed. An attempt to hasten improvement by giving larger doses at the start was abandoned in favour of repeated small doses of mepacrine (0·1 g. twice daily).

Apart from physiotherapy, 14 patients had been having salicylates only. As their skin became yellow their pain gradually eased and they needed less analgesics. Soft-tissue swellings subsided, and movement became free and more vigorous. Joints showing contracture or ankylosis, or with secondary degenerative disease, lost all signs of active inflammation. Power of grip and speed of walking gradually improved. Six to ten weeks of treatment were necessary before all signs of joint inflammation were lost.

6 patients who had been doing fairly well on cortisone were given mepacrine instead.

4 of them are now much better and almost free of pain. The 5th patient had severe psoriasis arthropathica which responded well to both A.C.T.H. and cortisone, but relapsed when treatment was stopped. Mepacrine was given instead, at first in large doses, and four months have now passed with no rash or active arthritis—an experience he has not had since 1944. The 6th patient has steadily deteriorated since cortisone was stopped, though mepacrine was tried for thirteen weeks. She is still far better than before she had cortisone, but she has been our only failure so far. Strangely enough she is the only patient with a normal erythrocyte-sedimentation rate; those of all the others have remained raised.

In 3 cases the patient had had a long course of gold without benefit, but swelling and tenderness of the joints subsided completely while they were having mepacrine.

The only serious complication was a widespread macular eruption which developed in a patient who had 0·8 g. daily for four days; this took a week to subside after mepacrine was stopped, and treatment was then resumed with smaller doses.

COMMENT

This series was quite uncontrolled, and, of course, the patients were aware that the treatment was unusual. However, spontaneous remission is unlikely to be the explanation of the improvement in every case, and we believe that mepacrine may have been the effective agent. It is far too early to be certain about this; for the course of rheumatoid arthritis is remarkably variable, and the multitude of apparently successful treatments in individual cases is notorious.

Those who wish to try mepacrine must not expect improvement for at least four weeks, even though the skin is quite yellow. Indeed, one of our patients, who has had two courses, believes that during the third week of each course there was an exacerbation. Initial large doses involve the risk of toxic complications. We can not yet say when to stop treatment.

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[1] Page, F. *Lancet*, 1951, ii, 755.

Reviews of Books

The Advance to Social Medicine

RENÉ SAND, professor of social medicine, University of Brussels. London: Staples Press. 1952. Pp. 656. 42*s*.

Prof. René Sand, that great apostle of social medicine, has taken mankind as his field of study, and the whole world as his parish. There is no book quite like this, which skilfully condenses the histories of the medical profession, the hospital services, the history of personal hygiene, public health, social hygiene, industrial medicine, and social assistance. The last two parts are devoted to histories of the studies of man and the advent of social medicine. The expression "social medicine," he tells us, was first used in 1848 by Dr. Jules Guérin, editor of the Parisian *Gazette médicale*. Guérin appealed to the French medical profession to play a greater part in social questions:

> "Who, if not the doctor, will assess the causes of physical debility in the classes which have lately benefited by the destruction of privilege, and will find ways to make them healthier, stronger and happier? One great question is present today in all our thoughts; what will be the effects of higher wages and shorter working hours? Let us not forget the important services which doctors are called upon to render to society. At a time like this when mistrust is everywhere, *we need someone to act as intermediary between factions and* opposing interests. Truly, social medicine is the key to the burning questions of this hour of regeneration."

It is necessary to remind ourselves that this was written over one hundred years ago.

Among the international contributions to social medicine described, we can have pride in the record of this country, and particularly in its part in the great sanitary awakening of the last century. Today, when so many problems are raised by the introduction of sickness benefit services on a national scale, we may well be grateful that Professor Sand gives us a glimpse of the forces of social evolution at work, and of the many men and movements which have contributed to the flowering of the idea and practice of social medicine today.

Early Care of the Seriously Wounded Man

HENRY K. BEECHER, M.D., chief, department of anæsthesia, Massachusetts General Hospital, Boston, Massachusetts. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 32. 6*s*.

THOUGH written by an anæsthetist, this little book is full of good advice about the general surgical care of seriously wounded people. Casualty officers in busy hospitals, as well as members of field ambulances, will find here good dogmatic advice. Professor Beecher believes in speedy evacuation to hospital where definitive surgery can be done. In describing early resuscitation and care, he rightly emphasises the harmful effects of morphine when used improperly, and he gives a valuable list of contra-indications to its use. As would be expected, the section on anæsthesia is well done, and he has clearly mastered all the lessons learnt in recent battlefields. Not the least of these is that the dose of any anæsthetic must be graded according to the condition of the patient. Professor Beecher is to be congratulated on a first-rate pocket book, and its reasonable price puts it within reach of everyone who has to treat injured people.

Control of Communicable Diseases

HUGH PAUL, M.D., D.P.H., medical officer of health for Smethwick. London: Harvey & Blythe. 1952. Pp. 526. 55*s*.

MANY books deal with the clinical aspects of infectious or communicable diseases but few describe their control. Although not everyone will agree with Dr. Paul's views or conclusions, his book will be read with profit by medical and lay workers interested in preventive medicine.

Dr. Paul includes as communicable diseases war (*facile princeps*), cancer, psychosomatic disorders, and accidents in the home and on the road. The term "communicable" is more usually reserved for diseases caused by the invasion of susceptible hosts by more or less readily transmissible parasites. This idiosyncrasy apart, he has compiled a valuable and readable account of the history, demography, and epidemiology of many major and minor, endemic and exotic, infectious diseases and of the available means of controlling them. When a single author covers so much ground inequalities are to be expected. The chapters dealing with diseases of which Dr. Paul has had long personal experience are unexceptionable, but some of the accounts of exotic fevers are not well arranged and contain inaccuracies. But this criticism does not appreciably detract from the usefulness of the work especially for the English reader, who will find an excellent chapter on smallpox, the chief exotic disease he is likely to meet. The accounts of the other major communicable diseases, notably tuberculosis and diseases associated with food and water, are also first class. An informative chapter on the hygiene of food establishments is contributed by Mr. J. H. Wright, chief sanitary inspector of Smethwick.

Urological Pathology

PETER A. HERBUT, M.D. London: Henry Kimpton. 1952. Pp. 1222. In two volumes. Price £8 10*s*. the set.

THE title of this book scarcely does justice to its contents, for besides describing fully the pathology of the genito-urinary system it gives a fairly detailed account of the embryology and anatomy of each organ and a useful summary of the clinical manifestations, prognosis, and treatment of each disease. The illustrations are well chosen and well produced. A long classified list of references is printed at the end of each chapter. Since "Herbut's Urological Pathology" is likely to take its place amongst standard works of reference, we wish, for the sake of younger urologists, that it were not so expensive.

Color Atlas of Morphologic Hematology

GENEVA A. DALAND, B.S., chief laboratory assistant in hematology, Thorndike Memorial Laboratory, Boston, U.S.A.; edited by THOMAS HALE HAM, M.D., assistant professor of medicine, Harvard Medical School. Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1951. Pp. 74. 32*s*. 6*d*.

THIS atlas is not a complete guide to the subject set out in the title; the foreword tells us that it is "a guide for reference in the study of films of peripheral blood stained with Wright's stain," and it can be said that within these limits it fulfils its task very well.

An atlas stands or falls by its colour plates; these are by Etta Piotti, an expert in water-colour representation of blood cells, and are reasonably clear; but nuclear detail is often not adequately defined. Moreover, registration of the different blocks is not always perfect, so there is some overlapping of colours. There are 14 plates; one shows the red-cell series, one the various leucocytes, and most of the rest have two fields representing composite pictures of the peripheral blood in various diseases. One plate has only a single field, giving an admirable picture of the changes in Mediterranean anæmia; the arrangement of line diagram keys on the page opposite to this plate is especially good. The developmental histories of the blood-cell types are simply outlined in black-and-white diagrams, and the text is adequate though undistinguished. It seems from the frequent cross-references that the atlas was designed to be used in conjunction with Dr. Ham's *Syllabus of Laboratory Examinations in Clinical Diagnosis*.

The choice of Wright's stain reduces the usefulness of the work because this technique is little used outside the United States, and even there many prefer the Jenner-Giemsa combination. Laboratories in Britain still often use Leishman's stain, and good atlases representing the appearances of peripheral blood with both these stains are available. The book is beautifully produced, and its very reasonable price is made possible by a grant from the Massachusetts division of the American Cancer Society.

Il Cancro (Verona: Mondadori. 1951. Pp. 156. L.250).—Dr. Mario Musella, of Naples, has written a popular account of cancer designed to induce patients to come for treatment as soon as possible. He touches on almost every aspect of the disease and has produced a very readable story, to which Prof. Hans R. Schinz, of Zürich, contributes a preface.

THE LANCET

LONDON: SATURDAY, AUGUST 16, 1952

War on Want

IN any society extremes of wealth and poverty are morally wrong, economically unsound, and politically inexpedient. This is a thesis acceptable to almost all thinking men in Great Britain, though we dispute heatedly about the ways and means of alleviating poverty and about the necessity for restricting individual wealth. In recent years, together with other countries bordering on the North Sea, we have gone a long way to prevent poverty, and its associated moral, economic, and political evils, in our own countries; and we are therefore apt to be blind to the fact that, in the world at large, poverty is probably increasing. The fifth annual report of the Food and Agriculture Organisation [1] showed that in most countries the supplies of food and clothing do not even suffice to keep up pre-war low standards, and except in a few favoured countries the amounts of fuel and power available do little to mitigate the toils of bodily labour or the severities of climate. Few of us are properly aware that the lack of these basic essentials in so many countries leads inevitably to international chaos. The first essential in the struggle for a good life is to reduce poverty, especially as it exists in South-East Asia, in most of Africa, and in many parts of Latin America. Unless this can be achieved, our domestic problems must in the end be swamped in international disorder.

A pamphlet lately issued by the Association for World Peace [2] gives a well-documented and sober account of world poverty and the ways in which governments are trying to introduce scientific techniques to the technically backward countries. It begins by refuting the arguments of the "isolationists" who would seek salvation each for his own country. That the average income per head in South-East Asia is the equivalent of $55 a year and in the United States is $1453 represents a maldistribution of wealth which, if we regard the world as a whole, is morally unjustifiable as well as economically disastrous. Such poverty and wealth cannot exist in equilibrium side by side, and war will be an inevitable consequence of failure to meet the basic needs of a large part of the human race. A later chapter reviews the British Commonwealth's attempts, integrated within the Colombo Plan,[3] to find the technical skill and capital needed to develop Commonwealth countries in South-East Asia. But Asian opinion is quoted as being apprehensive and even cynical about the progress of the plan: the efforts of individual countries within the scheme are not being matched by Commonwealth effort: "in the Asia of today, people are sick of paper plans and promises and are clamouring for results. . . ." From this we turn to the many United Nations organisations which are endeavouring to relieve world poverty. Though the specialised agencies are, in general, doing excellent work in their particular fields, such as education, health, and land development, they often lack coördination. Partly because the people in the privileged countries lack a sense of urgency, there is no really adequate world organisation for getting a comprehensive programme carried out, and the Association for World Peace therefore presses for a new international development authority, which would have the means and the power to promote the economic and social advancement of underdeveloped areas. In this criticism of the piecemeal nature of much of the work of the United Nations there is much truth. But the energy necessary for a bolder and more coördinated attack can come only from a public enthusiasm based on accurate knowledge. Here the pamphlet is invaluable. Concise, factual, and authoritative, it can be recommended not only to individual readers but also to study groups.

In this country our task is to provide a share of the technical skill much needed for development (not a little of which is medical), and to give this skill the backing of public opinion and the necessary means.

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1. See *Lancet*, 1951, ii, 626.
2. *War on Want. Obtainable only from the association,* 14, Henrietta Street, London, W.C.2. Pp. 96. 1s.
3. See *Lancet*, 1950, ii, 808.

Infantile Gastro-enteritis

GASTRO-ENTERITIS is still an important cause of death in infancy, for it is responsible for about a twelfth of all deaths in this age-group. Improved living conditions, more child-welfare clinics, and better treatment have helped to reduce the number of deaths fairly steadily since the war. But our control of what should be a preventable disease will not be complete until more is known about its cause and the reasons for its spread. In 1947 4606 deaths (5·2 per 1000 live births) were attributed to diarrhœa, whereas in 1949 the figure was 1963 (a rate of 2·7). Reports from various parts of the country suggest that there were many outbreaks in 1947, but few in 1949, so that the rate may not be maintained at this low level in the future. The disease is more prevalent in densely populated areas; the 1947 infant-mortality rates for county boroughs and rural districts were 8·7 and 3·1 per 1000 live births respectively, and the difference was still to be seen in 1949, when the corresponding rates were 2·7 and 1·9. It commonly breaks out in institutions where babies are gathered together under good hygienic conditions, suggesting that overcrowding of a susceptible population may be the most important cause of its spread. No simple classification of the disease is possible, for several unrelated agents may irritate the baby's gastro-intestinal tract. In spite of this difficulty it is clear that the disease may affect babies alone or babies and adults at the same time, and there is reason to believe that these are two ætiologically distinct conditions.

Many attempts have been made to identify a specific infective agent, and a number of these have been studied recently. As a result of work in America it is now accepted that some acute diarrhœas in adults are due to virus infection. KEITEL [1] investigated an outbreak affecting both adults and babies, and he found that in many cases the babies' sera gave raised titres to cold agglutinins and to Streptococcus M.G.; both these findings are suggestive of virus infection, but no attempt to isolate one

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1. Keitel, H. G. *J. infect. Dis.* 1950, 86, 219.

was made. Light and Hodes[2] believed that they were able to isolate a virus from some outbreaks affecting babies only, but this has not yet been confirmed. Gale[3] showed that some strains of *Strep. fæcalis* produced an enzyme that changes tyrosine to tyramine, which gives rise to diarrhœa in young rats; he suggested that such organisms might cause diarrhœa in babies. Sharpe[4] investigated streptococci from outbreaks of infantile gastro-enteritis and found that the number of *Strep. fæcalis* isolated from sick babies and their contacts was greater than from healthy non-contact babies. On the other hand, the specific enzyme activity of streptococci from both groups of babies was similar, and there was no evidence that these organisms were related to the disease. Strains of non-hæmolytic streptococci are known to cause food-poisoning, and, before finally dismissing this group of organisms, more information is needed on their incidence, particularly in relation to the mild outbreaks.

Infantile diarrhœa, obviously infectious, occurs in outbreaks, some of which are due to organisms of the salmonella and shigella groups; but from others no causal agent can be isolated. Organisms of the salmonella group cause a larger number of deaths in infancy than in any other age-group, suggesting that the baby is particularly susceptible. In spite of this, outbreaks occur in which babies excrete a salmonella organism without showing any clinical symptoms. In the ward outbreak described by Hinden et al.,[5] *Salmonella brancaster* was isolated from 10 babies, of whom 2, aged thirteen months, remained healthy and 4 others, including 2 only about four weeks old, were classified as mild. Although this age-group is particularly susceptible, the healthy-carrier rate is often much higher in other outbreaks. This must be borne in mind in assessing the importance of recent work on certain serological types of *Bact. coli* as a possible cause of gastro-enteritis. On numerous occasions *Bact. coli* type 0·111 (D433) and type 0·55 (β) have been isolated from sporadic cases and from outbreaks in institutions in all parts of the world. These organisms have rarely been isolated from healthy babies who have had no contact with the disease. Shanks and Studzinski[6] report that 39 of 158 babies with gastro-enteritis were excreting type 0·111, and they also state that there was no outbreak of gastro-enteritis in the locality during the period of investigation. This figure may be compared with that of Giles and Sangster[7] who found that 96 of 159 patients excreted type 0·111 during an epidemic mainly confined to an overcrowded part of Aberdeen. Type 0·111 has also been reported as important in some institutional outbreaks[8]; it was recovered from all babies involved in four outbreaks but it was absent in a fifth, and it was not isolated from 175 healthy babies.

On this evidence it must be accepted that *Bact. coli* type 0·111 is an organism which occurs in epidemics in the infant population both at large and in institutions. Experiments on the pathogenicity of type 0·111 have been carried out in the U.S.A. where Neter and Shumway[9] have shown that the feeding of this organism to a baby was followed by acute gastro-enteritis. Ferguson and June[10] carried out a carefully controlled feeding experiment, using varying doses of three type 0·111 strains isolated from sick babies, and an untypable strain of *Bact. coli* from a healthy baby. After large doses of 0·111, young adult male volunteers had diarrhœa and vomiting, but they had no symptoms after similar doses of the control strain; in addition, agglutinins to 0·111 developed in the patients' serum after recovery. In a carefully planned investigation of streptomycin treatment, Alexander et al.[11] found that *Bact. coli* 0·111 or 0·55 were more commonly isolated from those patients classified as severely ill on admission—an observation which agreed with the findings of Holzel et al.[12] and Shanks and Studzinski.[6] But Young et al.[13] found type 0·111 to be evenly distributed among severe and mild cases. This difference may be explained by the gradual replacement of one epidemic type by another, as has happened in Aberdeen, where type 0·111 was prevalent in 1947 and type 0·55 in 1949; there are very few cases in Aberdeen at present, and no identifiable type of *Bact. coli* can be isolated from them. No adults were affected in any of these outbreaks.

Rogers[14] has shown that type 0·111 can be isolated from the furniture, towels, and other materials which have been in contact with an infected patient, but as yet there is nothing to suggest what is the most important means of spread. The organism is rarely, if ever, isolated from milk feeds, but it has been isolated from teats and fluid in which teats are kept, and from nurses' hands. If the usual portal of entry is the mouth, special care in sterilising bottles, teats, and other things put into the baby's mouth should help to prevent the disease. In spite of the strict technique adopted in many institutions, the disease still appears in epidemic form; this may be the result of inadequate methods, or it may indicate another mode of spread. In Sweden it is believed that droplet infection may be important, for positive cultures have been obtained from the nasopharynx of babies immediately before the onset of clinical disease; but workers in this country have failed to confirm this finding. By analogy with other intestinal infections, one would expect the introduction of the organism into the baby's mouth to be the commonest way in which the disease may spread. It has been shown that the admission to a ward of a patient who is excreting type 0·111 results in a wide dispersal of the organism in the environment. The baby's napkin may be compared to a dressing on infected burns, which can load the air with organisms and so spread the infection to other patients in the ward.

Stevenson[15] isolated *Bact. coli* 0·111 from adults with diarrhœa, all of whom were suffering from some other debilitating illness. He also found a carrier rate of 1 in about 200 among healthy adults in

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[2] Light, J. S., Hodes, H. L. *J. exp. Med.* 1949, 90, 113.
[3] Gale, E. F. *Biochem. J.* 1940, 34, 846.
[4] Sharpe, M. E. *J. Hyg., Camb.* 1952, 50, 209.
[5] Hinden, E., Taylor, J., Walther, W. W. *Lancet*, July 12, 1952, p. 63.
[6] Shanks, R. A., Studzinski, L. P. *Brit. med. J.* 1952, p. 119.
[7] Giles, C., Sangster, G. *J. Hyg., Camb.* 1948, 46, 1.
[8] Taylor, J., Powell, B. W., Wright, J. *Brit. med. J.* 1949, ii, 117.
[9] Neter, E., Shumway, C. N. *Proc. Soc. exp. Biol., N.Y.* 1950, 75, 504.
[10] Ferguson, W. W., June, R. C. *Amer. J. Hyg.* 1952, 55, 155.
[11] Alexander, M. B., Benjamin, B., Maslen, L. G. C., Roden, A. T., *J. Hyg., Camb.* 1952, 50, 246.
[12] Holzel, A., Martyn, G., Apter, L. *Brit. med. J.* 1949, ii, 454.
[13] Young, W. F., Smith, G., Russell, A., McNicholl, B. *Ibid*, 1951, ii, 770.
[14] Rogers, K. B. *J. Hyg., Camb.* 1951, 49, 140.
[15] Stevenson, J. S. *Brit. med. J.* 1950, ii, 195.

Glasgow.[16] It is possible that these types of *Bact. coli* may behave in the same way as some serological types of pneumococcus which, though usually present in a healthy population, may occasionally cause epidemic disease.

Treatment with each new antibiotic in turn has been tried, and each one has had its supporters. It is now accepted that penicillin is only of value in specific parenteral infections. Alexander et al.[11] have shown conclusively that streptomycin is useless in infantile gastro-enteritis. Good results have been reported with chloramphenicol,[17–19] but others have found it of little help.[6] In a disease which is certainly caused by a number of different agents it is probable that the treatment will not be correctly assessed until the causes can be diagnosed.

To sum up, there are a number of agents which cause gastro-enteritis in babies, and some of them are undoubtedly infectious. As yet there is no proof that a virus is the cause, although work on adults suggests that this may be so, particularly in outbreaks affecting both adults and babies. Gastroenteritis may follow feeding experiments with *Bact. coli* type 0·111 in both babies and adults; and this type has been isolated in infantile diarrhœa in all parts of the world, and in diarrhœa in adults with debilitating disease. There is now good evidence that this type of *Bact. coli* may cause infantile gastroenteritis both as a sporadic and an epidemic disease.

Neurology Advances

The first two or three streaks of paint on a canvas convey very little, but as the brush strokes multiply and gain in complexity the picture paradoxically grows simpler. Neurologists, working hand in glove with the biochemists and neurophysiologists, are watching the appearance of some remarkable new landscapes in their field. In the Shattuck lecture[20] for 1952, Prof. D. E. Denny-Brown chose some of these to illustrate his theses that neurologists must keep the catholic outlook of the general physician, and that physicians in other branches of medicine can look to neurologists for practical help with their problems.

As an example of the kind of question an active neurological department can help to answer he mentioned the relation between liver and brain. In 1912 Kinnier Wilson established the association, in the disease named after him, of progressive lenticular degeneration with cirrhosis of the liver, and demonstrated the relation between extrapyramidal symptoms and disease of the basal ganglia. Later observers noted pigmentation of the cornea (the Kayser-Fleischer ring) which is pathognomonic of the syndrome, though not always present. The degeneration in the brain may go on to cavitation, but in some forms of the disease it is replaced by a pseudosclerosis—the condition studied between 1883 and 1898 by Alzheimer and Westphal, and long thought to be a separate entity. These different pathological aspects turn out to be related to different rates of evolution of the disease. Patients have also been shown to have amino-aciduria, huge deposits of metallic copper in the brain and liver, and a high urinary output of copper.[21] The neurological signs, usually starting with tremor of the limbs and sometimes athetosis, go on to rigidity, contractures, dysarthria, a parkinsonian facies, emotional lability, and mental deterioration; but lately it has been found that treatment with dimercaprol (Bal) mobilises some of the copper deposits, and—provided cavitation has not developed—ultimately causes most of the neurological symptoms to disappear.[22] The amino-aciduria, however, persists. The neurological symptoms thus seem to be caused by the deposits of copper; but the origins of the disease are in some other system. It was thought that the cirrhosis might interfere with the excretion of copper in the bile; but the biliary output of copper has been measured in several cases, and found to be within normal limits. Attention has therefore turned to the nature of the hepatic cirrhosis. It is of a coarsely nodular type, and during its development the patient experiences pyrexial attacks with slight jaundice, believed to be recurrent episodes of toxic liver disease, but without inflammation. We have no direct clue as yet, Denny-Brown says, to the mechanism of the disorder, but there is some suggestive collateral evidence.

> Thus in hæmochromatosis (like Wilson's disease, a familial disorder) an ordinary multilobular cirrhosis of the liver is associated with the deposition of large quantities of iron-containing pigment in different parts of the body. The deposits in the pancreas engender diabetes; and though there are no specific neurological signs, the patients show a characteristic drowsiness and torpor which is independent of their diabetes. Again, in chronic manganese poisoning, cirrhosis of the liver, tremor of the hands, and dysarthria develop, and here the metal is the cause of both the cirrhosis and the nervous symptoms. Other studies have shown that copper, too, can cause cirrhosis.

Wilson's disease thus begins to appear as a disorder in the metabolism of the heavy metallic ion of copper. Moreover these comparable conditions suggest that the trouble is not a disorder of the enzymes of which copper is normally a part, but a displacement of some other physiologically important ion by copper.

The study of the liver in Wilson's disease has clearly taken neurologists far into the realm of general medicine; and some of the findings in the brain lead in the same direction. The cavities found in the rapidly progressive forms of the disease are in the basal ganglia and dentate nuclei, and sometimes in the frontal lobes; otherwise the brain shows only pigmentation and a diffuse alteration in the glia—notably enlargement and proliferation of astrocytes. But similar enlargement of the astrocytes has been found in cases of chronic biliary obstruction, ordinary portal cirrhosis associated with "senile" chorea, and recurrent hepatic coma. Denny-Brown therefore postulates a primary metabolic disturbance of cerebral glia, parallel to the primary metabolic disorder of cerebral vascular epithelium in Wernicke's encephalopathy; and this, he says, opens "an extraordinary vista of possibilities in neurology."

We are fairly sure, for instance, that parkinsonism, Huntington's chorea, presenile psychosis, and the familial ataxias are not related to a disorder of *metallic*

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16. Stevenson, J. S. *Ibid*, 1952, ii, 123.
17. Rogers, K. B., Koegler, S. J., Gerrard, J. *Ibid*, 1949, ii, 1501.
18. Smellie, J. M. *Proc. R. Soc. Med.* 1950, 43, 766.
19. Laurell, G., Magnusson, J. H., Frisell, E., Werner, B. *Acta pædiatr. Stockh.* 1951, 49, 302.
20. *New Engl. J. Med.* 1952, 246, 839.
21. See *Lancet*, 1951, i, 1404; ii, 79.
22. *Ibid*, 1952, i, 199.

metabolism; but we are equally sure that some cumulative metabolic process underlies these disorders, for "in each of such diseases a progressive cell change documents the gradual failure of specific metabolic processes without gross anatomic lesions." This is very different from the old concept of abiotrophy; and the slightness of the anatomical damage in relation to symptoms suggests that reversal may be possible once we understand the chemistry.

Recent experience of young people in the first stages of Wilson's disease has impressed DENNY-BROWN strongly with the importance, as an early sign, of "small lapses and irregularities of movement, of the type characteristic of Sydenham's chorea." In Wilson's disease these signs clear rapidly with dimercaprol; and they give us good reason for believing that Sydenham's chorea is itself a toxic symptom, produced by some metabolic mechanism.

Another new scene in neurology is opening from the well-explored canyon of cerebrovascular disease. MONIZ, in 1937, described recurrent cerebral attacks due to carotid occlusion; but this thesis only gained recognition when carotid arteriography came into general use. It was then seen that patients with a history of repeated episodes of weakness of the same limb, with or without aphasia, were suffering from the effects of occlusion of the carotid on the opposite side of the body to the paresis. These symptoms are therefore due, not to vasospasm as we used to think, but to insufficiency of the circulation in the circle of Willis, and resultant ischæmia in parts of the brain not well supplied with collateral circulation. Moreover the episodes are provoked not by a rise but by a *fall* in the systemic blood-pressure; and a severe fall in the systolic pressure, such as occurs in syncope or with intestinal hæmorrhage, may lead to necrosis of a large part of the area supplied by the middle cerebral artery. In an interesting variant of the disorder, reduced flow in the ophthalmic artery is responsible for recurrent attacks of blindness in the eye on the side of the carotid occlusion. But sometimes the patient will develop a collateral circulation for the ophthalmic artery through the external carotid system, by way of the branches of the ciliary and meningeal arteries. This has the curious effect of reversing the flow in the ophthalmic artery, with the result that the internal carotid can be filled from the external carotid; and this explains why the attacks of blindness sometimes persist for a time and then disappear.

The cause of the internal carotid occlusion is usually arteriosclerosis with atheroma, and hence is usually seen in patients of 50–60, though it may appear in young people: DENNY-BROWN has seen it in a patient of 26. The common story is that a patient with long-standing arterial disease, who has had an unexplained episode of transient paralysis in the right arm with aphasia some years before, starts to waken from sleep with fleeting attacks of weakness of the right limbs and difficulty with speech. The important thing to keep in mind is that he needs not a vasodilator drug but a stiff whisky. Anything that *lowers* his blood-pressure still further is likely to provoke a severe hemiparesis. Apart from alcohol by mouth, inhalation of air containing 6% of carbon dioxide seems to be the most effective immediate procedure. But it is of course essential to get the diagnosis right. Carotid occlusion can be proved by arteriography, but DENNY-BROWN does not advise this in old people, whose atheromatous vessels are only too likely to thrombose. Instead, two clinical tests may be tried: the fundus on the side of the suspected lesion is watched while the opposite carotid is compressed, or while light pressure is exerted on the globe of the eye with the finger. If the retinal vessels are being filled from the opposite carotid these tests will cause them to narrow. But the tests are positive in only about half the cases, probably because in the others, collaterals from the external carotid have already developed. Compression of the suspected carotid will reproduce the symptoms in 30 seconds, also in about half the cases. But the surest clue to the diagnosis is in the history of repeated episodes of transient paralysis in the same limb.

Nicety of diagnosis was again his theme in discussing raised intracranial pressure; for here good judgment makes the difference between life and death for the patient. Brain tumours, we used to be taught, produce their symptoms by increasing intracranial pressure; but in fact they also act by distorting the anatomical relations within the skull. If the high pressure continues, the retinal veins are compressed and papillœdema develops, to be followed, unless relieved, by blindness. An expanding lesion in the skull causes herniation, first of the midbrain and temporal lobe through the tentorial opening, and then of the tonsils of the cerebellum into the foramen magnum. Herniation of the first type produces dilatation of the pupils, stupor, and a decerebrate state; herniation of the second type causes periodic headache, vomiting, slowing of the pulse, drowsiness, and finally respiratory failure. Either will eventually obstruct the circulation of the cerebrospinal fluid and cause a secondary rise of intracranial pressure. The important point is that lumbar puncture can only increase the herniation in cases with intracranial lesions; and that the signs of herniation are periodic bursting headache, dilatation of one or both pupils, vomiting, and resistance to passive flexion of the neck. In the absence of these signs, on the other hand, papillœdema must always be studied by examination of the cerebrospinal fluid obtained by lumbar puncture and cautious measurement of its pressure. Thus the mild degree of papillœdema produced by hypertensive heart-failure associated with high venous pressure should be treated by lumbar puncture; and so should the greatly raised pressure seen in some cases of otitis media with lateral sinus thrombosis, where the venous drainage of the sagittal sinus has become blocked by the spread of thrombosis. Both these conditions can be relieved, and the sight of the patient saved, by repeated cautious lumbar puncture. Again, there is a type of peripheral neuritis, recently observed, in which the cerebrospinal fluid clots spontaneously and plugs the pacchionian bodies, thus obstructing its own drainage. In time the blocks will be canalised afresh, but while this is happening lumbar puncture drainage is needed to save the patient's life and sight.

The neurologist, then (and even more the house-physician and general practitioner), must have a very clear idea of what he is about when he reaches for the lumbar-puncture needle, for, as DENNY-BROWN implies, the dangers of an ill-judged lumbar puncture which produces blockage of the foramen magnum may be as disastrous for the patient as loss of vision resulting from the doctor's inability to exclude a tumour. It is no use attempting to play for safety: in this situation masterly inactivity will not serve instead of accurate diagnosis.

Annotations

CRIMINAL STATISTICS

INDICTABLE offences known to the police amounted to 524,506 in 1951—almost twice the number of such offences in 1938.[1] Moreover this figure exceeds by nearly 2000 that for 1948, the former peak year. The number of people found guilty of offences of all kinds was 723,320. It must, of course, be remembered that more than half these offence were non-indictable traffic offences, failures to take out dog- or car-licences, breach of local regulations, and the like; only 3929 (0·5%) had committed acts of violence. But it is not the proportion of one type of crime, or even the incidence of a given type of criminal in the population which must engage us so much as the fact that on the whole crime is on the increase in our country. It is natural to ask what types of crimes are rising, and in which age-groups of the population.

The Criminal Statistics for 1951 show very large increases in larcenies of different kinds—from some 56,000 offences in 1938 to over 87,000 in 1951; but there are some odd exceptions to the general picture. Thus embezzlement is rather less popular than it was in 1938, though it has gone up since 1949; larcenies of horses, bicycles, and motor vehicles have been almost stationary since before the war, and larceny from automatic machines and meters was more than three times commoner in 1938 than it is now—though it has been picking up a little during the last few years. The offences which swell the figures are larceny by servants, from the person, in the house, of post letters, and from unattended vehicles, shops and stalls, and aggravated larcenies—lazy, petty thieving in the main, probably attempted without much risk, and for only small gains. The picture, in fact, seems rather one of rapidly falling standards than of growing malice. The change for the worse is very noticeable in the younger age-groups. Children over 8 and under 17 found guilty of larceny have risen from some 19,000 in 1938 to over 30,000 in 1951, whereas the figure for those aged 17–21 has remained almost steady in the neighbourhood of 8000–9000. Indeed, of the 87,201 people found guilty of larceny in 1951, 35% were under 17. A somewhat similar picture appears in the figures for breaking and entering: children under 17 composed 57% of those found guilty.

It is hard to assess what factors are at work in producing the increase in crimes of violence. The numbers found guilty have risen steadily, from 1583 in 1938 to 3929 in 1951. Every age-group has been affected, but in the group aged 21–30 the figure has remained in the region of 1500 for the last three years, while in other age-groups, and especially among those under 17, it has been rising. Nevertheless, those under 17 are responsible for only 9% of these crimes, while those aged 17–21 are responsible for 12%, and those aged 21–30 for 40%. Different types of violent crime are not all increasing at the same rate: some indeed are less common than they were in 1938. Those found guilty of murder, always an exceptional crime, have ranged between 20 and 40; and those who attempted murder have fluctuated between 15 and 40. On the other hand, those guilty of threats, conspiracy, and incitement to murder have risen from 9 to 23, and those causing manslaughter from 45 to 71. Those guilty of wounding and other acts endangering life (felonies) have trebled since 1938, but on the other hand their numbers fell off from 385 in 1950 to 354 in 1951. Convictions for malicious wounding and like offences (misdemeanours) form the largest group, and have gone up steadily from 1195 in 1938 to 3169 in 1951. Over the same period convictions for assault have risen from 39 to 103, but fell a little between 1950 and 1951. There were 30 convictions for cruelty or neglect of children, as against 12 in 1938; but both criminal abortion and concealment of birth are on the decline and child stealing does not seem to have been a popular pursuit in this country for many years. Endangering the life of railway passengers (it would be interesting to know exactly how) led to 52 convictions in 1951 as against only 9 in 1938.

On the whole there is evidence of a growing bent for threats, spitefulness, carelessness, and irresponsibility, among our people, as well as some growth of villainy. To this must be added an increase in sexual offences, which doubled between 1938 and 1951. The picture suggests a restless unhappy spirit which no doubt owes something to current history, but more, perhaps, to poor training in social living.

HOSPITAL COST ACCOUNTING

THE Hospital Costing Returns for 1950–51[1] were compiled according to a system proposed in an interim report of the costing subcommittee of the Committee of Regional Board Treasurers. This committee has now prepared a second report[2] which suggests how the "subjective" analysis set out in their interim report may be supplemented by an "objective" analysis of the expenditure of the larger general hospitals with special departments for inpatients and outpatients.

The need for a better basis of comparison is obvious, but it is perhaps a pity that the committee should feel "that the immediate purpose of this objective analysis should be to separate the cost of treating in-patients from the cost of treating out-patients" and that the production of truly comparative costs may perhaps be the most important result of any costing system. Surely the first object of accounting should be to provide the administrator with the information he and his departmental heads require for efficient management? If uniform costing emerges as a by-product of a process of management accounting, then indeed the hospital service will benefit. The committee has attempted to meet both needs, but its chief aim seems to have been to provide figures which will be of interest to the Ministry of Health and the general public rather than to hospital administrators.

The committee considers that the present subjective analysis of expenditure required under Ministry of Health regulations should remain and that the objective analysis should be produced by an additional accounting process, which must in the interests of economy be as simple as possible. Surely it would be simpler to substitute the objective analysis for the subjective analysis as the basis of hospital accounting. Moreover, unless this is done and hospital estimates are built up departmentally, the full benefits of functional costing will never be felt, and the cost of costing may then indeed be an extravagance.

The committee's proposals must be examined from two points of view. One is the need to provide the Ministry with yardsticks by which it may allocate national funds to regional hospital boards and compute comparative costs for publication. But information is also needed for efficient management and control at hospital level, and, unless costing is integrated in a system of budgetary control, it will not be of full use for administrative purposes.

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[1] Criminal Statistics, England and Wales, 1951. Cmd. 8616. H.M. Stationery Office. Pp. 92. 5s. 6d.

[1] See *Lancet*, 1952, i, 1243.

[2] Copies of the report are in the hands of the treasurers of the regional hospital boards.

Appendix C to the report sets out the forms of cost statements proposed. The cost summaries for inpatients and outpatients show in one total the proportion of direct and indirect expenditure allocated to each. To this is added the relative proportion of the expenditure on special departments such as radiology, pathology, and physiotherapy. In a subsidiary statement a full subjective analysis is given of the direct expenditure and a departmental analysis of the indirect expenditure. The allocation of expenditure between the cost of treatment of inpatients and outpatients is made on varying arbitrary bases, but this is inevitable. Neither of these statements alone, however, would give a comprehensive comparison and together they are far too detailed. But they do provide all the necessary information from which a statement of inpatient and outpatient cost, showing the more important items of expenditure, could be evolved.

These proposed forms would give a much better basis for inter-hospital comparison than the present costing return, but certain anomalies would still remain. For example, unless the cost of catering is treated as a separate department and the cost of patients' meals only is shown as direct expenditure under inpatients, there will still appear apparently inexplicable differences, and the reason for them will have to be sought by reference to another section of the cost statements. A full departmental accounting system would avoid these difficulties. Moreover, this comparison is to be restricted to the larger multi-purpose hospitals and the basis of comparison for all other hospitals is thus not improved.

The bulk of the report is a cost-accounting manual for hospitals dealing with the details of the proposed system —the allocation of expenditure, the cost units to be used, and the bases on which expenditure is allocated between inpatients and outpatients. Clearly much valuable work and thought have been given to this report, and it will be of interest to consider these proposals, made within the framework of the Ministry's regulations, alongside the forthcoming reports on the experiments on hospital costing carried out by the King's Fund and the Nuffield Provincial Hospitals Trust.

PREDICTING ADULT HEIGHT

By comparing skeletal age, as assessed by X-ray examination of the hand, with chronological age and height, Bayley,[1] was able to predict the height of the fully grown adult. Bayley and Pinneau[2] have now brought their tables up to date in the light of new data on skeletal age.[3] They show that there is a high correlation between skeletal age, as taken from Greulich and Pyle's atlas, and the proportion of final adult stature that has been reached when the X-ray film is taken. They suggest that this shows the close relation between growth in size and skeletal maturation, as well as the possibility of predicting the adult height.

Growth is a dynamic and highly complex process influenced by nutrition, illness, hormonal changes, and hereditary traits, to name only a few of the factors involved. To make an assessment of skeletal maturity at one point during this process, and then to predict the mature height for a particular child, seems an uncertain business. The results may be reliable enough in a homogeneous sample of children, but we must also consider the children whose growth is retarded or advanced at the time of the assessment. It appears that "supplementary" tables should be used in such cases.

Nevertheless this work is of great interest; it will attract the attention not only of geneticists but of those engaged in studies of longitudinal growth. The first set of results from such a study in the British Isles has just been published.[4] Detailed and varied measurements were made of the same sixty-six boys and sixty-six girls at the ages of 3 days, 1 year, 2, 3, 4, and 5 years. This work, when combined with that of Bayley and Pinneau and others, may help in the "somatotyping" of children into various groups according to build; it may then be possible to predict the adult somatotype from the childhood assessment. Perhaps adult physique is determined at a very early stage in the development of the embryo; perhaps the predominant influence comes later.

FOOT-AND-MOUTH DISEASE AND BIRDS

For nearly forty years birds have been suspected of introducing foot-and-mouth disease. Mettam[1] suggested it in connection with an outbreak of this disease in Ireland in 1912. Stockman and Garnett[2] tried to link primary outbreaks in England with the immigration of birds from the Continent. Eccles[3] succeeded, with difficulty, in infecting wild starlings and found that, after the ingestion of infected material, they excreted the virus in their droppings for 10–26 hours, and that, when their feet and feathers were contaminated, the virus could be recovered up to a maximum of 91 hours later. Eccles also transmitted foot-and-mouth disease from an infected starling to a healthy beast. There is no evidence that the ingested virus multiplies in the birds, and the birds are not susceptible to the disease; hence they can but carry the virus mechanically.

A big step forward has been taken by Wilson and Matheson,[4] who analyse the migration of birds to, from, and through the British Isles. The man in the street knows vaguely that some birds, such as swallows and nightingales, come north for the summer and go south in autumn, but it is not generally realised what enormous hordes of different species of birds, notably starlings, come to the British Isles from the Baltic area in autumn and spend the winter here. It is, of course, from this direction that new outbreaks of foot-and-mouth disease in the south-east of England must be introduced. Wilson and Matheson show that, between April 1, 1938, and Oct. 31, 1950, there were 365 primary outbreaks in Great Britain, and that, of these, 223 were in pigs, 134 in cattle, and 8 in sheep. Of the 142 in cattle and sheep, 50 might have been due to contamination by pig-swill, and 49 of the remaining 92 were concentrated in the eight coastal counties (from Lincolnshire to Dorsetshire) nearest to the Continent, and these counties contained only a seventh of the live stock of the country. On the other hand, the number of outbreaks due to swill in these coastal counties was only a sixth of those in the rest of the country. These facts proved that in most of the primary outbreaks the proximity of the Continent was an important factor, birds being the obvious suspects when swill was not responsible.

Wilson and Matheson further point out that, since the numbers of immigrant starlings do not fluctuate much from year to year, the primary outbreaks of foot-and-mouth disease in England should, if these birds are the vehicles of transmission, be definitely correlated with the outbreaks in the neighbouring parts of the Continent: Holland, Belgium, and Pas de Calais. They prove that not only is this so but also the danger to England is greatest, and in fact only exists, when foot-and-mouth disease has attained certain proportions in the coastal provinces of East and West Flanders in Belgium, and of South Holland, North Brabant, and Sealand in Holland, just where most of the starlings congregate before crossing to England, where the primary outbreaks of foot-and-mouth disease are shown to hug the coast

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1. Bayley, N. *J. Pediat.* 1946, 28, 49.
2. Bayley, N., Pinneau, S. R. *Ibid*, 1952, 40, 423.
3. Greulich, W. W., Pyle, S. I. Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford University, California, and London. 1950.
4. Growth of Children. By Prof. ALEXANDER LOW. University of Aberdeen, 1952. 10s.

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1. Mettam, A. E. *Int. vet. Congr.* 1914, 2, 105.
2. Stockman, S., Garnett, M. *J. Minist. Agric.* 1923, 30, 681; *Vet. Rec.* 1923, 3, 903.
3. Eccles, M. A. *Bull. Off. int. Epiz.* 1939, 18, 118.
4. Wilson, W. W., Matheson, R. C. *Agriculture, Lond.* August, 1952; also issued separately by Ministry of Agriculture and Fisheries as Bird Migration and Foot-and-Mouth Disease. H.M. Stationery Office. 4*d.*

to a conspicuous degree. The multiplicity of types of the virus[5] facilitates the establishment of this correlation.

Finally, the starlings migrate from the Continent to England in the daytime in a season which provides ten hours' daylight; and, even if they cross by the longest sea trip—i.e., from Holland to Yorkshire—they have ample time to contact beasts in both countries on the same day.

REMUNERATION OF GENERAL PRACTITIONERS

On July 28, before rising for the recess, Parliament passed without debate the outstanding votes of the Civil Estimates which included provision for the Danckwerts award.[6] Before the new rates of pay can be introduced, the modifications in the organisation of general practice recommended by the Working Party[7] must be put into effect. This pre-holiday legislation has left the way clear for the Ministry of Health during the summer months to start to make the necessary administrative changes. Apparently unmoved by the doubts which assail Mr. H. A. Marquand,[8] the Ministry of Health announce that they hope to make the changeover on April 1, 1953.

As a first step they have asked the Medical Practices Committee[9] to reclassify the "practice areas" into three categories instead of four. The new categories will be:

designated, where an application for admission to the medical list will be granted automatically by the Medical Practices Committee and where, on admission, a doctor who is genuinely setting up a single-handed practice will be entitled to receive an initial practice allowance;

intermediate (referred to in the Working Party's report as "doubtful"), where an application for admission will be considered in the light of the particular circumstances and where, if the application is granted, the doctor will not be entitled to the initial practice allowance;

restricted, where there are already enough doctors practising and the admission of new doctors will be exceptional.

The criteria for classifying areas into these categories have been agreed between the Medical Practices Committee, the General Medical Services Committee, and the Ministry. Although the new classification will not come into effect until April, the Ministry realise that doctors who are setting up in practice will be anxious to know whether they will be entitled to the initial practice allowance, and the Ministry hope to publish the new classification by the middle of October.

INTERNATIONAL BIOLOGICAL STANDARDISATION

BIOLOGICAL standardisation began when Ehrlich adopted one of his diphtheria antitoxic sera as a standard by which other sera could be compared, and it is fitting that the new international unit for tetanus toxoid should be approximately equivalent to the "*Schutzeinheit*" of the standard tetanus toxoid of the Paul Ehrlich Institute in Frankfurt-on-Main. The confusing number of different units for tetanus antitoxin gave the stimulus which led to international standardisation of antitoxic sera: before an international unit was established, the American unit equalled 2 British units, approximately 1/64th of a Frankfurt unit, and 40 French units. The first international unit, established for diphtheria antitoxin by the League of Nations, was defined in 1922, and this unit remained the only example of international coöperation in this subject until 1928, when units for tetanus antitoxin, antidysentery serum (Shiga), and ouabain were adopted. Since then progress has been more rapid, and standards have been adopted for antigens, vitamins, hormones, arsenicals, and antibiotics. Assay of some undefined substances can only refer to their biological activity, and certain complications may arise when one member of a group sharing common biological activity is compared with another member of the same group. In the vitamin-A group the international unit had to be redefined in the light of assessment by a non-biological method: and vitamin D_2 can have two values, depending on the experimental animal.

The World Health Organisation Expert Committee on Biological Standardisation which has just issued its fifth report,[1] has added several standards, including blood-grouping sera, *b*-carotene, vitamin D_3, adrenocorticotropic hormone, *d*-tubocurarine chloride, and streptomycin. There are also reference preparations, to which units have not yet been assigned, for diphtheria toxoid, cardiolipin, lecithin, and penicillin-K. Investigations are in hand to establish standard preparations of bacteria for making diagnostic sera and for prophylactic inoculation, and standards for mammalian and avian tuberculins and for enzymes, such as hyaluronidase and thrombin. New antibiotics need standardising, and the committee have advised that author's preparations should be collected by W.H.O., and the nature and size of provisional units assigned after consultation with the author. Material has been collected for standards for aureomycin and terramycin, and is now being collected for chloramphenicol and bacitracin. The committee has asked the National Institute for Medical Research to undertake a study of pyrogens, both as therapeutic agents and as unwanted contaminants of other preparations. The aim is to establish an international reference preparation of pyrogens. In collaboration with a subcommittee on the serology of venereal diseases, stable reagents, including freeze-dried syphilitic sera, for the calibration of serological tests, are being developed.

Ultimately all biological materials may be defined completely by chemical analysis when there will be no need for assay; but the time seems a long way off.

SIR JACK DRUMMOND, F.R.S.

Sir Jack Drummond, whose untimely death was reported from France on Aug. 5, was a biochemist of rare versatility. As professor at University College, London, he was keenly alive to the importance of the biological aspects of his subject; and he was always reluctant to separate his department from that of physiology. His own investigations, begun at the Royal Cancer Hospital, were mainly on the fat-soluble vitamins; but in the academic sphere his most important contribution was not through research but through training younger men, and two successive holders of the chair at Cambridge are among those who passed through his department. To the public he was best known as scientific adviser to the Ministry of Food in the late war. Here his bent for applied science found full play; and he played a large part in evolving the successful rationing system in this difficult time. Industry, too, owes him much. No false academic pride inhibited him from giving of his best to this field, in which, after the war, he concentrated his energies; and here once again he led in the training of others.

To those who knew him he was a good friend and colleague, always ready to help anyone; his unobtrusive aid enabled more than one student to attend the university. Vigorous and well informed, with a keen sense of humour, he enlivened any gathering. Himself friendly and sociable, he sought to avert discord between others. Some will recall an important scientific meeting when two violently opposed points of view were to be expressed. When the day came, the expected collision did not take place; he had helped to bring the protagonists together informally. In the war his characteristic determination to see every job through to the end often took him far from his desk. To this work, as to all else, he brought an integrity that none could dispute.

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5. See *Lancet*, 1952, i, 1056.
6. *Ibid*. Aug. 2, 1952, p. 248.
7. *Ibid*. 1952, i, 1155.
8. *Brit. med. J.* Aug. 9, 1952, suppl. p. 93.
9. E.C.L. 61/52.

1. *World Hlth Org. techn. Report. Ser.* 1952, 56. Pp. 23. 1s. 3*d*. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

Public Health

SEARCH FOR EPIDEMICS OF TUBERCULOSIS

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> "Epidemics of tuberculosis are rarely reported, probably rarely discovered. The outbreak reported this week . . . leads one to believe that it is the detection of outbreaks which is rare, and not their occurrence."—*British Medical Journal*, 1951, ii, 840.

DURING the past eighteen months sporadic cases of tuberculosis in children attending nine day-schools in the Edgware and Harrow Chest Clinic areas have led to the examination of 3422 school-children between the ages of 6 and 18, and 118 teachers. Nothing in the nature of an epidemic was discovered but in view of the comment quoted above we report the results and our conclusions.

METHODS

In all cases the coöperation of the headmaster and the medical officer of health was sought. The latter arranged for all the parents to be asked to consent to the examination of their children. It was also arranged with the individual school authorities that the presentation by them of a child for medical examination implied that the requisite written permission had been obtained from the parents. In some cases this permission was refused, but 94% of the parents approached gave their consent.

Different methods of making the survey were tried:

(1) The first method was to ask the appropriate mass-radiography unit to make the survey. At the first school only a radiological examination was made, but at the second a tuberculin-jelly test was incorporated at our request. Although we were grateful to the staff of the mass-radiography unit for doing this work, the method was not ideal. In the first place it was found that, owing to the heavy commitments of the unit, such a survey could not be undertaken without an interval of several weeks. Secondly, although the results of the tuberculin tests were given in age-groups, the clinic had no knowledge of the result in any individual case, and it was felt that this information could be valuable if the child was subsequently referred to the clinic. Further, any child absent from school on the day of the unit's visit missed examination altogether.

(2) The second method tried was for the clinic staff to do the tuberculin testing and for the mass-radiography unit to radiograph the pupils immediately afterwards. Difficulty was experienced, however, in arranging a mutually convenient time for the unit and the clinic staff within the school's time-table.

(3) In the schools subsequently surveyed the clinic staff conducted the whole survey.

Tuberculin testing was done with 0·1 mg. of tuberculin injected intracutaneously by one of the clinic physicians. Although we consider the patch test to be equivalent (Anderson et al. 1951), this method was considered to be quicker; we could test 700 children in a morning. It was also found that the plaster tended to come off accidentally or was removed deliberately, its significance not being appreciated.

Each pupil, on attending for tuberculin testing, brought with him a piece of paper on which was written his name, age, address, school, and class, and the name of his private doctor. These pieces of paper were collected and the names entered in a book under classes. A similar piece of paper was presented when the tuberculin test was read by the physician, who wrote the result on this paper. All positive reactors were passed on to a clerk, who gave them a letter asking them to attend at the Chest Clinic on the following Saturday morning for X-ray screening. This scheme was very satisfactory and expeditious. The senior teacher was also informed that any child absent could be seen at the Chest Clinic if the mother would telephone for an appointment.

Some children who did not attend the school survey were later referred by general practitioners to the "X-ray only" sessions (Trenchard and Grenville-Mathers 1952) for tuberculin testing and X ray; so nearly all the school-children were eventually examined.

At one school this procedure unfortunately could not be followed. Three cases of presumed tuberculosis in this school were found only after the school had broken up for the summer vacation, and it was therefore arranged that the medical officer of health should circularise all the parents, pointing out the advantage of having their children X-rayed, and facilities were offered at the Chest Clinic on the next six Saturday mornings. This did not prove very satisfactory: 72 pupils were not examined at all, and many were found next term to have left the school.

At all surveys the school-teachers were urged to come forward for examination, but only 118 out of some 150 were examined.

ORIGINAL CASES AND RESULTS OF X-RAY SURVEYS

The following are the details of the cases leading to examination of the schools, and the number examined out of the total on the school roll.

School 1

At this school a boy, aged 12, was found to have a pleural effusion, and a month later another boy, aged 12, was found to have enlarged hilar glands. The domiciliary contacts were healthy. The mass-radiography unit examined 385 boys out of 437, and 7 teachers out of 22. No further cases were found.

School 2

A boy, aged 15, was found to have primary tuberculosis, and the mass-radiography unit did the tuberculin-jelly testing and radiography of 490 children out of 550. No teachers were examined. No further cases of tuberculosis were found.

School 3

A girl, aged 16, was found to have tuberculosis, with positive sputum, in August. All the 688 pupils and 28 teachers were examined in November without any further cases being discovered.

Schools 4 and 5

A girl, a domiciliary contact aged 14, was found to have tuberculosis, with positive sputum, in August, and in October a boy, aged 13, was found to have a pleural effusion. The two schools shared the same buildings, and some of the staff taught in both schools; so they were treated as one unit, and the pupils of both were examined in October. Of the 1030 pupils 998 were examined and 52 out of the 61 teachers. No cases of tuberculosis were found, but one pupil, aged 14, had a small round focus in the left second intercostal space and has been kept under observation at the clinic.

School 6

During July, 1951, the mass-radiography unit was operating in the Harrow area and offered to radiograph those girls of this school who were aged 15 or more. One girl, aged 15, was found to have tuberculosis with a positive sputum, and another girl, aged 15, enlarged hilar glands. This latter girl lived outside the area, and it was later found that she was a domiciliary contact. A third girl, aged 15, was found to have a pulmonary lesion, but on further investigation this was proved to be non-tuberculous.

Of 550 pupils 478 were screened, and 16 of the 32 teachers. These 16 included all the teachers who taught the above-mentioned girls. Again no further cases of tuberculosis were found.

School 7

At this school a girl, aged 16, was found to have bilateral tuberculosis, with positive sputum in July. In November a girl, aged 19, who had recently left the school, was found to have bilateral tuberculosis with positive sputum; a teacher, aged 30, was diagnosed as tuberculous with positive sputum; and a pupil, aged 15, was found to have a pleural effusion. 308 of the 310 pupils were examined and 15 of the 16 teachers. No further cases of tuberculosis were found.

Schools 8 and 9

A girl, aged 12, living outside the area, developed a pleural effusion. The domiciliary contacts were reported to be free from tuberculosis. She attended a school inside the area, which eighteen months before had been included in a survey by the mass-radiography unit during its visit to the district. Tuberculin-jelly tests were made on 35 children of her class at school, among whom 5 positive reactors were discovered,

RESULTS OF TUBERCULIN TESTS

Age-group (yr.)	School 2		School 3		Schools 4 and 5		School 7		School 8		All schools	
	No. tested	No. tuberculin-positive	No. tested	No. tuberculin-positive	No. tested	No. tuberculin-positive	No. tested	No. tuberculin-positive	No. tested	No. tuberculin-positive	No. tested	No. tuberculin-positive
11+	58	5 (*8·6%*)	66	12 (*18·1%*)	202	21 (*10·4%*)	35	2 (*5·7%*)	..	..	361	40 (*11·0%*)
12+	80	5 (*6·2%*)	108	9 (*8·3%*)	275	45 (*16·3%*)	38	8 (*21·0%*)	35	*5 (*14·3%*)	536	72 (*13·4%*)
13+	91	15 (*16·4%*)	146	20 (*13·7%*)	192	31 (*16·1%*)	66	8 (*12·1%*)	..	..	495	74 (*14·9%*)
14+	83	10 (*12·0%*)	139	29 (*20·9%*)	236	*33 (*13·9%*)	53	6 (*11·3%*)	..	..	511	78 (*15·2%*)
15+	63	*10 (*15·8%*)	106	21 (*19·8%*)	79	16 (*20·2%*)	57	8 (*14·0%*)	..	..	305	55 (*18·0%*)
16+	57	7 (*12·3%*)	49	*10 (*20·4%*)	7	2 (*28·5%*)	33	*9 (*27·2%*)	..	..	146	28 (*19·2%*)
17+	35	6 (*17·1%*)	31	9 (*29·0%*)	..	..	9	3 (*33·3%*)	..	..	75	18 (*24·0%*)
18+	5	1 (*20·0%*)	7	2 (*28·5%*)	..	..	5	1 (*20·0%*)	..	..	17	4 (*23·5%*)
Total ..	472	..	652	..	991	..	296	..	35	..	2446	..

At schools 2 and 8 tuberculin jelly was used: at the remainder 0·1 mg. of tuberculin intracutaneously.

but these were normal on radiography. The headmistress was most reluctant for further examination to be undertaken, and in view of the low proportion of positive reactors in the class concerned it was considered reasonable to accede to her request. The teachers were not radiographed but had been included in the earlier mass-radiography survey.

A girl, aged 6, was found to have a primary tuberculous lesion. The domiciliary contacts were normal on examination. Tuberculin-jelly tests were performed on 40 children aged 6 at the school she attended. The results were negative in the children, and 3 teachers who had been in contact with the group of children were radiographed and found to have normal lung fields. In view of these findings no further survey was undertaken at the school.

RESULTS OF TUBERCULIN TESTS

Of the 3422 pupils examined 2446 had a tuberculin test. The results for the different schools are given in the accompanying table, an asterisk being placed against the age-group from which the original cases came at that school. The differences in the percentage found positive do not seem to be of any significance for the relatively small numbers involved, and do not point to any spread of infection among the school-children. This is confirmed by the failure to discover further cases of tuberculosis.

COMMENTS

It is not surprising that a pupil with open pulmonary tuberculosis (as in schools 3, 4, 5, and 6) is not responsible for gross dissemination of tuberculosis in day-schools, since such a child usually makes his friends among those in his own class and does not mix with others to any great extent. Even in the dining-room the pupils do not, as a rule, mix.

The position seems to be very different if a school-teacher has pulmonary tuberculosis; for in school 7, where a teacher had the disease, 2 other cases of moderately advanced tuberculosis and 1 case of pleural effusion occurred. This danger from school-teachers is confirmed by the reports of school epidemics (Arnould 1933, Bevan et al. 1951, Hyge 1947, Pache et al. 1943, Roe and Dick 1949) in each of which a teacher was the source of infection.

CONCLUSIONS

As a result of these surveys we feel that, where a case of tuberculosis occurs in a day-school child, full examination of all the school population is not necessarily required. As reported here, it is probably only necessary to radiograph the staff and examine the other pupils in the same class by tuberculin testing, and later to radiograph the reactors.

The position is vastly different where a school-teacher is the source, and all the school population then needs to be examined. The better way is to prevent such occurrences by the regular radiological examination of school-teachers. Many local authorities stipulate that teachers *may* be required to undergo radiography, but this has not always been enforced even at the preliminary medical examination on entering the school service, and the teachers themselves are strongly averse to periodic radiography. Thus one headmaster in this series, when sent dates on which further members of his staff could be examined, refused to inform his staff. Since the parents had had the option of refusing to have their children examined, he felt that the staff should have the same option. As from the summer of 1953 the Ministry of Education have made it compulsory for all school-teachers to undergo a preliminary radiological examination, and teachers resuming duty after absence due to tuberculosis will be required to produce frequent medical certificates, but there is no compulsion for periodic radiography of presumably healthy teachers, and no supervision is required of those having questionably active disease.

The reluctance of teachers to be radiographed frequently is understandable, since a diagnosis of tuberculosis can be catastrophic for them. We have recent knowledge of a school-teacher having considerable difficulty in finding suitable work when he could not return to teaching. Yet, if tuberculosis in children and young adults is to be prevented, it is advisable that the radiography of adults working in close contact with children be made compulsory. Such a regulation could not be introduced, however, without at the same time guaranteeing to any teacher found to have tuberculosis full pay for an unlimited period during treatment until he could safely return to his post or find other remunerative employment.

We are indebted to Dr. T. Paxon for the assistance of his mass-radiography unit in some of these surveys and Dr. H. J. Trenchard for his criticisms and some of the figures. Our thanks are also due to Dr. W. E. Caryl Thomas, the area medical officer, and to Miss E. Last.

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Infectious Diseases in England and Wales

Disease	Week ended July			
	5	12	19	26
Diphtheria	30	33	25	21
Dysentery	180	151	140	135
Encephalitis:				
Infective	3	1	2	3
Postinfectious	2	2	1	2
Food-poisoning	168	144	180	231
Measles, excluding rubella	6724	7544	7225	7363
Meningococcal infection	23	24	25	34
Ophthalmia neonatorum	38	30	34	39
Paratyphoid fever	21	25	39	75
Pneumonia, primary or influenzal ..	315	329	259	247
Poliomyelitis:				
Paralytic	61	78	105	157
Non-paralytic	25	41	59	96
Puerperal pyrexia and fever	234	276	213	260
Scarlet fever	1036	1038	1038	1173
Smallpox	—	—	—	—
Typhoid fever	2	3	2	5
Whooping-cough	2347	2243	2206	2040

Poliomyelitis

Poliomyelitis notifications in the week ended Aug. 2 (the 31st week of the year) were (previous week in parentheses): paralytic, 139 (157); non-paralytic, 91 (96); total, 230 (253).

The following table compares this year (up to and including the 31st week) with the preceding five years.

Year	*Total cases up to and including 31st week*	*Cases in 31st week*
1947	1628	487
1948	873	43
1949	1203	187
1950	2593	367
1951	1399	117
1952	1660	230

Up to and including the week ended Aug. 2, the over-all notification-rate for England and Wales was 3·8 per 100,000 population.

Points of View

THE PROSPECT OF GENERAL PRACTICE

FROM A CORRESPONDENT

THE general practitioner is repeatedly said to be the really important man in medicine; but every influence, professional, official, social, and economic, goes to make his position less secure and his work less satisfying.

In the great medical schools the finger of scorn is often pointed at general practitioners, though some lip-service is paid to the institution of general practice. The reasons for this are not far to seek. In the prevailing atmosphere of intense specialism much of the interest in hospital wards centres in cases which are not only beyond the scope of treatment of general practice but also beyond its experience. It is inevitable that the "poor old G.P." attitude should develop; and it is of course exacerbated by the often appalling mistakes seen in hospitals as a result of low professional standards, and lack of opportunity for good work, of individual practitioners. At the same time an intense respect is inculcated for academic brilliance and high technical skill in scientific medicine. Add to this the great personal influence of a respected physician or surgeon upon a newly qualified man, compounded as it is of personal affection, admiration, and a good deal of envy, and it becomes clear that very powerful mental and emotional influences are at work to turn students from the consideration of general practice as a career.

In my own case five years of academic research (which nevertheless had a severely practical application) followed on the year and a half of hospital work, and provided intense intellectual satisfaction. But my leaning to general practice persisted in the background, and recently has recurred strongly as a dominant vocation. There is therefore an acute tension to be resolved, which can most simply be expressed by drawing up a balance-sheet.

ON BALANCE

First, general practice is the field of closest and most intimate professional relationships. The general practitioner, especially in the country, has great opportunities of knowing the sort of experiences which have influenced the life of an individual patient, and will influence it in the future. There is also the attraction of dealing with a whole family; for, after all, the family matters in society above all else. It is the natural social unit, it is the source of personality in a way which is only beginning to be appreciated, and it is the natural sphere in which men and women are, on the whole, required to work out their own salvation. Apart from the family there is no society, no order, no moral code, no peace, no love, no joy. For the common man, the family is the vehicle of the kingdom of heaven as certainly as it is the only stay of a stable and creative society. Knowledge of the family enables a doctor to assess more reliably the interplay of factors producing a given illness, and his relationship gives him an influence—out of all proportion to his ability and training—on the most vital human relationships. Moreover, he can enter general practice without using the faces of his fallen colleagues as stepping-stones to success. Many of my generation know this unpleasant necessity in the rush for specialism.

Turning to the objections to general practice, these are not based solely on the existence of the National Health Service, though this has undeniably intensified some dissatisfactions. The trouble lies in the whole trend of general practice since the early part of the century, and the whole situation as it stands at present.

For the younger generation, especially the brighter ones, general practice is only to be resorted to when all else fails. My own reasons against it can be put down in order of precedence, as follows:

1. I have been trained as a scientist and a specialist and taught to admire high technical skill and professional competence; a high standard of intellectual attainment has constantly been set before me throughout my training and I value it very greatly. Is there any chance of my having conditions of work in general practice which will allow me to exercise my technical skill or satisfy my intellectual thirst? Emphatically, no. I shall be too busy to examine or follow any case adequately, and I shall not be able to have the equipment for scientific diagnosis and treatment; nor, if I had it, should I have time to use it.

2. My wife and I want to be able to bring up our family under decent conditions; we want them to be moderately civilised and well-educated and to have a happy family life. Whatever kind of schooling the children may get, there must be order and leisure in their home. Will general practice allow us to do this? Once more, emphatically, no. If I have sufficient patients to make a good living,[*] I shall work roughly from 9 A.M. to 11 P.M. six days a week, and at any rate for my first five years shall be able to have no holidays because locums are so expensive. My wife will have to bear the whole domestic burden, with such daily help as she can tempt into a doctor's house, and my children will have to be kept out of the way so that the consulting- and waiting-rooms are not disturbed by their exuberance. Someone must be on duty in the house 24 hours a day 365 days in the year, since it is an indictable offence to leave the telephone unattended. My wife will either become a saint, or a slut, or leave me; my children will be sent to boarding-schools as soon as possible, so that the practice may go on undisturbed; as they grow up they will be left entirely to their own devices and we shall never go out with them together again. Of course, we are already resigned to our never going to entertainment or worship together again for the next 10 years, just because we have children.

3. If medicine is to be adequately practised it must be pursued without thought of gain and without the blackmail of hostile circumstances. Does general practice under the N.H.S. allow this? No. I shall be more a tradesman than ever my father was. The State patient has the whip hand; whatever insult, stupidity, thoughtlessness, or unnecessary demand he may submit me to, I must smile and comply. Not only can he leave me (with his whole family) without inconvenience or compunction, but he can involve me in endless anxiety, loss of time and legal expenses by reporting me to the local committee, without any inconvenience to himself.

4. If my health falters, if my principles conflict with the Ministry of Health, if my work leads me to make mistakes in my records, if an influential competitor gets a seat on the Regional Board not only are my hopes of advancement killed, but my very livelihood endangered.

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[*] We should perhaps make it clear that this article was written before the Danckwerts award was announced.—ED. L.

Shall I enter general practice? Not if I can avoid it!

WHAT ARE THE HOPES?

So it is that the queue for specialisation grows and grows, and those that at last sink into general practice are bitter and frustrated near-specialists, hating themselves and their jobs. Their chances of getting out again, once they have got in, are nil. The family doctor is urgently needed and is anxious to come forward in the service of many families, and of his own. If he risks everything on his gamble he may fail the many families by betraying his scientific training and being too busy to listen or examine, or with failing his own family by exposing them to a neglect they ought not to be asked to bear. Is there then no hope? Must he be either professionally incompetent, poor (because he limits his list to what he can adequately deal with), or a stranger to his wife and children?

It has been suggested that the only hope for general practice is to create chairs of general practice at the universities, so that there may no longer be a divorce between learning and practice, between medical education and the occupation of most doctors. This is an idea with a sound basis, but so far divorced from practical possibility at present as to be quite out of court. A G.P. elevated to a professorial chair could be little more shrewd than Sancho Panza in his governorship—and as ridiculous to his academic colleagues and students. He would carry no academic weight, and so get no hearing.

A man's work must itself satisfy his creative potentiality—it must justify him as made in the image of God. This principle, expressed by every poet and artist at odds with society, was perhaps practised sometimes in the Middle Ages; it is anathema to our industrialised society, and only exemplified now by the few surviving craftsmen and farmers still able to devote themselves wholly to a whole job. In medicine it is an ideal less and less attainable—in general practice because the personal relationship is shorn of intellectual and technical satisfaction, and in the specialties because the academic and technical skill operates in a sphere approaching more and more closely to a vacuum.

There is one great opportunity of redressing the balance at this time, and that is research, carried on in general practice.

> "General practice," the old men say, "offers endless opportunity for research, both social and medical."
>
> "When I am in general practice," a few young men say, "I shall do real scientific work."
>
> "I have done two surgeries and twenty visits to-day," says the general practitioner. "If I work every night from 8 to 11 this week I should get my paper-work done; but I know Mrs. X always has her babies at 3 in the morning."

Unless some young men can find opportunity, intention, strength of purpose, and financial backing to restore to general practice a scientific and academic respectability—not by talking about it, but, by being good family doctors and good scientific workers both at once—the outlook for general practice must be black indeed. A salary would help, by freeing them from the tyranny of the bottle of medicine and the time-waster (and why the medical profession should consider that a salary is the most stultifying manner of remuneration is one of the greatest mysteries of the contemporary social scene; it can only mean that its faith in its own standards has fallen to zero); but that is now a political issue and probably will not be decided for years to come. Some few with an academic background and a vocation to family medicine must find sufficient funds to go into general practice, limit their list to 1500 or so, and tackle a research programme with seriousness and ability. It is only by results that general practice can now re-establish itself in the academic scene.

Special Articles

MALARIAL FEVER THERAPY

P. G. SHUTE
M.B.E., F.R.E.S.

ASSISTANT DIRECTOR, MALARIA REFERENCE LABORATORY, HORTON HOSPITAL, EPSOM

THE reports that malaria therapy has benefited several cases of nephrosis (Byrne 1952, Gairdner 1952) have led to numerous requests to the Malaria Reference Laboratory, Horton Hospital, Epsom, for malaria material and for suggestions about the care and management of induced malaria.* The applicant is informed whether mosquitoes will be brought to his hospital, or whether parasitised blood will be sent. As live mosquitoes are not allowed to be sent through the post, they are carried by an assistant, who induces them to bite the patient to cause malaria.

INFECTION BY MOSQUITOES

A hot-water bottle should be placed against the patient's thigh an hour or two before the mosquitoes are applied. No other preparation is necessary, and on no account should the patient's skin be cleaned with soap and water or other antiseptics. Irritation from the bites of the mosquitoes can be relieved by dabbing the area of the bites with cotton-wool soaked in methylated spirit or methyl alcohol. Some patients experience irritation immediately after being bitten, whereas in others it may be delayed for as long as twenty-four hours.

Parasite Used

Only one species, *Plasmodium vivax* (benign tertian) is recommended for malaria therapy. Malaria due to *P. falciparum* (malignant tertian) is too severe; that due to *P. ovale* is too mild, recovery usually occurring spontaneously after 4–6 pyrexial peaks; quartan malaria, due to *P. malariæ*, is erratic in its behaviour and usually has a very long incubation period.

The strain of *P. vivax* supplied by this laboratory is known as the Madagascar strain. It was originally isolated from a lascar seaman in May, 1925, and since that date it has been kept in man-mosquito-man. The advantage of using this strain is that, as it has been under continuous observation for twenty-seven years, its behaviour in man and mosquito is known and its response to various drugs has been tested. For example, it is susceptible to mepacrine, quinine, proguanil, and 'Daraprim' (pyrimethamine).

Incubation Period

With this strain of parasite the incubation period is 9–14 days. Even if the mosquitoes inject enormous numbers of sporozoites the incubation period cannot be less than 9 days, because it takes 7 or 8 days for the sporozoite to complete its cycle in the parenchyma cells of the liver; and, when this is completed, at least one generation of the erythrocytic cycle must develop before fever can begin.

INFECTION BY INOCULATION

When whole blood containing malaria parasites is used to infect a patient, venous blood is taken from the donor and is either defibrinated, citrated, or heparinised. Our present technique is to send heparinised blood, about 5 ml. for each case, in a small screw-top container.

Just before use, the syringe and the needle should be thoroughly bathed in cold sterile saline solution. Spirit would kill the parasites.

Our practice is to inject the blood intramuscularly just below the scapula. The blood can be given intravenously, but the incubation period of malaria induced by erythrocytic parasites, unlike that of mosquito-induced malaria, is influenced by the number of parasites injected. It has been our experience over many years that where the incubation period is only 2 or 3 days, as it often is when large numbers of parasites are injected intravenously, the *subsequent fever is more severe than* it usually is when the incubation period is 9–14 days. When about 5 ml. of blood is given intramuscularly, the *incubation period is 10–16 days, seldom longer.* Failures sometimes occur because (1) the parasites may have died in transit; (2) they may have been killed by antiseptics; or (3), if the patient has had malaria before he may be immune.

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* Any doctor may send to this laboratory blood films for examination and mosquitoes for identification.

Subinoculation

Where there are several patients to be treated and one of them has been successfully infected with malaria from this unit, the rest can be infected by inoculation from the first patient. If the donor is in the same ward, a few millilitres of venous blood can be drawn off and injected without delay; but if the patients are in different wards, or if the blood has to go to another hospital, the blood should be treated with heparin to prevent clotting. As already stated, the syringe should be bathed in cold sterile saline solution immediately before the blood is drawn off.

Time for Taking Blood for Subinoculation

It is often *supposed that during certain periods of an* attack of malaria the peripheral blood is free from parasites, and that subinoculation can therefore only be successful at certain times. Though this is true for *P. falciparum*, which completes its asexual cycle in the internal organs, it is not so for *P. vivax*, whose complete cycle takes place in the peripheral circulation, and therefore the blood is infective at all hours from the beginning of the attack until antimalarial drugs are given. However, it is advisable to take blood for subinoculation a few hours after the termination of an attack of malaria because *at this time the young parasites are securely* attached to fresh erythrocytes, and the patient is usually feeling fairly comfortable after the cold and sweating stages. Blood should always be taken when young forms of the parasite are present if it is to be kept for a day or two, and it should be stored on ice.

PYREXIA IN PRIMARY *P. vivax* MALARIA

In about 86% of our primary cases of benign tertian malaria the fever has been quotidian and not of classical tertian type. There is abundant evidence to show that this quotidian fever is due to an absence of tolerance or premunition, because when relapses occur in the same patients the fever is almost without exception tertian and *after a few attacks of fever the tendency is towards* a spontaneous recovery clinically but not necessarily parasitologically.

The over-all clinical picture of benign tertian malaria of the Madagascar strain can be divided into five distinct phases:

(1) *Initial fever* usually lasts 3–5 days and is irregular, the temperature seldom rising above 102°F, and it may not return to normal throughout this period.

(2) *Developed stage.*—Fever is quotidian, temperatures of 104°F and 105°F are usual, rigors may or may not occur, and after 5 or 6 attacks the patient feels rather exhausted.

(3) *Terminating stage.*—After ten or more uninterrupted attacks of fever the tendency is towards spontaneous recovery, but this depends on the amount of resistance which the patient has built up as the result of his previous attacks. The first indication of spontaneous recovery may be the fever's sudden change from quotidian to classical tertian; but *this does not always* happen, and patients who are having quotidian fever may recover spontaneously, although parasites may be plentiful in the blood.

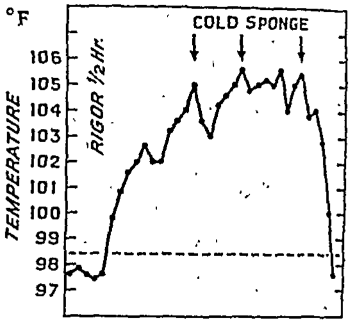

Fig. 1—An attack of benign tertian malaria due to a single group of parasites and lasting 8–10 hours.

(4) *Chronic stage.*—After a spontaneous recovery, either from the primary attack or from a relapse, parasites may be quite numerous in the blood and may continue to be so for several weeks unless antimalarial drugs are given. Although there is no pyrexia, the parasites are continuing their development, and therefore antimalarial drugs should be given to prevent anæmia.

(5) *Immunity.*—In primary benign tertian malaria patients who have had ten to twelve attacks of fever and perhaps one relapse some months later, can seldom be successfully reinfected *with the same strain of the same species of parasite.* If, however, the primary attack is cut short, subsequent relapses at about monthly intervals over a period of several months are frequent. Such patients have not been allowed to build up much tolerance or immunity and are therefore susceptible to reinfection. In other words, *relapses are evidence of* non-immunity, and the cessation of relapses, unless due to antimalarial drugs, is evidence of immunity.

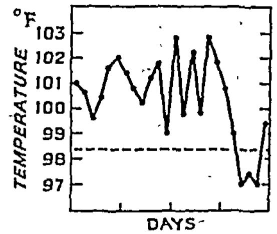

Fig. 2—Intermittent fever for 2 or 3 days in early stages of benign tertian malaria due to two or more groups of parasites.

(6) *Rigors* are common in benign tertian malaria, especially in the developed stage (stage 2). If, *however, the patient develops his* attack either daily or every other day with clock-like precision, much of the discomfort and severity of the rigor can be reduced if hot-water bottles and extra blankets are applied an hour or so before it is expected.

CARE AND MANAGEMENT OF INDUCED MALARIA

An attack of benign tertian malaria due to a single group of parasites usually lasts about 8 hours (fig. 1). In the early stages, where the fever is intermittent for 2 or 3 days, this is because two or more groups of parasites are present and each group is capable of causing fever (fig. 2). If the fever is quotidian, it is usually advisable to change it to tertian or to abort the attack temporarily. A single intramuscular injection of 0·2 g. of 'Thio-Bismol' (Parke Davis) will in most cases change quotidian fever to tertian. This drug seems to have a selective action on the half-grown asexual parasites, with the result that there is no pyrexia on the day after it is given, and subsequently the fever is tertian (fig. 3). This dose is for an adult and should be adjusted

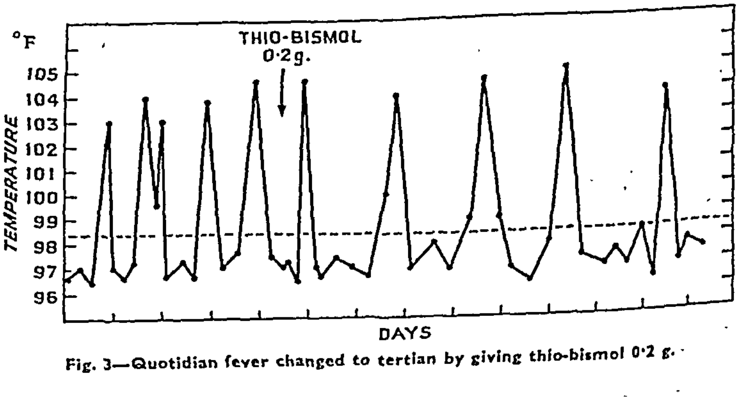

Fig. 3—Quotidian fever changed to tertian by giving thio-bismol 0·2 g.

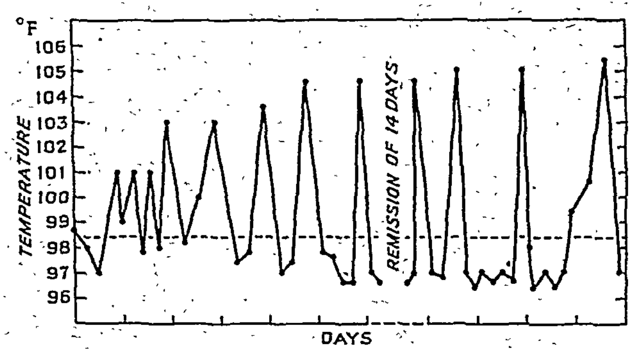

Fig. 4—Remission of fever for 14 days after quinine gr. 5, followed by recrudescence of fever as tertian instead of quotidian.

for children. If thio-bismol is not available, or if it is decided to give the malaria therapy in two stages, a single dose of quinine gr. 5 or of mepacrine 0·3 g. given orally will abort an attack for 10–14 days, when the fever will begin again, and often the fever of a recrudescence will be tertian (fig. 4). These doses are for adults.

Termination of Attack

Proguanil 0·2 g. daily for 10 days, mepacrine 0·3 g. daily for 7 days, and quinine gr. 5 daily for 15 days are adequate against the Madagascar strain of benign tertian malaria. These doses are based on observations for adults and should be adjusted for children.

Recording of Temperature

Although an attack of fever usually lasts about 8 hours, the peak of pyrexia may last only 1 or 2 hours; so 4-hourly temperature recordings are insufficient. It is our practice to take the temperature every 20 minutes or at least every half an hour once the attack has started, and this is continued until the temperature falls two or three degrees and it is seen that the attack is over. These frequent temperatures are recorded in a notebook, and the following day six readings are selected and recorded on the 4-hourly chart. If temperatures are taken only 4-hourly, the highest temperatures may be missed.

There is considerable dehydration as the result of an attack of malaria. Accordingly, after the sweating stage, glucose drinks, sweet lemonade, &c., should be given.

The Spleen

In primary malaria the spleen quickly becomes much enlarged, but it is very soft and often not palpable, probably because the patient is resting in bed; it is very different from the hard enlarged spleen of chronic parasite carriers in hyperendemic areas where the patients are up and about. Patients undergoing malaria therapy should be safeguarded from sharp active movements when changing position in the bed, so as to avoid spontaneous rupture of the spleen.

Relapses

With the Madagascar strain of benign tertian malaria relapses occur in about half the patients infected by mosquito bites. Usually there is only one relapse within a year from the primary attack; after this the patient is apparently immune to this species and strain of parasite. This, however, is conditional on the amount of fever in the primary attack. Patients who are allowed to have 12 or more peaks of fever in the primary attack seldom relapse more than once; but, if only 2 or 3 attacks are allowed, usually there are several relapses at monthly intervals or twice a month unless suppressive treatment is given. A relapse seldom occurs more than a year after the original infection. It is therefore suggested that patients who are allowed to have only a few attacks of fever in the primary attack and who relapse within 2 months of a course of antimalarial treatment should be given suppressive treatment for at least 6 months. Proguanil 0·2 g. twice a week will in most cases be sufficient. Relapses following infection by direct blood inoculations are unknown.

BLOOD FILMS

It is seldom if ever necessary to examine a thick blood film in induced malaria. The parasites are usually numerous, and except during the first 2 or 3 days of a primary attack one or more can be found in each of 25 micro-fields. A thin film is all that is wanted.

Slides.—Wherever possible new thin half-white slides with smooth edges should be used. Usually it is sufficient to pass new slides through methyl alcohol and to wipe them with a clean grease-free cloth. If, however, the slides are greasy they should first be cleaned with a detergent, such as diluted 'Teepol,' washed thoroughly, dried, and passed through methyl or absolute alcohol (methylated spirit should not be used).

Preparation of blood film.—The pad of the middle finger is cleaned thoroughly and when quite dry is sharply but gently pricked with a straight triangular needle. It is advisable to wipe off the first drop of blood and then, by a little pressure, to cause a bead of blood to form. The slide should be held by the edges to prevent grease from the fingers from getting on the surface of the slide. A bead of blood, no larger than the head of a pin, is brought into contact with the slide about half an inch from one end. The slide is then laid flat on a bench or table, and the edge of a second slide, held with thumb and index finger at an angle of 45°, is brought into contact with the bead of blood; after a slight pause, the slide is pushed along quite slowly but smoothly so that an unbroken film of blood covers about two-thirds of the slide. If the bead of blood is too large, the film will be too thick and if too much pressure in spreading the film is used, all the blood will be carried with the spreader. A little practice is required in preparing good thin films.

Staining malaria parasites.—Giemsa stain and Leishman stain are both satisfactory, but the sharpest picture is produced with Leishman stain. If Giemsa is used it should be bought in solution. 1 ml. of stain to 15 ml. of *neutral* distilled water is used for staining; but, because this is a watery stain, blood films must first be fixed for about half a minute *in methyl or absolute alcohol* (methylated spirit is unsatisfactory). Films should be stained for 15–20 minutes.

If Leishman stain is used, it is best to buy the crystals and make up the stain in the laboratory. 0·15 g. of the stain is added to 100 ml. of good-quality methyl alcohol. The bottle is shaken two or three times at short intervals on the day of preparing the stain, and it is then ready for use on the following day. Preliminary fixation of the blood film is unnecessary; but, if there is any delay and the film is lying uppermost on the laboratory bench, it is best to fix the film to prevent flies from devouring and contaminating the film. The film is stained by dropping on 4 or 5 drops of stain, and after 15 seconds (not longer) 10–12 drops of neutral or very slightly alkaline distilled water (pH 7·2) are added. The diluted stain is mixed thoroughly by rocking and allowed to stand for 15 minutes. The stain is washed off with a flood of distilled water and placed in a slanting position, with the blood film underneath, to dry. Artificial heat should never be used to dry a film stained by any of the Romanowsky modifications; but, if necessary, a film can be dried quickly by blotting with high-grade filter paper.

Parasite-count.—During the first day or two of a primary attack prolonged search is necessary to find even a single parasite, and sometimes none are found. From the third day onward there are usually at least two or more parasites in 25 micro-fields; in a well-prepared blood film, when the red cells are not overlapping but are nearly touching each other, there are about 400 red cells per micro-field when a $^{1}/_{12}$ in. oil-immersion lens and a no. 6 eyepiece are used. In the fully developed stage of a primary attack of benign tertian malaria there are usually about one or two parasites per field. In my opinion, in the practice of malaria therapy an attack should be aborted when this number is exceeded. It should be remembered, however, that for about 2 hours following a rigor, or in the absence of a rigor at the height of an attack, small ring forms of the parasite may exceed this number, but these will be seen to be much fewer if another film is taken an hour or so later, presumably owing to phagocytosis.

PREVENTION OF INFECTION OF LOCAL ANOPHELES

Thirty-two species of mosquitoes are known to be indigenous in Britian, but there are only four species of anopheles, and of these only one, *Anopheles maculipennis*, enters houses. The parasite of benign tertian malaria can develop in the tissues of anopheles when the temperature is 60°F or more. At about 75°F the cycle in the mosquito takes 10 days, but at 60°F it takes at least 30 days. In low-lying coastal regions where there is much brackish water *A. maculipennis* may become very numerous, and 50 or more are often seen in one bedroom. In inland districts the numbers are comparatively few. Patients undergoing malaria therapy between May and September should therefore be protected from mosquitoes, especially at night, either by sleeping under a mosquito net or in a side-room with the outer windows covered with mosquito netting. In hospitals in large towns the risk of spread is negligible or absent altogether.

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MEDICAL APPOINTMENTS TO THE QUEEN

THE following appointments to Her Majesty's household have been announced:

Physicians.—Sir Horace Evans, K.C.V.O., F.R.C.P.; Sir John Weir, G.C.V.O., M.B., F.F.HOM.; R. Bodley Scott, F.R.C.P.

Physician-Pædiatrician.—Wilfrid Sheldon, F.R.C.P.

Extra Physicians.—Lord Horder, G.C.V.O., F.R.C.P.; Sir Henry Tidy, K.B.E., F.R.C.P.; Sir Daniel Davies, K.C.V.O., F.R.C.P.

Sergeant-Surgeon.—Sir Arthur Porritt, K.C.M.G., O.B.E., F.R.C.S.

Surgeons.—Sir James Paterson Ross, K.C.V.O., F.R.C.S.; Ralph Marnham, F.R.C.S.

Surgeon-Gynæcologist.—Sir William Gilliatt, K.C.V.O., F.R.C.P., F.R.C.S., F.R.C.O.G.

Extra Surgeons.—Sir Thomas Dunhill, G.C.V.O., C.M.G., F.R.C.S.; Sir James Walton, K.C.V.O., F.R.C.S.; Sir Lancelot Barrington-Ward, K.C.V.O., F.R.C.S.

Extra Manipulative Surgeon.—Sir Morton Smart, G.C.V.O., D.S.O., M.D.

Extra Surgeon-Apothecary.—Sir Frederick Hewett, K.C.B., K.C.V.O., K.B.E., M.D.

Surgeon-Oculist.—Sir Stewart Duke-Elder, K.C.V.O., F.R.C.S.

Extra Orthopædic Surgeon.—Sir Reginald Watson-Jones, F.R.C.S.

Aurist.—J. D. McLaggan, C.V.O., F.R.C.S.

Surgeon-Dentist.—A. C. R. McLeod, F.D.S., R.C.S.

Extra Physician to the Household.—Sir Arnold Stott, K.B.E., F.R.C.P.

Surgeon-Oculist to the Household.—A. J. B. Goldsmith, F.R.C.S.

Extra Surgeon-Oculist to the Household.—F. A. Juler, C.V.O., F.R.C.S.

Apothecary to the Household.—J. N. Loring, M.R.C.S.

Surgeon-Apothecary to the Household at Windsor.—R. W. L. May, M.B.

Extra Surgeon-Apothecary to the Household at Windsor.—E. C. Malden, C.V.O., M.B.

Surgeon-Apothecary to the Household at Sandringham.—J. L. B. Ansell, M.R.C.S.

Coroner of the Household at Windsor.—Lieut.-Colonel Leslie McCarthy, D.S.O., M.D.

SCOTLAND

Physicians.—A. Greig Anderson, C.V.O., F.R.C.P.; Sir John McNee, D.S.O., F.R.C.P.; Prof. L. S. P. Davidson, F.R.C.P.

Surgeons.—Sir James Learmonth, K.C.V.O., C.B.E., CH.M.; G. G. Bruce, F.R.C.S.

Surgeon-Oculist.—John Marshall, M.C., F.R.F.P.S.G.

Surgeon-Dentist.—R. C. S. Dow, L.R.C.P., H.D.D., F.D.S.

Surgeon-Apothecary to the Household at Balmoral.—G. P. Middleton, C.V.O., M.B.

Surgeon-Apothecary to the Household at the Palace of Holyroodhouse.—George Brewster, M.D.

In England Now

A Running Commentary by Peripatetic Correspondents

A PRECLINICAL colleague of ours has a profound distrust of electrons, even when suitably emboxed and under the strict surveillance of an expert. It appears that this distrust is mutual, for he has always been able to exert an inimical influence on the performance of any electrical apparatus merely by his presence in the vicinity. At his approach his friends cover up their electric clocks and muffle their refrigerators. In his lab. they have learned by experience to keep the thermostats in the basement and the embedding ovens in inaccessible corners.

Judge then of our colleague's dismay on finding that in his absence abroad his room had become the seat of feverish electrical activity. The whole of one bench was submerged beneath a smothering blanket of condensers, amplifiers, and rectifiers, while there were also several sinister black japanned cases mounted on rubber and undoubtedly containing numerous valves of the small malignant kind which never fit into any socket. Beneath the bench lurked two enormous batteries, and in the window, on his favourite seat, there stood the final ignominy, a trickle-charger. The floor was knee-deep in wire.

Our friend at once recognised the spoor of the electrophysiologist next door, who had not expected him back so soon. His wrath rose, and he said a naughty word. Revenge, however, was easy. He walked slowly round the room, pausing before each individual component of the prevailing chaos and fixing it solemnly with his eye. The immediate results were not spectacular, but the long-range effects are mounting daily. The apparatus has to all appearances been safely removed, but our colleague understands that square-wave pulses have been replaced by monophasic spikes, that the trickle-charger has caused acid to splutter all over various electrophysiological objets d'art, and that several dollar-consuming valves have blown. He is confident there will be no further encroachments the next time he goes abroad.

* * *

It is easy to introduce a new word into medical currency, but to discard it is more difficult. Hurst in 1915, with his enormous gusto, supplanted the word *cardiospasm* by *achalasia* and in 1921 could write, complacently and correctly, that "since I introduced it, it has been adopted by most writers on the subject." And now, in 1952, Douthwaite congratulates Avery Jones on excluding the inept word from his new book. Not only have the old gods fallen but their gospel is in fragments. Little enough remains of the codex, but how magnificent it looked in the 1920s.

Who would now do battle for these Hurstian concepts: the absent acid-barrier in pernicious anæmia; the inability of the cardiac sphincter to relax as a sequel to the degeneration of Auerbach's plexus; the ascending infection in acute hepatitis; the rôle of infection in gastric and duodenal ulcer; and the ætiological importance of chronic gastritis and chronic appendicitis?

And who practises these outworn therapies: rigid ulcer diets, intestinal lavage, dental clearance in pernicious anæmia, hexamine in cholecystitis, gastric lavage by iced water in hæmatemesis, the mercury bougie in cardiospasm, antidysenteric serum in ulcerative colitis, adrenaline by the minim-a-minute method, and the elimination of septic foci—teeth, tonsils, and appendices?

And what remains? A conviction that hysterical conditions can be quickly relieved by suggestion; an irreversible notion that the physician should take a look for himself, radiographically, sigmoidoscopically, and gastroscopically; and some fundamental work in gastro-intestinal radiology.

These are not inconsiderable legacies. But any physician who knew Hurst would say that the half has not been told. His enthusiasm and confidence were a consuming flame that cured his patients, convinced his colleagues, and warmed the coldest conferences. He was a magician whose faith made miracles possible and whose miracles created faith. Is such therapeutic magic part of the forgotten art of medicine? I am not sure, but it was certainly the glory that was Hurst.

* * *

As a junior peripatetic, I sometimes wonder if senior colleagues undergo what I undergo. In the past ten months I have had three mild attacks of Acute Appendicitis. With November came my First Disc, now happily back in hibernation. After Christmas I developed Bronchiectasis for 8 days, but surgical intervention was fortunately unnecessary. A week later I contracted Specific Disease, the result of too close an inspection of a beastly old aorta in the post-mortem room. This lasted for a fortnight, and was succeeded by a spasm of Carcinoma of the Gall-bladder—the anterior end, I could feel it quite distinctly. After a symptom-free month, I went down with my most trying illness to date—Primary Tuberculosis of the Epiglottis. For 5 weeks I suffered with sore throat, intermittent aphonia, and general malaise. Finally, rest, sedation, and spirits were instituted, and I went rapidly uphill, for by the time I could see my vocal cords in the mirror, all traces of the disease had disappeared.

With the exception of this last episode, my diseases have needed no treatment, but I would emphasise that this did not reflect an ignorance of available measures on my part. In fact the opposite was true, and I would strongly recommend all fellow juniors with a personal pathology to make good use of an invaluable aid to the learning of medicine.

At the moment I have an Œsophageal Hiatus Hernia. With reference to your excellent leader on the subject last week, I have to point out that I am not a middle-aged overweight woman of nervous disposition. The diagnosis was confirmed by the finding of borborygmi over the left atrium.

* * *

Not many people know how they are going to die, but I do. I shall be found dead in a taxi-cab. I shall die of the mounting threepences.

It is really a subtle form of homicide, this tormenting of frugal passengers with the detailed exactness of the sums dribbling from their pockets. Must we know it? Need there be an inside clock to draw our eyes with its horrid truths? Is it not enough to know the worst on alighting?

My health deteriorates only moderately at the initial one and threepence, for I am reconciled to that in advance. Nor do I suffer greatly from the grand total at the end, for I have a fair idea of what it will be. In fact I am sometimes restored to buoyant health by an over-estimate. No, it is the gradual and visible attrition which destroys my *élan vital*.

Try as I will I cannot withdraw my eyes from this menacing and implacable dial. If I sit with my back to it, it draws them irresistibly over my shoulder, and every time another threepence registers an iron hand clutches my heart.

How is it to be expected that the faithful son of a Scottish university should look on such a sight unmoved? Though long years of residence here have given me, I like to think, a little of the English phlegm. If I have company in a taxi I hope my cheek does not blanch nor my eye turn glassy, but I fear they do.

Naturally I avoid taxis as much as I can. My knowledge of bus routes and connections is unequalled, and my reputation with bus-conductors as a short-distance sprinter stands high. Nevertheless, emergencies will arise when only a taxi will answer. For instance, a sudden shower giving rise to acute hat-anxiety in the female. And then, the horrid ordeal of listening with affected pleasure to social chatter, and feigning nonchalance while this infernal machine ticks my substance away!

Yes, I shall die at my front door. The driver will send for a doctor. The police will arrive too. The taxi-man will state that he had been held up by several traffic jams, during which I had shown great agitation, and that I was alive immediately before arrival as I had pointed out the house to him in a voice trembling with emotion. Yet when he opened the taxi door I was dead.

The constable will murmur something about inquests and post mortems. But the doctor will smile knowingly. "Heart for a certainty," he will say. "See these stains on his waistcoat? Obviously porridge. The metre shows a fare of seven and sixpence. And just as the cab stopped *it ticked up another threepence*, and that finished him off. Couldn't take it. Quite simple——"

Letters to the Editor

ISONIAZID FROM THE RECEIVING END

SIR,—Isoniazid, since it is cheap to manufacture and easy to administer, is already being used extensively in the treatment of tuberculosis. So far little evidence of toxicity has been recorded. In the words of one doctor, "there was no toxicity worth talking about." Perhaps his patients were not very talkative. At any rate, I would like to register a protest from the receiving end.

After a total of 25 g. streptomycin, in association with P.A.S. 12 g. daily, I developed a mildly staggering gait. The streptomycin was, therefore, replaced by isoniazid 100 mg. t.d.s. (a daily dose of 6 mg. per kg. body-weight) and the P.A.S. continued. At this stage I had been afebrile with a steady pulse-rate of 70–80 for several weeks and, apart from mild gastro-intestinal disturbance due to P.A.S., was feeling well.

I was lying happily in bed under an oak-tree, reading the first volume of Sigerist's *History of Medicine*, when, to my surprise, about an hour after the first dose of isoniazid every nerve in my body seemed to have been stimulated. All the sites where streptomycin had been injected became painful, there was a sensation of tingling all over, together with generalised muscular twitching, and cardiac action became rapid and bounding. This state was associated with a complete inability to concentrate on the mysteries of medicine in ancient Mesopotamia. A period of drowsiness followed, but was soon dispelled by the next dose.

After a few days' treatment I had completely lost my appetite and was unable to sleep or even lie still. Sigerist was replaced by Sapper, but even the adventures of Bulldog Drummond were unable to hold my restless mind. I was uncomfortably aware of my physical surroundings; the trees seemed greener and the sky bluer; minor irritations had a greatly exaggerated importance. I was subject to attacks of palpitation and at rest alarming extrasystoles. After 6 days I had lost $3^{1}/_{2}$ lb. in weight and treatment was stopped.

I would like to remind those responsible for the treatment of tuberculosis that Keats wrote his best poems while dying of this disease. In my opinion he would never have done so under the influence of modern chemotherapy.

A PATIENT.

BLOOD-PRESSURE ESTIMATIONS IN CHILDREN

SIR,—Your leading article of Aug. 2 on the Treatment of Bacterial Meningitis says: "Meanwhile, doctors treating meningococcal infections will do well at first to chart the blood-pressure every fifteen minutes . . . they will certainly obtain useful evidence of the pressures to be expected in septicæmic children without adrenal damage."

I would be interested to know how the blood-pressure is to be taken, not every fifteen minutes, but at all, in a baby of, say, 10 months. In such a child (as in the case described by myself and my colleagues[1]) the manometer-cuffs currently available may cover the upper limb from the shoulder to the wrist, and the lower limb from the upper thigh to the middle of the leg. Which vessel is then to be selected? Moreover, the child, unless moribund, must be expected to resist, which will not enhance the accuracy of the results.

Again, for how long are these fifteen-minute readings to be kept up? The process would seem to offer abundant employment to at least one doctor for some twelve to twenty-four hours. In fact, Sir, I would venture to suggest that you have not considered the practical problems involved with your usual care.

South Middlesex Hospital,
Isleworth.

G. E. BREEN.

*** We should have made it clear that we were referring to research on the value of cortisone in the Waterhouse-Friderichsen syndrome. As Dr. Banks[2] pointed out in his letter commenting on Dr. Breen's paper, the diagnosis of the syndrome is extremely difficult. When a drug as powerful and as expensive as cortisone is in question, all possible care is indicated in its trial. The blood-pressure is, we understand, recorded as a matter of routine in many children younger than 10 months—e.g., in children with burns and scalds, and in pink disease. In those centres where retrolental fibroplasia is treated with A.C.T.H., regular readings are made on premature infants weighing less than 4 lb.[3] Dr. Breen is unfortunate in having only the adult-type manometer cuff: cuffs for children are now obtainable, and the 'Crista' range, sold by Messrs. Hawksley & Son, 17, New Cavendish Street, London, W.1, has three sizes. In older infants the mercury sphygmomanometer is sufficiently reliable if serial measurements are made. In smaller infants and newborn children, a Pachon oscillometer and 2·5 cm. cuff have been found more accurate by some workers.[4] The correct size and application of the cuff are important in measuring the blood-pressure at any age.[5]—ED.L.

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[1] *Lancet*, 1952, i, 1141.
[2] Banks, H. S. *Ibid*, p. 1305.

HOSPITAL HYGIENE

SIR,—The letter by "M.O.H." in your issue of Aug. 9 leads me to raise another aspect of hospital hygiene. I speak from experience as a patient in four hospitals in recent years. The Ministries of Health and of Food, the public-health authorities, and others, have long been trying to inculcate in the public the doctrine that the hands should be washed after using the W.C. Are the hospitals doing anything to spread this doctrine by example? In which, if any, are patients provided with means of washing after a bedpan? The defence will probably be that the practice would throw still more work on an already scanty nursing staff. But is it not at least a desideratum?

PUBLIC HEALTH.

RECURRENT ATTACKS OF MENINGITIS

SIR,—A young woman, aged $19^{1}/_{2}$, was admitted to this hospital on March 6, 1952, with headache and vomiting. Her previous history was as follows:

At the age of 11 she had been diagnosed as having meningitis, and there was no reason to doubt this for both she and her mother gave a description which fitted in very definitely with an attack of meningitis—meningococcal meningitis I would have thought, for they both described a typical rash.

She made an uninterrupted recovery and kept perfectly well until the age of 16 when she was admitted to this hospital on Jan. 17, 1950, with suspected meningitis. She had had a cold for a fortnight before admission, and then suddenly developed a severe headache.

There was marked rigidity of the neck and spine, and she was very toxic and lethargic. A lumbar puncture showed a very turbid cerebrospinal fluid under increased pressure. The pathologist reported: cells 17,400 per c.mm. (polymorphonuclears); stained film showed gram-positive diplococci; culture gave a scanty growth of pneumococci.

A further lumbar puncture on Jan. 24 showed: cells 130 per c.mm. (mononuclears); protein 45 mg., chlorides 734 mg., glucose 56 mg., per 100 ml.; no organisms seen on gram film; cultures sterile.

She was given intrathecal penicillin (50,000 units), intramuscular penicillin (500,000 units b.d.), and $1^{1}/_{2}$ g. of sulphamezathine 4-hourly. She had three intrathecal injections, and the other treatment was maintained for 11 days. She made an uninterrupted recovery and was discharged on Feb. 4.

The findings in her latest illness were:

On admission there was definite neck rigidity with some extension of the head. The reflexes, superficial and deep, were slightly exaggerated. Kernig's sign was positive on both sides. Temperature 102°F, pulse 122, respirations 22. Lumbar puncture showed turbid fluid under slight pressure. The pathologist reported: cells over 10,000 per c.mm., glucose 69 mg., protein 800 mg., per 100 ml.; no organisms seen on film or culture, but the C.S.F. gave a positive precipitin reaction with type II meningococcal antiserum.

She was treated with intrathecal penicillin (20,000 units), intramuscular penicillin (500,000 units at once, then 200,000 units 4-hourly), and 2 g. of sulphamezathine 4-hourly. Her temperature became normal within 24 hours, and only one *intrathecal injection of penicillin* was given. The patient was treated with 'Duracillin' (500,000 units b.d.), and progressed steadily to complete recovery.

She has now had three attacks of meningitis: meningococcal at 11; pneumococcal at 16; and meningococcal again at $19^{1}/_{2}$.

She is now being seen at monthly intervals, and so far she has been in perfect health with no sequelæ whatever.

Infectious Diseases Hospital,
Portsmouth.

IAN M. MCLACHLAN.

FRACTURES OF THE NECK OF THE FEMUR

SIR,—I was very interested to read Mr. Stamm's article of July 12; but, as on many previous occasions, there is one point I should like to comment upon.

For many years now I have given up nailing these fractures in *internal* rotation, and instead have fixed them in a few degrees of *external* rotation. The improvement in the results is almost startling.

I have published elsewhere the reasons for this. Here I shall mention only one. In many of these cases the back of the neck of the femur is so fragmented that if the fracture be rotated internally, and nailed in this position, there is no real bony contact posteriorally. This obviously diminishes the chances of bony union.

London, W.1.

F. P. FITZGERALD.

HASHISH

SIR,—Dr. D. McI. Johnson, in his letter of April 19 (p. 820), gives an interesting and plausible explanation of the symptoms observed at Pont St. Esprit. His quotation of Théophile Gautier from *Le Club des Hachichiens* and of the recent American studies on this subject have a counterpart in the experience of Carl Ludwig Schleich, the surgeon who in 1891–92 introduced infiltration anæsthesia into surgery. In his memoirs[1] he relates his short but nearly fatal connection with hashish addicts.

Invited by a fellow-student and driven by sheer curiosity, Schleich, who then had just passed his first M.B., went to this "Klub der Resignierten." He found about eight young men there, lying about in a half-naked condition, humming, muttering, and singing to themselves; one of them playing a flute and two others reciting parodies of Goethe's Erlkönig and of other poetry. They all pretended to be followers of Buddha and the then fashionable Schopenhauer, the philosopher of pessimism; they styled themselves *candidati mortis*. Schleich recalls that there was a lot of cigarette-smoking and drinking of liquor, and also of tea; he does not relate whether there was any hashish smoking or drinking, but after he had been solemnly addressed by one individual wearing a turban he was asked to uncover his arm in order to be "initiated" into the "club." Rapidly he was given an injection, after which he immediately lost consciousness. He recovered from this (cardiac?) collapse after a professor of medicine who had been summoned had administered three injections of camphor.

This happened around 1880, in the small university town of Greifswald in Northern Germany. Schleich further relates that five of the members of this "club" of hashish addicts became inmates of mental hospitals or committed suicide. Not one of the others was ever cured of the addiction to hashish in the form of injections.

Port Stanley,
Falkland Islands.

F. K. M. HILLENBRAND.

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[3] Bembridge, B. A., Coxon, M., Houlton, A. C. L., Jackson, C. R. S., Smallpeice, V. *Brit. med. J.* 1952, i, 675.

[4] Bevis, D. C. A., Schofield, S. F. *Arch. Dis. Childh.* 1951, 26, 109.

[5] Woodbury, R. A., Robinow, M., Hamilton, W. F. *Amer. J. Physiol.* 1938, 122, 472.

[1] Besonnte Vergangenheit: Lebenserinnerungen 1859–1919. Berlin, 1922.

ŒSOPHAGEAL HIATUS HERNIA

SIR,—In reading your leading article of Aug. 2 I was interested in the close parallel between the probable mechanism whereby reflux from the stomach is prevented (Allison[1]) and that which prevents dribbling of urine in the female (Jeffcoate[2]).

As I understand it, reflux from the stomach may occur when the œsophageal hiatus in the diaphragm is relaxed, allowing the angle between the œsophagus and the upper surface of the cardiac end of the stomach to be straightened out. Jeffcoate has shown that stress incontinence of urine in the female occurs when the angle between the base of the bladder and the urethra is straightened out. The parallel to Allison's "parahiatal hernia" is cystocele. Each of these may occur without incompetence of the retaining mechanism. Each may be associated with incompetence when the retaining angle is lost.

University of Leeds. A. AMBERY SMITH.

REASON AND UNREASON IN PSYCHOLOGICAL MEDICINE

SIR,—It seems likely that Dr. Dillon (Aug. 2) missed the main point that I tried (perhaps unsuccessfully) to make in my first Croonian lecture. My argument was that, if in the human sciences one's approach to causality is limited to the establishment of efficient or final causes, one is apt to be bogged down in a false metaphysic. I cannot however go the whole way with Dr. Dillon and admit that natural science can altogether dispense with the notion of "dependable sequences" and remain scientific.

London, W.1. E. B. STRAUSS.

FEEDING DISORDERS IN INFANTS

SIR,—I hesitate to comment upon Miss Morrison's letter in your issue of Aug. 9, because Professor Vining manifestly needs no support from me; but the assertion that the cause of digestive disorder in infants is "practically always a wrongly balanced mixture" and "seldom due merely to underfeeding or overfeeding" cannot be allowed to pass unchallenged.

It is somewhat disturbing to read the advice given on occasion in the infant-management columns of the lay press. Infants with such symptoms as "fretfulness," "colic," "never seems satisfied," constipation, vomiting, and failure to thrive, are said to be suffering from dyspepsia, wind, and even overfeeding.

I remember one case in particular of an infant with these symptoms which had been given a weaker feed by its mother with no success. The comment and advice given was: "How right you were Mother, to weaken the feed, even so it should be weaker still." A specially balanced formula was sent under separate cover.

Now there is absolutely no mystery about most of these infants; they are simply underfed, some of them grossly underfed. Anyone offering more feed can prove this.

Underfeeding is one of the commonest faults of infant management, as Professor Vining, Professor Illingworth, and Dr. Charlotte Naish have repeatedly averred. One reason for its frequency may be that mothers tend to read not THE LANCET but Nurse Blank's column in their weekly journal. Such publications have a considerable responsibility to their readers, and because of this I suggest that their watchword should be simplicity rather than complexity.

Cow's milk is so similar to breast-milk that some simple modification only is necessary. The suggestion that "ingredients" should be "balanced" merely baffles a harassed mother, causing her to ignore the often obvious symptoms of hunger in her baby.

There seems to be a belief that the mere male, by virtue of his sex, cannot understand these problems. Prof. Alan Brown does not subscribe to this view; he describes in his Ingleby lectures of 1948 the father of a young child supposedly suffering from "tummy-ache" rending the night air with its cries; the ignorant and ignored male observes, "If that were a puppy I'd say he was hungry and feed it."

Birmingham. B. S. B. WOOD.

LIVER EXTRACT FOR HERPETIC PAIN

SIR,—Dr. Christopher Howard's letter in your issue of Aug. 2 prompts me to write in support of his findings. My own experience has been that liver extract, apart from the relief of herpetic pain, can have a most beneficial effect on the whole course of herpes zoster. The response varies from one case to another, but I have yet to meet a case which has failed to respond in some degree provided injections are started as early as possible and repeated if necessary. At best, the results can be little short of dramatic, and it was a case of this nature that drew my attention to an interesting side-effect.

A middle-aged woman came to see me in the autumn, with an early typical herpes of the left loin. I gave her 2 ml. 'Anahæmin' which resulted in rapid relief of symptoms and disappearance of the local lesions. About a year later she asked me if the injection could have been responsible for her freedom from chilblains throughout the winter; she was normally a "martyr" to these, and had not enjoyed such comfort for years. A further trial injection seemed justified, and the result was again satisfactory.

I have since used liver extract for a number of chilblain cases. Again the response varies from one patient to another. Injections may have to be repeated in the more obstinate cases, but I have found no other form of therapy so rapid in its effect, the relief of irritation often becoming apparent in a matter of hours, and the healing of broken chilblains being much expedited.

Ashwell, Herts. J. H. MOYNIHAN.

SYRINGE-TRANSMITTED TUBERCULOSIS

SIR,—I think that one point in this subject, discussed in your annotation of July 5, has not yet received sufficient attention. Most people seem to agree that the tubercle bacilli enter from without and that they are carried by infected needles or syringes. The fact that these abscesses have become more common since the introduction of penicillin is partly explained by the use of the small rubber-capped bottle for penicillin. The cap is pierced with the needle when withdrawing the solution; and, as these bottles may be used for multiple injections, once the contents are infected an abscess may follow each subsequent injection. The point is, however, that this kind of bottle and rubber cap is nothing new—insulin has been kept in this way for years. Admittedly the number of penicillin injections given to children (in whom the majority of abscesses have developed) is larger than the number of insulin injections, but I cannot find a single report of a tuberculous abscess after an insulin injection. And diabetics are certainly not resistant to tuberculosis!

The use of the bottle instead of the ampoule does not explain everything. I think the basic point is this: the needles and syringes that carry tubercle bacilli are usually loaded with other germs as well, mainly gram-positive cocci, which are sensitive to penicillin. Inside the bottle the antibiotic exerts some sort of bacterial selection, and only the tubercle bacilli survive. When the solution is injected a tuberculous abscess ensues. When insulin or some substance other than an antibiotic is injected, a trivial pyogenic abscess occurs.

Novara Civil Hospital,
Italy. EDGARDO RUCCI.

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1. Allison, P. R. *Surg. Gynec. Obstet.* 1951, 92, 419.
2. Jeffcoate, T. N. A. Address to the 13th British Congress of Obstetrics and Gynæcology, 1952; see *Lancet*, July 26, 1952, p. 189.

CLINICAL MEASUREMENT OF BLOOD-FLOW

SIR,—Few problems in experimental medicine and surgery have taxed the ingenuity of research-workers so much as the direct measurement of blood-flow in various organs, such as the kidney, heart, brain, and liver; and the use of so many different methods shows that a satisfactory solution has not been found.

All these methods suffer from such disadvantages as the necessity of severing blood-vessels, clotting of the blood in the glass connections and tubes, alteration of the hydraulic properties of the flow by the introduction of resistances, eddy currents, volume changes, and interference with the nerve-supply. Many are too complicated and unstable for clinical use.

I should like to describe a new and simple method.

If AB (fig. 1) represents a small known distance along a blood-vessel, say 1 cm., the speed of the blood can be determined by measuring the time taken by a given particle (P) to travel from A to B. The particle may be any harmless substance introduced into the blood-stream some little distance above A. It should differ from blood in some physical property, such as electrical conductivity, radioactivity, colour, refractive index, or density, which will enable it to be differentiated and picked up at A and B as it flows along in the blood-stream.

The actual way in which the arrival of this tracer substance first at A and then at B is recorded depends entirely on its nature. It may be done with a resistance bridge, a photoelectric cell, or in many other ways which will readily suggest themselves according to the physical property selected. Some methods will require the insertion of one or two fine needles into the vessel wall; in others more contact with the wall will be sufficient.

For example, an experiment was designed on the basis of the difference of electrical conductivity between blood and the tracer substance. Two extremely fine needles which just penetrated the lumen were used at A and B, and AB formed one arm of a resistance-bridge. Alternatively, only one needle (B) need be used, and the needle of the injecting syringe can serve as A; or the release of the syringe plunger can produce the starting impulse by some electrical coupling at the instant the tracer substance is released.

Fig. 2 shows the oscillograph recording obtained when an air-bubble was injected a little above A. Its passage is clear cut, and its speed can be measured absolutely accurately to the nearest $^1/_{100}$ second, for the tracing constitutes a modulated 50-cycle carrier wave and thus is self-timing. The lower tracing is an optional time-base with superimposed 1 second impulses.

Other substances tried were hypertonic and hypotonic saline, distilled water, very dilute organic acids, and oils; and all gave good deflections. The disadvantage of employing aqueous solutions is that unavoidable diffusion occurs which obscures the wave front and renders it less distinct. No matter which tracer substance is used and what receptor mechanism is employed to detect its passage, the aim is to get as sharply defined a wave front as possible. An ideal substance would be an innocuous liquid, more or less immiscible with blood, devoid of any tendency towards adhesion to the walls, and of a specific gravity approaching that of blood, but differing in some other physical characteristic. Some of the higher alcohols are under investigation, and octyl alcohol has given excellent results. I am carrying out further experiments with this method which will be reported later.

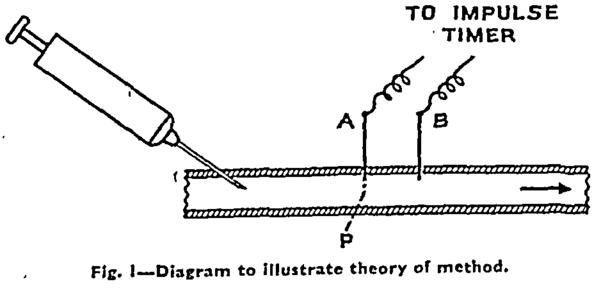

Fig. 1—Diagram to illustrate theory of method.

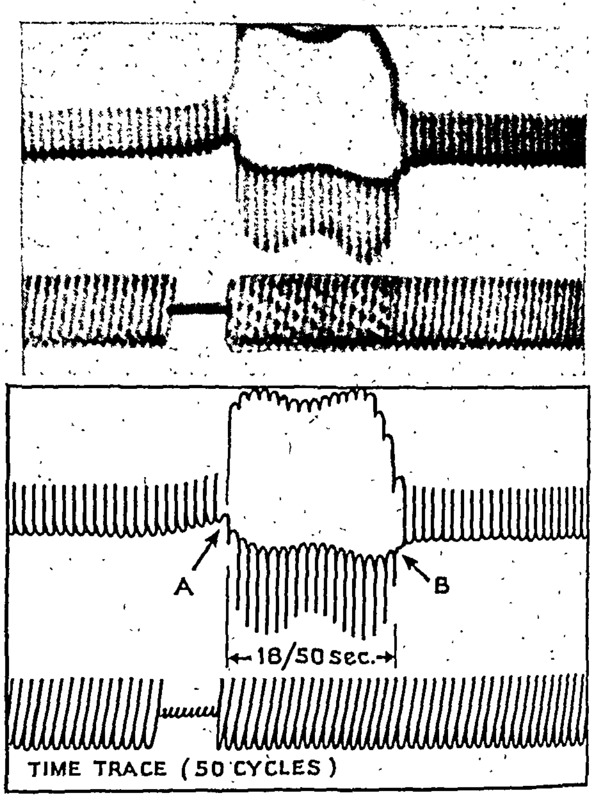

Fig. 2—Oscillograph recording of passage of air-bubble between 2 needles 1 cm. apart. Time of transit = $^{18}/_{50}$ sec. Speed of flow = 2·78 cm. per sec.

I am indebted to Prof. W. E. Underwood and Mr. P. Theron for their encouragement and for the provision of the necessary experimental facilities.

Johannesburg. ARTHUR SKOWRON.

PLEA FOR PSYCHOTHERAPY

SIR,—Dr. Marion Greaves (July 26) seems to be pleading for a wider application of psycho-analysis on Freudian lines.

At a time when psychiatry struggles for the acceptance of its terminology, an extension of such treatment seems unjustified. As she rightly stated, treatment must be preceded by correct diagnosis, and, I may add, based on scientific knowledge of the subject. Psychiatry is not yet a science; its principles and conclusions are purely hypothetical and empirical, and its methods are derived from medicine. She also admits that the body-mind relationship has so far been insoluble. How then can a correct diagnosis be reached? Although Freud did valuable work in mapping the human mind, his interpretations are too imperative and many of his *deductions* do not stand logical reasoning. The Roman Catholic Church has applied psycho-analysis for nearly 2000 years in the more agreeable and much less dangerous form of confession. Reactivation of dreadful past experiences can produce irreversible psychosis—a danger *not to be treated lightly*. Unfortunately we lack frank statistics from analysts about cures and failures.

To take another interesting aspect of the subject, there are no more scientific proofs *for* the existence of mind than there are *against* the existence of the soul. Can they be the same?

In my opinion this problem should be approached with more respect. Analysing the psyche without knowing its nature seems the equal of undertaking a major operation without anatomical knowledge. Freudian analysis should wait until we have more knowledge.

As Dr. Strauss said in his Croonian lectures (July 5 and 12), psychiatry is, from a scientific point of view, some fifty years behind medicine. So let us pass along the accessible way, proceeding from the lesser to the greater complex, and tackling the subject from the physical aspect. That was the path of progress for medicine and should be for psychiatry as well.

Barnsley Hall Hospital,
Bromsgrove. J. W. MULLNER.

HOSPITAL ADMINISTRATION

SIR,—One would imagine from the number of committees set up for the purpose that the medical profession was not without interest in hospital administration. What the present system lacks—and it is to this that I presume Dr. Bruce refers in his letter of Aug. 2—is some means whereby what might be called "administrative emergencies" are dealt with on the spot. The need for this varies in different hospitals; but it is generally agreed that it makes for smoother administration, and so "closely concerns the interests of the patients," if someone with a knowledge of medicine is willing to undertake this responsibility in addition to his clinical work.

London, S.W.1. J. R. M. WHIGHAM.

HYOSCINE IN TREATMENT OF SEASICKNESS

SIR,—On a long sea voyage recently I had the opportunity of observing the effect of hyoscine on fully developed seasickness. The patients were three women (aged 30–61) and four girls (one aged 11, the others under 3 years). The *l*-hyoscine hydrobromide was given as a powder in gelatine capsules or in water. The initial dose for adults was 0·5 to 1 mg. and that for children 0·25 to 0·5 mg.; maintenance doses of 0·5 mg. every 7 to 8 hours up to a maximum of 2 mg. in 24 hours were given to the adults, and the children were sometimes given a second 0·25 mg. after 8 hours. All patients were made to lie down for the first hour of treatment.

Fifteen bouts of seasickness were treated; with one exception all the patients were pale and prostrate, and on ten occasions they were vomiting, when treatment began. The drug was always retained. The children were soon up and about, and though the adults continued to have slight nausea they were able to take food and did not vomit. These observations suggest the *l*-hyoscine can cure or improve seasickness in women and children, and that large doses of this drug can be given repeatedly without ill effect.

Singapore. E. M. GLASER.

TUBERCULOSIS IN PREGNANCY

SIR,—I have closely observed a group of 28 tuberculous pregnant women with a follow-up period of more than three years. The following observations were made:

> 5 had an abortion in the first trimester of their pregnancy. Subsequently all of these women had an exacerbation of their disease. 23 bore the pregnancy well and had full-term normal deliveries; only 6 of these women had an exacerbation of their disease. From these results it would appear that abortion is more dangerous than continuing the pregnancy to full term. In my opinion pregnancy itself does not influence unfavourably the course of tuberculosis if the patient submits to appropriate and adequate treatment.
>
> It is of interest that 42% of women whose tuberculosis was diagnosed during pregnancy had aggravation of their disease; whereas only 20% of women whose tuberculosis was recognised before the pregnancy had aggravation. This, I feel, is due to earlier and more adequate treatment of the disease in the latter group.

In my opinion, the prognosis of tuberculosis in pregnancy depends on: (1) the extent and type of the lesions; (2) appropriate, adequate, and timely treatment; (3) the obstetrical course of the pregnancy. Only in rapidly progressive tuberculosis with severe toxicity should abortion be considered. It should be used only during the first trimester of pregnancy. In all other cases, whatever the form of pulmonary tuberculosis or duration of pregnancy, I recommend continuation of the pregnancy under close supervision and appropriate treatment. A difficult delivery is to be avoided, and the baby should be separated from the mother immediately after delivery.

I also suggest that all women should undergo radiographic examination of the chest before conception and periodically during pregnancy. Ideally, tuberculosis should be inactive for at least two years before pregnancy is permitted.

Athens, Greece. CONSTANTINE P. STAVROPOULOS.

FUNGUS INFECTIONS OF THE FEET

SIR,—Your annotation (June 7) on this subject indicates that the condition is difficult to treat effectively. It is certainly widespread, but for those living near the sea the following simple method will often prove effective:

> Allow the scrubbing action of sand particles to take away dead and sodden skin. At the same time the action of brine will help to rehabilitate the feet. Paddling in sea-water for an hour a day will enable the skin to regain its normal texture.
>
> Prevention of reinfection is also simple. All footwear should be disinfected. This may be done by rinsing with 1 in 8 'Cyllin,' and allowing the disinfected articles to lie twenty-four hours inverted to drain and dry. Clean socks daily are essential. Thorough daily washing of the feet with soap and water is equally important, and may not be omitted by those who are liable to fungus infection of the feet.

Prince Albert, Saskatchewan,
Canada. A. ROTHWELL.

SUCCINYLCHOLINE

SIR,—In view of the recent correspondence about succinylcholine, the following case may interest your readers.

A man, aged 58, who gave a history of angina pectoris for 3 years, underwent a partial gastrectomy for peptic ulcer. His weight was 140 lb., blood-pressure 150/90 mm. Hg, and Hb 94%.

The course of the operation was as follows:

12.23 P.M. Induction of anæsthesia with 0·5 g. of thiopentone, followed by 100 mg. of succinylcholine. Oral intubation with a cuffed tube, and administration of 20% oxygen in nitrous oxide. Intravenous saline drip started.

12.31 P.M. Spontaneous respiration established. 5 mg. of decamethonium iodide (C10) mixed with 25 mg. of pethidine hydrochloride into drip. Controlled respiration for 15 min., after which respirations were again spontaneous.

12.57 P.M. 3 mg. of C10 given. Spontaneous respiration continued.

1.7 P.M. 2 mg. of C10 given. Spontaneous respiration continued.

1.11 P.M. Saline drip changed to 500 ml. of 1 : 1000 lignocaine ('Xylocaine').

1.28 P.M. 100 mg. of succinylcholine given. Controlled respiration for 15 min. Respirations again spontaneous.

1.52 P.M. 3 mg. of C10 given. Assisted respirations for 3 min.

2.6 P.M. 50 mg. of succinylcholine given. Controlled respiration for 3 min. Immediately after this dose of succinylcholine, blood was substituted for the lignocaine drip which was almost finished, the patient having had 0·5 g. of lignocaine in 38 min. Diaphragmatic breathing returned within 3 min., but complete paralysis of the intercostal and abdominal muscles persisted.

2.20 P.M. Patient returned to the ward, maintaining himself on oxygen given through an endotracheal tube, with occasional assistance.

2.45 P.M. Patient given 10% carbon dioxide. Colour remained good with assisted respiration.

3 P.M. 6 ml. of nikethamide given into drip. No respiratory response, but fibrillary twitchings of both deltoids noted.

3.20 P.M. 6 mg. of neostigmine given into drip. Within 90 seconds the patient was breathing deeply, using intercostal and abdominal muscles. As was expected, he salivated freely, but was soon able to clear his throat himself. His subsequent recovery was uneventful.

During anæsthesia the patient received two doses of succinylcholine and three of decamethonium iodide from which he recovered spontaneously, indicating an adequate concentration of plasma cholinesterase. But he did not recover from the third dose of succinylcholine, despite a blood-transfusion, until after 6 mg. of neostigmine was given.

It should be remembered that after a long anæsthetic, or in debilitated subjects, failure to regain muscular tone may not necessarily be due to the persistence of a relaxant drug in the system. In patients who have previously responded normally to succinylcholine neostigmine may be used with benefit.

Northallerton, Yorks. J. SHEGOG RUDDELL.

SORE THROAT AND RHEUMATIC FEVER

SIR,—In your excellent leading article of July 12 you state, " to Coburn in the United States, and to Schlesinger and Sheldon in this country, goes the credit for bringing again to general notice the clinical relation of upper respiratory infection to rheumatic fever." It does not really matter who the credit goes to now that group-A, β-hæmolytic streptococcus has been accepted as causal agent, but the actual facts are these :

> Sheldon and I were working on the epidemiology of rheumatic fever about 1930 at Great Ormond Street and certain convalescent homes for rheumatic-fever patients. We were greatly helped and encouraged in these studies by J. A. Glover and Fred Griffith. It was Griffith who said to me, on studying our epidemiology charts, that he believed the infecting organism was a hæmolytic streptococcus, and it was he who typed those I found by his own method. Schlesinger's contribution was his observation of the silent period between the initial throat infection and the subsequent rheumatic-fever attack, or relapse, and the effect on the subsequent attack of salicylate if given during this silent period. This aspect was omitted from your article.

It is interesting to note also that Coburn's manuscript and those of Sheldon and myself[1] (both published the same day in THE LANCET as complementary papers) were in the press at the same time, both he and we having come to the same conclusion, though his studies were all carried out in America and ours in London. I think I can claim definitely to have been the first person on this side of the Atlantic to state in a paper that the hæmolytic streptococcus was *a*, if not *the*, infective factor in rheumatic fever.

Rotunda Hospital, Dublin. W. R. F. COLLIS.

Medicine and the Law

Fatal Injection of Sulphuric Acid

ON July 31 an inquiry was held in Glasgow into the death of a 13-month-old boy who died 9 days after a rectal operation.

The baby had been suffering from diarrhœa and later developed piles. He was admitted to hospital on May 31, and two days later an injection of what was thought to be absolute alcohol was made under an anæsthetic. A surgeon, who was asked to see the baby a few days later, said at the inquiry that the child's condition was inconsistent with alcohol having been administered. The tissues into which the fluid had been injected had been destroyed, and there was extensive inflammation spreading round to the groin and the abdominal wall, with severe swelling in the rectum. The bottle from which the fluid had been drawn was investigated, and it was discovered that the bottle, though it was labelled " absolute alcohol," did in fact contain 20% sulphuric acid.

The surgeon who gave the injection said in evidence that when the theatre sister handed him the syringe, he had not tested the contents. The appearance of the liquid had been consistent with that of absolute alcohol, and, even had he not been wearing a mask, he could not have told by smell whether it was sulphuric acid or not, because of the various other smells in the theatre.

The theatre sister said that she had filled the syringe from a bottle which had been received from the dispensary about a month before and which had been kept under lock and key until first used on the day of the injection. Sulphuric acid was never kept in the theatre.

The hospital superintendent said that on June 5, having learned that the baby was very ill and that there was doubt about the contents of the bottle, he went to the hospital pharmacy and examined the cupboard where the pure alcohol was kept. He had found a large green bottle marked " absolute alcohol," and beside it another bottle marked " sulphuric acid, 20%." Both bottles were coloured green and were the same size.

The two dispensers agreed that one of them must have filled the bottle, but neither could remember which. Asked how such a mistake could have happened, one replied that her attention might have been distracted by a telephone call or someone coming into the dispensary with a message.

Prof. John Glaister, professor of forensic medicine in the University of Glasgow, said that on June 21, with another doctor, he conducted a post-mortem examination. Death had resulted from rectal necrosis and peritonitis. Asked if he had any suggestion to make about ways of avoiding such mistakes, Professor Glaister said that bottles could be of different colours, and those containing acid could be corrugated. Bottles could be initialled by the dispenser after filling and labelling. The contents could be checked in the theatre or ward to which they were sent.

The jury returned a verdict in accordance with the medical evidence, adding a rider that " dangerous toxic substances and acids should be kept in distinctive bottles."

Hypnotist's Successful Appeal

At the end of March Miss Rains-Bath was awarded damages at Sussex Assizes against Mr. Ralph Slater, a stage hypnotist, for his conduct towards her during a demonstration at the *Brighton Hippodrome*.[1] The Court of Appeal has now ordered a re-trial of her claim in respect of the major item in the award.[2] The jury gave her £25 for a not very serious assault: he had placed his fingers on her neck and jerked her head forward; on this part of the case the award is to stand. They also gave her £1000 (and £107 special damages) for his alleged negligence; on this part of her claim the Court of Appeal found the trial unsatisfactory. The trial judge, it seems, was not properly informed of the issues, though one would suppose that the pleadings must have disclosed the particulars of the allegations of negligence on which she relied; he did not, it seems, adequately direct the jury. He directed the jury carefully, says Lord Justice Singleton, as to the nature of negligence and as to the duty of Mr. Slater in respect of the issues as the trial judge understood them. On the other hand he never directed the jury's attention to Mr. Slater's denial of having ever said that the demonstration was harmless. The Lord Justice could not find that the trial judge had suggested the following questions to the jury:

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[1] Collis, W. R. F. *Lancet*, 1931, i, 1341. See also Collis, W. R. F. *Amer. J. Dis. Child.* 1932, 44, 785. Collis, W. R. F., Sheldon, W. *Lancet*, 1932, ii, 1261. Collis, W. R. F., Sheldon, W., Hill, N. G. *Quart. J. Med.* 1932, 1, 511. Collis, W. R. F. *Proc. R. Soc. Med.* 1932, 25, 1631. Collis, W. R. F. *Practitioner*, 1935. 134, 617. Collis, W. R. F. *Lancet*, 1939, ii, 817.

[1] *Lancet*, 1952, i, 725.

[2] *Times*, July 31, 1952.

> Had Mr. Slater implanted in the plaintiff's mind something of a frightening or terrifying nature?
>
> If so, was it something wrong and dangerous—in other words was it negligent?
>
> If so, had Mr. Slater taken sufficient steps to remove it?

There had been no direction that the measure of duty placed on Mr. Slater was that to be expected of one who practised as a stage hypnotist, and no higher.

It was, says the Court of Appeal, an unusual case; "no one could describe it as a strong one"; the medical witnesses must have found difficulty in connecting the plantiff's condition some 18 months after the occurrence with the occurrence itself, though there was some evidence on that point.

There were members of the public who read the result of the trial last March with a certain surprise. They will await with interest the fresh trial, reflecting perhaps that a good deal of money has been spent by the parties upon getting a decision and that this expense, through no fault of the parties, has been thrown away.

Obituary

EDWARD ROLAND GARNETT PASSE

B.D.S.Melb., F.R.C.S., D.L.O.

Mr. E. R. Garnett Passe, senior consulting aural surgeon to King Edward Memorial Hospital, Ealing, and aural surgeon to Wembley Hospital, who died on Aug. 1, had made a substantial contribution to the development of the fenestration operation for otosclerosis.

Garnett Passe was an Australian, and he took a dental qualification at Melbourne in 1926 before he came to this country to study medicine. He had intended to take his medical course at Glasgow, but the chance recommendation of a fellow passenger on the boat coming over to this country deflected him to London, and he qualified from the London Hospital in 1929. One of the house-appointments he held at the London Hospital was that of house-surgeon to the aural department, and there his interest in otology grew, so that he gave up his original intention of returning to practise in Australia and remained in this country to take further qualifications in his chosen specialty. After holding a house-appointment at the Central London Throat, Nose and Ear Hospital he obtained the D.L.O. in 1931 and the F.R.C.S. in 1936. Later he was appointed first assistant and registrar at the London Hospital. Soon afterwards he joined the staffs in the aural department of the King Edward Memorial Hospital, Maida Vale Hospital, Hounslow Hospital, and Wembley Hospital. During the late war he served with the R.N.V.R. with the rank of acting surgeon commander.

Despite a busy and successful practice he still found time for research on clinical problems. Since the war his main work had been the development of the fenestration operation for otosclerosis, and he was one of the group of British surgeons who have practised this procedure. Several times of recent years he was invited abroad to demonstrate his technique for this operation. Lately he had also become interested in the effect of the sympathetic nervous system on conditions such as Ménière's syndrome, tinnitus, and nerve deafness; and at the time of his death he was studying surgical methods for dealing with these conditions. He had performed several dorsal sympathectomies, and it was a measure of his surgical ability that he could perform these operations himself and need not hand them over to a neurosurgeon. In the same way during the war he often turned his hand to general surgery when occasion arose.

A colleague writes: "Garnett Passe was a man of quiet personality who was tremendously keen on his work. A loyal friend and colleague, he was particularly kind to juniors, and he would go out of his way to help a former assistant. On his winter sports holidays he showed the same quiet determination to deal with the job in hand—though this might be a rather nasty-looking steep run. It is a tragedy that his career should end so early, for he was capable of so much and there was so much that he wanted to do."

HAROLD ETTRICK MOORE

O.B.E., M.B. Manc.

Dr. H. E. Moore, who died on Aug. 6 at his home at Crewe, will be remembered for the years of service he gave to the railway community and for his work as an adviser on reablement to the Navy and the Air Force during the war.

He was born in 1878, at Silverston, Northamptonshire, where his father, the Rev. George Moore, was vicar. The family later moved to Denham Vicarage, near Bury St. Edmunds, where he spent his boyhood. He was educated at a preparatory school kept by his uncle, near Alnwick, Northumberland, and later, after a short period at Denstone College, won a scholarship to King's School, Ely. The family moved to Lancashire on the appointment of his father to Parkfield Vicarage, Middleton, Lancashire, and Moore began his medical studies at Owens College, graduating M.B. in 1904. At the university he was an outstanding athlete and he captained both cricket and rugby. He played for three years in the Lancashire county rugby side, and he was awarded a North of England cap. He was also a first-class golfer.

Moore's first appointment was at Manchester Royal Infirmary as house-surgeon to the late Sir William Thorburn. After holding other resident appointments at Salford Royal Hospital, Withington Hospital, and the Mental Hospital at Ayr, he worked as an assistant in a general practice in Oakham, and in 1908 he started in practice on his own at Bollington, Cheshire. He gave up this practice after a year to join his uncle in practice at Stourport-on-Severn, Worcestershire. In 1915 he joined the R.A.M.C. He served in Gallipoli where he was attached to the hospital on Cape Hellas. After the evacuation he served in the Hospital Ship *Asturias*, and when she was torpedoed in the English Channel he was one of the last to leave the ship.

On demobilisation he returned to Stourport to find most of his practice gone. He therefore took an appointment with the Ministry of Pensions as D.C.M.S. at Newcastle upon Tyne and later at Darlington. But his natural bent was towards active surgical practice, and in 1922 he was appointed surgeon to the London and North Western Railway Works Hospital at Crewe, his old chief, Sir William Thorburn, being at that time consulting surgeon to the L.N.W.R. Moore immediately began to develop and modernise the hospital, which undertook all the casualty work and traumatic surgery for the Crewe works and the other railway staff in the locality. From 1922 till his retirement in 1949 his life and work were spent in the care of the railway workers. He gave the strictest attention to detail, supervising the treatment of even trivial injuries himself, and he obtained excellent results.

He was appalled by the wastage and length of incapacity of many workmen's compensation cases, and he made these his special study. He tried his new ideas of active reablement and movement at first with a small number of cases. Later, convinced that his ideas were sound—and he was a man of such integrity that he was not easily convinced—he persuaded the L.M.S. Railway Company to build an extension to the Crewe Hospital with a large gymnasium and physiotherapy rooms for rehabilitation treatment, where patients not only from the Crewe area but also from other parts of the railway system were treated.

Owing to Moore's modesty and shyness, this pioneering work on reablement is not as well known as it should be; but in the orthopædic world it was recognised, and, with the coming of war in 1939, Moore was appointed civil adviser in rehabilitation to the Royal Air Force and later to the Royal Navy. He played a vital part in developing the reablement schemes for both these services; in recognition of this work he was appointed O.B.E.

After the war he continued in active practice as surgeon to the Accident Hospital at Crewe, and in 1947 he was appointed acting chief medical officer of the L.M.S. Railway.

He is survived by his wife, two sons, and one daughter.

DR. LESLIE CUNNINGHAM

A surgical colleague writes: "I shall always remember Leslie Cunningham as a first-class physician upon whose services I might call with confidence and without hesitation at all times. He believed in the closest coöperation between the physician and surgeon: he did not hesitate to advise operation in the appropriate case, nor to seek the views of his surgical colleagues if in doubt. He was exceptionally successful in dealing with difficult post-operative cardiac or pulmonary complications.

"Although he practised as a general physician, he had special interests. In his earlier years he had done research for the Liverpool Cancer Research Organisation, and he published work on the toxic effect of lead and on tissue metabolism. Cardiology, however, had a greater attraction, and one of his earlier appointments was that of medical officer in charge of the cardiographic department at the Northern Hospital. No doubt the frequent association of thyroid and cardiac disorders led to his closer study of thyroid disease and ultimately to the formation of a thyroid clinic at the Northern Hospital. Hospital commitments and private practice made heavy calls on his time; for his quiet, helpful, unassuming, and always friendly manner appealed alike to doctors and patients.

"He was a good teacher and he was always popular with the students, who realised his worth. Both his house-physician and registrar appointments were highly prized. The high esteem of the nursing staff was well expressed by one of his ward sisters on the day he died: 'How good he was to us and how we shall miss him!' He leaves behind many friends—doctors, nurses, and patients—who will echo these words."

Appointments

BATE, J. G., M.B. Edin.: pathologist, St. Mary's Hospital and Princess Louise (Kensington) Hospital for Children, London.
CURRIE, J. D., M.B.: asst. psychiatrist, Pewsey Mental Hospital, Wiltshire.
DAVIES, G. D., M.B. Lond., D.M.R.: consultant radiologist, Rhymney and Sirhowy Valleys H.M.C., Wales.
DAVIES, I. M., M.R.C.S., D.P.M.: consultant psychiatrist, Pen-y-Val Hospital, Wales.
GARSON, R. A., M.R.C.S., D.I.P.: asst. pathologist (S.H.M.O.), Halifax group of hospitals.
GRACE, R. F. T., M.D. Edin., M.R.C.P.: assistant (consultant status), department of psychological medicine, National Hospital, Queen Square, London.
HOLME, V. P., M.B., D.OBST.: asst. M.O. (maternity and child welfare), Coventry.
HOLMES, P. J., L.R.C.P.I.: superintendent, Sub-Regional Sanatorium, Ardkeen, co. Waterford.
MASTERS, P. L., M.D. Lond., D.C.H.: pathologist, St. Mary's Hospital and Paddington Green Children's Hospital, London.
NICHOLSON, HOWARD, M.D. Lond., F.R.C.P.: asst. consultant physician, Brompton Hospital, London.
PRINCE, G. S., M.B. Dubl., M.R.C.P.I., D.P.M.: part-time psychiatrist (consultant), Woodberry Down Health Centre.
THOMAS, ELIZABETH, M.B. Glasg.:
ZALESKI, W. A., M.B. Polish Sc : asst. psychiatrist, Pewsey Mental

Manchester Regional Hospital Board:

BOLTON, HAROLD, M.B. Manc., F.R.C.S.: consultant asst. orthopædic and accident surgeon, North Manchester hospitals, main duties at Ancoats Hospital.
COVELL, N. A. G., M.CH. Lpool, F.R.C.S.E.: consultant asst. orthopædic and accident surgeon, Preston and Chorley hospitals.
CULLEN, C. H., M.CH. Belf., F.R.C.S., F.R.C.S.I.: consultant orthopædic surgeon, orthopædic and accident services in the North Manchester hospitals, and Booth Hall Children's Hospital.
HARRIS, RONALD, M.C., M.D. Leeds, D.PHYS. MED.: consultant physical medicine), Devonshire
., F.R.C.S.: consultant asst. and district hospitals.
asst. venereologist, St. Luke's Clinic, Manchester.
WINSTON, M. E., M.B. Edin., F.R.C.S.: consultant asst. orthopædic surgeon, Bolton and district hospitals.

South Western Regional Hospital Board:

LINDSAY, IAN, M.B. Edin., F.R.C.S., F.R.C.S.E.: surgical registrar, Bath group of hospitals.
MCSWINEY, M. J., M.B. N.U.I.: asst. anæsthetist, Bath clinical area.
NEVE, C. R., M.B. Lond., F.R.C.S.: senior surgical registrar, Bristol clinical area.
NEVIN, H. M., M.A., M.B. Dubl., D.P.H., D.T.M. & H.: asst. clinical pathologist, North Gloucestershire clinical area.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital p otherwise stated. Canvassing disqualifies, but visit the hospital by appointment.

Notes and News

THE SITUATION OF THE MENTAL HOSPITALS

OF all patients, those with disorders of the mind might be expected to profit most from rest and quiet; and it is the great misfortune of our mental hospitals that these are the forms of therapy which they are least able to offer. Last year, as the annual report of the Board of Control for 1951[1] tells us, the number of patients in mental hospitals in England and Wales rose to 135,626, a gain of 436 on the previous year. For many years now this figure has been rising, and even our vast service is too small to cope with the demands on it. Accommodation in terms of bedspace, the report says, was for 123,906 patients; but not all accommodation was in use: 1071 beds were still diverted to other services, 1748 could not be used because there were no nurses to staff them, and 1585 beds were unoccupied because the wards were being put in order. In all there was a deficit of no less than 16,124 beds. Of course this is only a manner of speaking, for, in fact, beds must have been found for every one of the 135,626 patients; and what this meant in terms of overcrowding, noise, and misery only the nurses, spread thinly among them, could fully report. Recruitment in other branches of nursing has reached a peak, but in mental nursing the number of student nurses is still declining, though there has been some increase among trained nurses. Nursing assistants and part-time staff have given some help, but the ratio of male nurses to patients is 1 to 5·5, and of female nurses 1 to 7·1. "The remedy is not yet in sight," says the report, not altogether helpfully, "but the problem is one which is constantly before all concerned."

The need for a solution is all the more urgent because patients are beginning to show a livelier trust in the resources of the mental health service. Many more are being admitted as voluntary patients, though the report notes that practice varies in different parts of the country: a few hospitals receive more than 90% as voluntary patients, while others take almost half their patients under certificate. The social importance of avoiding certification is considerable, and if patients see a psychiatrist before they are admitted to hospital, he can explain this to them. Besides, it is easier to treat a coöperative voluntary patient than a resentful certified one. Outpatient centres staffed by the doctors who also treat the inpatients have done much to foster early treatment, and the board find that where outpatient departments are active the voluntary admissions tend to be high. Fortunately such departments are increasing in number: in 1939 there were only some 200, but there are now almost twice as many. With so much gained, and every promise of further advances, we shall be foolish if we forget that mental treatment depends finally for success on adequate nursing. The problem of recruiting mental nurses needs special study.

PRESCRIPTIONS IN JUNE

THE new charges for medicines, dressings, and appliances were introduced on June 1 this year; and figures issued by the Ministry of Health show that in England and Wales the number of prescriptions declared as having been submitted during that month was 14,416,800, representing a decrease of 15·57% on the number in June, 1951. The number of forms in June this year was 8,545,000, representing a decrease of 20·4% on the number in June, 1951; and the number of prescriptions on each form averaged 1·69, compared with 1·57 in the previous June. The proportion of forms on which one or more of the prescriptions cost over 5*s.* net was about 24%, compared with 20% in June, 1951. The estimated average total cost per prescription was about 1¼–1½*d.* higher in June this year than in the previous month, judging by the findings from a 1% sample of chemists; the comparable increase between May and June, 1951, was just under 1*d.*

YOUNG CONVALESCENTS

Dr. Frank Falkner's account of his inquiry into the care of convalescent children in this country, in the United States, and in Switzerland, which he summarised in our issue of March 29, has now been published in full under the title of *The Convalescent Child.* Copies may be had from the Department of Child Health, Alder Hey Children's Hospital, Liverpool, 12.

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[1] London: H. M. Stationery Office, 1952. Pp. 8. 4*d.*

TUBERCULOSIS ERADICATION AREAS

The Ministry of Agriculture have declared the following two districts to be tuberculosis eradication areas:

Counties of Cardigan and Carmarthen (except the Bettws Mountain district) and part of Pembrokeshire, in Wales.

Counties of Ayr, Dumfries, Kirkcudbright, Renfrew, and Wigtown, and parts of Argyll and Bute, in Scotland.

After Oct. 1 all herds in these areas will be tested and reactors will be slaughtered, with payment of compensation. When bovine tuberculosis has been eradicated, they will be declared attested areas.

STATISTICS OF CAUSES OF DEATH

The World Health Organisation Centre for Classification of Diseases has prepared a booklet[1] designed to indicate the difficulties encountered in maintaining continuity of statistics of causes of death, and to show how those difficulties may be overcome. Rearrangements of the International List, changes in the form of death certificate, and the many different ways in which the principal cause of death may be selected for tabulation from several causes stated on the certificate have all made it increasingly difficult to compare figures accurately. These difficulties are partly illustrated in a section devoted to statistics of diabetes, where it is shown how the rigid rules used in the past for selecting the principal cause placed too much weight on diabetes as the cause of death—an emphasis out of proportion to its actual significance as a fatal disease. These rules necessarily produced statistics of diabetes which could not be compared with those of countries which relied on the opinion of the certifying doctor as to the principal cause of death. This publication is intended to help those who prepare and study the trends in death-rates from separate causes. Methods of preserving the continuity of statistics of mortality-rates are discussed and examples of possible situations given.

HOSPITAL FOR TROPICAL DISEASES, LONDON

Attention was lately drawn in Parliament[2] to the help which this London hospital now offers to patients with tropical diseases in whatever part of the country they live. Since it moved last year into its new building in St. Pancras Way, N.W.1, its accommodation includes 68 beds, an outpatient department, and pathological laboratories. It is intended that the hospital, as part of the National Health Service, should be a consultative centre for the specialised treatment of tropical diseases, and any general practitioner in any part of the country can send a patient direct to the hospital, where there is a comparatively short waiting-list for inpatient treatment. The Ministries of Health and Pensions are particularly anxious that these facilities should be known to Servicemen and pensioners.

TREATMENT OF RABIES

A new development in the treatment of rabies was described at a conference sponsored by the World Health Organisation and held at the Pasteur Institute in Coonoor, Southern India.[3] A serum, prepared from the blood of horses whose immunity to rabies virus has been raised by repeated vaccination, is under trial in Iran. It is being given to people who have been attacked by rabid wolves. Incidentally, it seems that a bite from one of these animals is more often the cause of a fatal infection than the bite of an infected dog. Hitherto, treatment has involved daily vaccination for 2–3 weeks with a vaccine usually obtained from the brain of an infected sheep. But the method is not altogether satisfactory; for one thing, the use of the vaccine occasionally promotes the formation of demyelinating antibodies which may cause paralysis. Though no results of the trial have yet been reported, there are good hopes that the serum may prove a simpler and safer means of reducing the mortality of rabies, which is responsible for about 3000 deaths every year in India alone. The serum is not yet available commercially.

University of Oxford

On Aug. 2 the degree of B.M. was conferred on C. T. M. Wilson and E. H. Jellinek.

University of London

At recent examinations the following were successful:

M.D. Branch I (medicine).—M. W. Arthurton, D. W. Barritt, D. C. Beatty, Brian Creamer, F. E. Dische, D. D. Gellman, E. W. Hughes, C. B. Ingor-Willey, A. H. Levy, Joyce J. P. Lomas, Mohamed Ajawad Macan-Markar, D. Y. Mackenzie, R. G. Moore, P. W. Nathan (*mark of distinction*), James Parkyn, M. G. Philpott, A. E. A. Read, I. P. Ross, G. W. Scott, H. T. N. Sears, D. G. H. Sylvester, Alfred Wiener (*mark of distinction and university medal*), Eirian Williams, T. C. P. Williams.

M.D. Branch II (pathology).—J. V. Dacie, L. R. Davis, J. H. O. Earle, H. V. J. Fernando, Harry Greenburgh, T. D. S. Holliday, A. C. Hunt, Margaret P. Jevons, B. W. Meade, W. D. Ratnavale, J. H. Shore, J. M. Talbot, Phyllida M. M. Thornton, J. R. B. Williams, T. B. Williamson.

M.D. Branch III (psychological medicine).—A. A. Baker, R. A. Hunter, E. J. Rich, J. D. Richardson, Ebben Roderic-Evans.

M.D. Branch IV (midwifery and diseases of women).—A. C. Barthels, D. P. Cocks, G. M. Evans, C. M. Flood, G. T. Hammond.

M.D. Branch V (hygiene).—L. J. Clapham, N. R. E. Fendall, Kathleen M. Harding, G. R. Holtby, Mary M. E. Rutter, J. F. Skone, M. D. Warren.

M.D. Branch VI (tropical medicine).—J. R. Harries.

M. S. Branch I (surgery).—J. W. P. Gummer, R. E. Horton, P. G. Large, K. W. Martin, A. J. H. Rains.

M. S. Branch III (ophthalmology).—H. N. Reed.

D.M.R. (diagnosis).—A. T. Broadbridge, R. J. Callander, David Datt, J. J. Geere, Victor Roseverne.

D.M.R. (therapy).—K. A. Newton, R. C. S. Pointon, L. C. Robson, Jean K. M. C. Wilson.

Mr. H. A. B. Simons, PH.D., has been appointed to the readership in physics at the Royal Free Hospital School of Medicine from Oct. 1.

University of Birmingham

Dr. P. H. Davison has been appointed clinical lecturer in medicine. The title of research fellow has been given to Dr. C. N. D. Cruickshank of the department of experimental pathology.

On July 5 the following degrees were conferred:

M.D.—F. G. W. Marson, H. W. Pooler.

M.B., Ch.B.—Christine C. Wade (with second-class honours); J. G. Ball, Geoffrey Baum, W. G. C. Bearcroft, Graham Beaumont, L. A. W. Bellamy, Beatrice W. Boulton, *P. A. Bramley, Iona M. Brereton, J. R. Brown, Michael Cooke, N. F. D. Cooper, G. H. C. Daley, O. W. Deacon, Dennis Dean, J. M. Dolphin, H. A. Ellis, Lucy M. Ellis, D. I. Ferguson, H. W. Goldfarb, R. N. Gunness, R. J. Halpin, Joan E. Hancock, Kenneth Harrison, R. C. Hartley, Margaret A. Hartshorne, Betty D. Heap, Laurence Henry, E. R. Hitchcock, B. D. Hodge, Jane C. Iles, Barry Ingham, G. H. Jeavons, Thelma D. Johnson, Olive G. Jones, Edward Kinnear, R. C. Lambert, *Judith M. Leather, C. G. Lloyd, Patricia M. Lumb, Ursula R. Mindelsohn, J. T. F. Morrall, G. A. I. Namsoo, Cecile E. Needham, Kathleen M. Neville, C. D. Oakley, J. R. Owen, J. S. B. Preece, G. J. Rice, *E. J. Rix, D. P. W. Roberts, G. G. Roberts, C. R. Salisbury, J. L. Skinner, E. A. Smith, Jean G. Smith, J. H. Smith, A. T. Spencer, K. A. Tomlinson, Meriel F. Underwood, D. H. Wadelton, Desmond Watton, H. E. Wells, Cleon White, George White, H. E. Wilson, R. G. Woodwards, Howard Young.

* In absentia.

Institute of Psychiatry

A two-year postgraduate course in psychiatry will begin on Oct. 6 at the Maudsley Hospital, Denmark Hill, London, S.E.5. Further particulars may be had from the dean of the institute at the hospital.

Chartered Society of Physiotherapy

The annual congress of this society is to be held at St. Pancras Town Hall, Euston Road, London, N.W.1, from Sept. 18 to 21. The speakers will include Dr. T. F. Main, Dr. J. B. Mennell, Dr. A. T. Richardson, Mr. R. Guy Pulvertaft, Dr. Ian Curwen, Mr. Terence Cawthorne, Dr. William Morton, and Dr. W. S. C. Copeman. Further particulars may be had from the secretary of the society, Tavistock House (South), Tavistock Square, London, W.C.1.

Committee on Venereal and Treponemal Infections

At their recent meeting in London this expert committee of the World Health Organisation elected Dr. G. L. M. McElligott (Gt. Britain) chairman, and Dr. M. Soetopo (Indonesia) vice-chairman. Since the committee last met in 1949, over 5 million people have been tested and over 2 million treated in demonstration and mass control campaigns supported by W.H.O. and Unicef.

Medical Women's Federation

The federation is to hold a congress in London from Oct. 31 to Nov. 2, to celebrate the 35th anniversary of its foundation. During the congress Dame Hilda Lloyd will deliver the Christine Murrell lecture, on Domiciliary Midwifery. There will also be a discussion on the Care of the Child in the National Health Service. Application for tickets should be made to the secretary of the federation, Tavistock House (North), Tavistock Square, London, W.C.1.

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[1] Comparability of Statistics of Causes of Death according to the Fifth and Sixth Revisions of the International List. W.H.O. Geneva. Pp. 59. 2s. 9d. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

[2] See *Lancet*, 1952, i, 1263.

[3] *New York Times*, Aug. 7, 1952, p. 7.

Increased Family Allowances

Arrangements for paying the increased family allowances to more than three million families are announced by the Ministry of National Insurance. The allowance goes up from 5*s*. to 8*s*. a week from Sept. 2 at an extra cost to the Exchequer of £39 million a year.

King's College Hospital, London

Messrs. Boots Pure Drug Company have renewed for a further seven years the deed of covenant under which they have, since 1945, paid £1000 a year to the diabetic research fund of this hospital. This subscription has enabled a new technique to be developed for the estimation of insulin in plasma.

Medical Conference in Jerusalem

A conference of Jewish doctors was opened in Jerusalem on Aug. 10. The programme includes a discussion on medical problems arising from the mass immigration of Jews to Israel. The British delegation of 30 doctors is headed by Dr. Eustace Chesser.

London Hospital Old Students' Dinner

Notices of this dinner, which is being held on Oct. 9, have now been sent to all Old Londoners whose addresses are known. Anyone who has not received a notice should write to the secretary, London Hospital Medical College, Turner Street, E.1.

Society for the Study of Addiction

The society will meet at 8 P.M. on Aug. 26 at 11, Chandos Street, London, W.1, when Dr. Francis T. Chambers, jun., of the Philadelphia Hospital Institute will deliver a lecture on the Analysis and Comparison of Three Treatment Measures for Alcoholism: Antabus, the Alcoholics Anonymous Approach, and Psychotherapy.

New Blood-transfusion Centre

On Aug. 7 Mr. Iain Macleod, the Minister of Health, opened the new North London Blood Transfusion Centre at Deansbrook Road, Edgware, Middlesex. The centre has been built by the North West Metropolitan Regional Hospital Board, at a cost of £45,000, out of their normal capital allocation. Till now the North London Blood Transfusion Centre was at New Barnet where it used a converted first-aid post as temporary premises. Mr. Macleod made a special appeal to young people to join the National Blood Transfusion Service. "If the future of the service is to be safeguarded," he said, "the younger generation must play their part to an even greater extent than they do at present." The importance of blood-transfusion in modern medicine, he added, was shown by the steady increase in the number of donations, which in England and Wales had now reached some 600,000 a year.

National Ophthalmic Treatment Board Association

This association held its 23rd meeting on July 18. It was reported that a great deal of work has been done by the medical appointments subcommittee in dealing with appointments to N.O.T.B. medical eye centres, and monthly meetings have been necessary. After a discussion of the report of the Crook Committee, it was agreed that certain recommendations should be made by the representatives of the association at the Ophthalmic Group Committee meeting on July 19 to ensure that the proper functions of ophthalmic opticians were clearly defined and to emphasise the great care needed in the composition of the proposed General Optical Council. The report on Future Eye Services was re-examined in the light of the Crook report, and, apart from the strengthening of two of the paragraphs, this report is being submitted unchanged to the Ophthalmic Group Committee. The need for an early upward revision of the sight-testing fee is to be emphasised.

The following is an extract from a Ministry of Health letter in reply to a point raised by the association:

> "We have always advised Ophthalmic Services Committees that there is nothing in any of the regulations made under the National Health Service Acts to prevent a general medical practitioner from supplying a patient with the name of either an ophthalmic medical practitioner or an ophthalmic optician provided that no attempt is made to conceal from the patient the fact that the patient has a free choice in selecting an ophthalmic medical practitioner [illegible] to test his sight.
>
> "As [illegible] on the back of Form O.S.C.1 clearly informs [illegible] purpose of having his sight tested he may [illegible] ophthalmic medical [illegible] has undertaken to provide supplement [illegible] under the National Health Service."

Consultants' Prescriptions

In Northern Ireland the Hospitals Authority has decided that consultants shall not issue prescriptions to outpatients referred to them by general practitioners. In a letter to hospital management committees, described in the Irish edition of the *Sunday Express* (Aug. 3), the authority gives the following reasons for its decision: (1) the issue of prescriptions by consultants tends to deny the practitioner his right to decide whether he will accept the consultant's advice; (2) this practice has proved wasteful; and (3) occasionally it discourages patients from visiting their doctors on return from hospital. According to the *Sunday Express*, some consultants have pointed out that the new arrangement may cause hardship to patients coming from remote districts.

A Health Centre for Sheffield?

A further attempt is to be made to organise a health centre in Sheffield. The proposal was turned down in 1950 by the local medical committee, on the ground that they could not guarantee that the centre would be fully manned by them. Last April the Ministry of Health was approached by Sheffield's town clerk with a request to convene a conference of all interested parties "to survey the problem anew, and without any reference to what has previously transpired." The city council was anxious to see the scheme working, and felt that circumstances were now different. At the Ministry's request, the executive council sought the comments of the local medical committee, which asked in what way the circumstances were different and more favourable. The town clerk replied that the city council had watched later developments in establishing health centres, some of which had been approved by the Minister. The council hoped that the further experience gained by the Minister might help in Sheffield if a conference were convened. The local medical committee have now expressed their willingness to take part in the conference, while not agreeing that circumstances are more favourable.

The executive council has also decided to join a conference, proposed by Sheffield regional hospital board, of representatives of local authorities, executive councils, and hospital management committees, to discuss coördination of all the branches of the National Health Service.

The address of the Medical Practices Committee is now 3, Deans Yard, Westminster, London, S.W.1 (tel.: Abbey 2357–58).

The British Standards Institution (24, Victoria Street, London, S.W.1) has prepared a draft standard for theatre-stretcher trolleys (CO[M]3318), and comments on it should reach the institution before Sept. 12. A revised standard for density bottles (B.S.733: 1952) has been published.

Births, Marriages, and Deaths

BIRTHS

GOULDING.—On July 31, at Guy's Hospital, London, to Molly (née Fowler), wife of Dr. Roy Goulding—a son.

HARLAND.—On Aug. 5, at Kachhwa, India, to Dr. Grace Harland (née Mellows), wife of the Rev. R. P. Harland—a daughter.

LORD.—On Aug. 7, at the County Infirmary, Louth, to Reda (née Williamson), wife of Dr. W. J. H. Lord—a son.

MARRACK.—On Aug. 2, at the London Hospital, to Pat (née Franklin), wife of [illegible] daughter.

NORMAN.—On Aug. 7, a [illegible] London, to Elisabeth (née Roosegaarde [illegible] r. A. P. Norman—a son.

STEIN.—On Aug. 5, at Old Court Clinic, W.5, to Lore (née Rachwalsky), wife of Mr. Gerard Stein, F.R.C.S.—a son.

MARRIAGES

ABERNETHY—DENNIS.—On July 25, Barclay Chivas Abernethy, M.B., of Aberdeen, to Isobel Ellen Dennis, M.S.R., of Aberdeen.

BUTCHER—BORDER.—On Aug. 9, at West Wickham, Kent, Anthony Sidney Fairbank Butcher, M.B., to Peggy Elizabeth Border, S.R.N.

CAMERON—BURGE.—On Aug. 2, at Braunton, Devon, Michael Cameron, M.B., to Enid Mary Burge.

MEASDAY—RANDALL.—On Aug. 9, at Woldingham, Surrey, Brian Measday, M.B., to Jean Margaret Randall, M.B.

DEATHS

BANNISTER.—On Aug. 5, at Morwenna, Lidden, Penzance, Marmaduke Bannister, M.D. Lond., formerly of Blackburn, aged 86.

GRUNBAUM.—On Aug. 2, Lionel Grunbaum, M.A., M.B. Camb., M.R.C.P., of Clifton Hill, London, N.W.8.

LEE.—On Aug. 9, at Muswell Hill, William Edward Lee, M.D. Lond., F.R.C.S., aged 81.

McWHAN.—On Aug. 6, at Cheeklaw House, Duns, Berwickshire, Andrew Alexander McWhan, M.B., B.SC. Glasg., D.P.H.

MUNRO.—On Aug. 4, at Denham Leys, Quainton, Bucks, John Douglas Ross Munro, M.D. Edin., aged 82, late of Nantwich, Cheshire.

RECENT TRENDS IN THE TREATMENT OF PULMONARY TUBERCULOSIS*

F. A. H. SIMMONDS
M.D. Camb., D.P.H.
MEDICAL DIRECTOR

ROBERT LAIRD
Ch.M. Glasg., F.R.C.S.E.
THORACIC SURGEON

NORMAN MACDONALD
M.B. Edin., M.R.C.P.E.
PHYSICIAN

CLARE HALL HOSPITAL, SOUTH MIMMS, MIDDLESEX

Causes of the Fall in Mortality

(F. A. H. S.)

THAT there has been a continued decline in mortality from tuberculosis is generally known: it has been evident since the figures were first recorded a hundred years ago. The two brief exceptions occurred in the major wars.

The comparative mortality index (C.M.I.), defined in the following formula, provides a useful method of assessing the change year by year.

If m is the death-rate at a particular group of ages, and r is the ratio of the population at those ages to the total population at all ages, in the relevant year; and if m' and r' are corresponding values for the base year 1938, then

$$\text{C.M.I.} = \frac{\sum m \, \frac{(r + r')}{2}}{\sum m' \, \frac{(r + r')}{2}}$$

Fig. 1 illustrates the almost steady decline of the C.M.I. It is easy to read into this curve the end of a long declining epidemic wave and to speculate on its continuation. Thus there is the suggestion of an improvement in the rate of decline after 1933: but is this because social and economic conditions were improving faster than before, or because methods of treatment had begun to make some impression on the incidence of the disease? Despite the unemployment prevalent at that time, the general advance in living standards was probably responsible; certainly it is unlikely that methods of medical treatment before 1933 lowered national mortality-rates substantially. Then, is the fall from 1933 to 1938 more rapid than that of previous years? If so, medical treatment may indeed have begun to have some effect; and some other factors point this way—notably the decline in tuberculous laryngitis and enteritis.

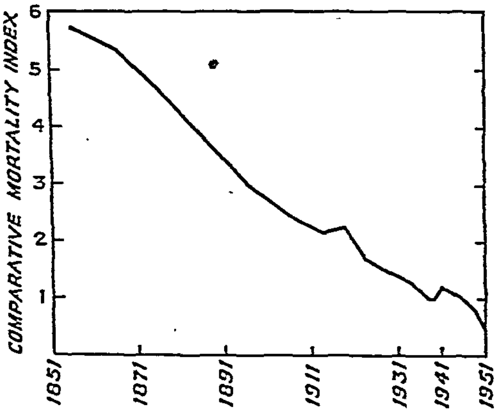

Fig. 1—Comparative mortality index, 1851–1951.

If the C.M.I. is plotted on a logarithmic scale, the *rate of change* can be more easily detected (fig. 2). From 1860 to 1933 the curve is almost a straight line—i.e., there is a constant rate of decline. Then the rate of change accelerates somewhat, but the war prevented a continuation of this trend.

Tuberculous laryngitis has shown a noteworthy fall in incidence. Formerly common, it is now becoming rare; we see it in less than 1% of patients now admitted to Clare Hall, and Professor Ormerod (1950) has reported a similar fall at Brompton Hospital. This fall began about twenty years ago, and a similar change has been noted in tuberculous enteritis. There seems reason to believe that the decline in these complications may depend partly on a more determined attack on pulmonary tuberculosis by collapse therapy: certainly it began long before chemotherapy was used. Does this link up with the accelerated fall in the C.M.I. which began about 1933?

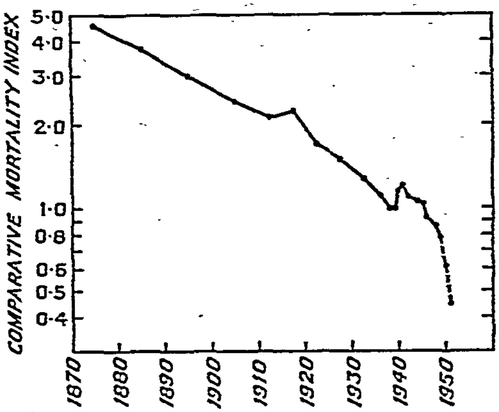

Fig. 2—C.M.I. since 1870, plotted on a logarithmic scale. Index for 1938 arbitrarily chosen as unity. Figures for all years till 1949 from the reports of the Chief Medical Officer of the Minister of Health. The figures for 1950–51 are an estimate based on the recorded mortality from pulmonary tuberculosis.

If recent treatment is proving more efficient in reducing the national mortality-rate from tuberculosis, this should be reflected in the rate of decline. An interesting fall in mortality during the last two or three years (fig. 2) has been concurrent with two important developments.

First, efficient chemotherapeutic agents have been introduced. Streptomycin, assisted by *p*-aminosalicylic acid (P.A.S.) is now used widely, and whatever may be the long-term effect it seems likely that these drugs, during the last two years, have prolonged life in many patients. If the effect is merely to prolong life for a few years the rate of change in the C.M.I. may shortly become slower; if a more permanent gain has been achieved we may expect it to continue at its present rate.

The second important development has been the strengthening of the tuberculosis service. Modern methods have therefore recently had a better chance. Chest clinics have increased in numbers and efficiency, and most places in the country are now at least fairly well served in this respect: before the war the service in many areas was meagre and of poor quality. Hospital beds have increased in number and adequacy in most regions. In both clinics and hospitals there are more medical staff, with better qualifications, and more nurses and other professional assistants: more surgeons have closed more cavities. In fact the resources of treatment are now well diffused, and for the first time begin to approach the standard required to make an impression on national mortality-rates.

The rapid acceleration of the rate of decline in the last two years must therefore be due to chemotherapy, supplemented by the other resources of treatment.

Chemotherapy has, however, had another effect—one seen at the introduction of each new advance in treatment. The advance is always declared likely to diminish the need for beds, and to shorten the stay of patients in hospital; this optimism always proves premature. It is true that, for some patients, the total period of treatment has been less than if they had been ill some decades ago; but the new methods have drawn into the treatable group patients for whom little could previously have been done, and now a high proportion of patients are likely to receive specific treatment—treatment which has a reasonable chance of producing substantial improvement or even complete recovery. Thus, as always, there seems to be an increasing demand on treatment facilities. Now that treatment is able to help such a high proportion of the tuberculous, and that its influence is reflected in the mortality-rates, we may really hope that the day is coming when the demand will begin to decline; but that time is not yet. The trend of treatment may follow two lines. One group of patients will probably have minimal disease, discovered early, treated promptly with a large measure of success. The other group will contain a diminishing number of patients with untreatable disease requiring an increasing length of institutional treatment; and finally there will become a small number kept under treatment for life. More and more will be treated less and less, and less and less be treated more and more.

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* Based on contributions to a symposium of the Middlesex County Medical Society on May 14, 1952.

MODES OF TREATMENT USED AT CLARE HALL IN 1950 AND 1951 ON SPUTUM-NEGATIVE AND SPUTUM-POSITIVE PATIENTS: PATIENTS DISCHARGED

—	1950		1951	
Sputum on admission ..	−ve	+ve	−ve	+ve
Males				
No. of patients	70	177	116	149
Pneumoperitoneum ..	34	41	47	54
A.P. or extrapleural A.P...	30	41	19	24
Thoracoplasty	7	23	11	32
Resection of lung ..	—	2	2	3
Chemotherapy	44	74	50	86
Females				
No. of patients	97	241	210	170
Pneumoperitoneum ..	36	39	29	41
A.P. or extrapleural A.P...	39	41	29	33
Thoracoplasty	5	25	10	35
Resection of lung ..	—	5	3	11
Chemotherapy	40	67	62	82

Figures against treatment are percentages of the total of patients: these do not add up to 100, because a patient may have combined treatment.

In selected groups treatment was able to improve the chance of survival even before the advent of modern chemotherapy. At Clare Hall Hospital the more effective use of collapse-therapy improved the general survivor-rate of patients during the early war years, 1939–43 (Simmonds and Martin 1948).

The emphasis on various forms of active treatment, however, has changed during the last ten years. The table shows the frequency with which we at Clare Hall have been using various methods in the last two years. We have noted a great increase in the proportion of patients admitted with negative sputum: in 1950, only 28·5% of both the men and women admitted were sputum-negative on admission, but in 1951 this rose to 44% of men and 45% of women (fig. 3). More patients, then, have been rendered sputum-negative by treatment before admission—partly by rest at home, but especially with the aid of chemotherapy. Such sputum-conversion might well be transient but for further treatment by collapse or active measures; and the table, in fact, confirms that disease in the sputum-negative may be just as extensive and need other treatment almost as often as disease in the sputum-positive.

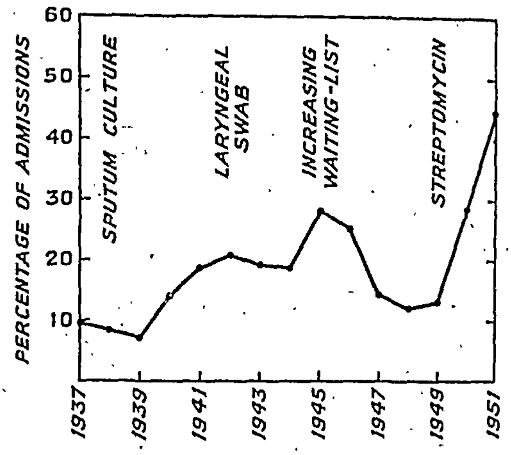

Fig. 3—Percentage of patients sputum-negative on admission to Clare Hall, 1937-51.

Fig. 4 shows how the use of various treatments (or the fashion) has changed in the last ten years. Pneumothorax, once the only active method of treatment available, is now almost abandoned in some quarters. At Clare Hall, though, we still use it moderately; this is often because the lesser disease is controlled by pneumothorax while a more severe lesion on the other side is treated by different means. Nor would this degree of popularity survive if chemotherapy had not rendered artificial pneumothorax safer in its limited field than formerly.

Pneumoperitoneum remains a very useful weapon, mostly employed for a limited purpose and restricted period. Its old associate, phrenic nerve crush, is now rarely done, for pneumoperitoneum plus chemotherapy is a better combination. Modern trends have given chemotherapy a large part in treatment, but we do not expect effective control of pulmonary tuberculosis by this means alone. Mechanical methods of cavity closure, or excision of tuberculous foci remain the chief treatment of destructive tuberculosis. Even apparent success by chemotherapy alone is usually temporary. The combination of rest, chemotherapy, and pneumoperitoneum is very valuable for the less extensive type of lesion. Most patients with post-primary pulmonary tuberculosis requiring treatment need chemotherapy at *some* stage, but it must be wisely integrated with rest and active methods.

Surgical Trends

(R. L.)

The present trend in the surgery of tuberculosis is towards excision rather than collapse of the affected part

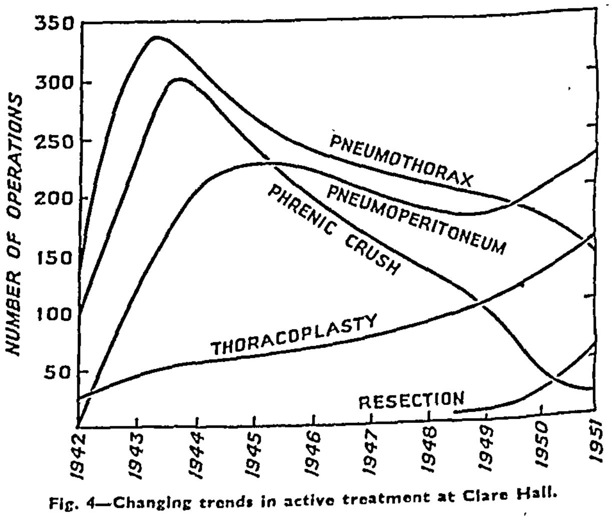

Fig. 4—Changing trends in active treatment at Clare Hall.

of the lung: indeed, in some centres excision has almost replaced surgical collapse.

SURGICAL COLLAPSE

I have begun an investigation into the results of thoracoplasties performed at Clare Hall for pulmonary tuberculosis—that is, excluding those done to close empyemata and pleural spaces after pneumonectomies. In the six years 1944–50 there have been 580 patients treated in this way; 12 died within six months after the operation—a mortality-rate of 2·1%; and since the operation is usually done in two or more stages this means a mortality-rate of less than 1% per operation. The cases were of all types, some good and some bad, and in some patients there had been little hope of sputum-conversion by thoracoplasty. Nevertheless, 72% of the 580 were sputum-negative to the most searching tests for tubercle bacilli during the two months before their discharge. If the worst cases are excluded, the percentage of negatives rises to over 80. These figures are on the whole satisfactory and show that thoracoplasty has still a very definite place in the treatment of pulmonary tuberculosis.

In modern thoracoplasty, usually done in two stages, the upper 5–7 ribs are removed. Not all types of disease are suitable, and we now have a much better idea which will not respond to collapse. Unsuitable cases are in the main those with associated severe and persistent bronchial disease, and those with large solid foci, gross cavitation, or disease of lower lobes.

Various extrapleural and extrafascial operations without extensive rib resection may be grouped with thoracoplasties. Until about eighteen months ago we did some 20–30 extrapleural pneumothorax operations yearly at Clare Hall, usually for patients needing bilateral surgery. After the extrapleural pneumothorax operation, the space was maintained by refills of air at high pressures; but a few years ago surgeons began filling the space with plastic substances instead of air refills. ‘Lucite’ balls were, and still are, used, but these hard round spheres offer pressure points. Morriston Davies et al. (1951) use a ‘Polythene’ pack filled with strips of polythene. This seemed a more congenial substance and I was considering using it when I was sent, for trial, a ‘Polystan’ sponge made of polyethylene. This has proved most satisfactory. It is readily sterilised by boiling, and we have seen few complications from its use. I tried it first in October, 1951, and since then we have used it in some 50 operations. The method is to bare the upper five or six ribs, and reflect down most of their periosteum and intercostal muscles, still adherent to the lung. A good solid roof is thus formed which separates the lung from the filling material. This type of operation is popular with the patients, since it is a single event and there is no deformity. We use it in patients with apical disease, in whom the ribs can be stripped reasonably easily. Cases with large solid foci and constrictive bronchial disease are not suitable. We do not know yet whether the sponges will need to be removed later, but I earnestly hope that they will become part of the patient and remain happily in situ for the remainder of his life.

RESECTION

We now use pneumonectomy, lobectomy, segmental resection, and wedge excision of the lung in the treatment of pulmonary tuberculosis; and fortunately many of the patients who are unsuited for collapse can have the affected part of the lung removed. The indications are:

1. *A destroyed lung where the other lung is healthy, or has a small amount of disease which is now stabilised.*—About a third of the resections performed at Clare Hall Hospital have been done for this type of lesion, with dramatic results. Patients who have been ill, toxic, and bedridden have been restored almost to normal health: they are able to do sedentary work, and, except for slight breathlessness on exertion, lead a normal life.

2. *Permanent bronchial stricture with tuberculous disease beyond.*—Collapse therapy has little to offer these patients and the diseased area, including the stenosed bronchus, should be removed.

3. *Large solid foci or tuberculomata.*—Some of these lesions run a comparatively benign course, others erupt and cause spread. It is difficult to tell which will cause trouble later, but on the whole it seems wise to remove the larger foci. These lesions can readily be removed by segmental resection or wedge excision of the affected part.

4. *Large or tension-type cavities.*—Where these are present in the upper lobe, lobectomy can be done. At times, at thoracotomy, disease is found in the apex of the lower lobe, which did not show on X-ray examination. This can be removed by segmental resection or wedge excision; if it is left the over-expansion which follows lobectomy may cause breakdown in such areas.

5. *Failed collapse therapy.*—If cavitation persists under a pneumothorax, or following a thoracoplasty, lobectomy should be performed.

6. *Lower lobe cavitation.*—Lobectomy should be done when a lower-lobe cavity fails to respond to a pneumothorax, or to phrenic crush and pneumoperitoneum. It is important to know something of the natural history of the disease, for a cavitated primary focus may be followed by apical deposits later. It is best to avoid extensive resections if further pulmonary disease is expected.

7. *Empyema associated with gross lung disease.*—A pleuropneumonectomy is performed.

The results of resection in the right type of case are excellent; sputum conversion is over 90%. At Clare Hall the number of deaths after 132 resections for pulmonary tuberculosis has been 6 (4·5%) in the six months following operation.

Artificial Pneumothorax and Pneumoperitoneum

(N. M.)

ARTIFICIAL PNEUMOTHORAX

In the past few years artificial pneumothorax has suffered a considerable decline in popularity, and it is instructive to consider why this has befallen such an important and established method of treatment.

First, there has been an alteration in the type of case admitted. A large proportion of those now reaching us require major surgery. Patients with a lesion of limited extent, suitable for treatment with pneumothorax, now reach us comparatively seldom: they are being treated by the physician at the chest clinic. Pre-sanatorium selection, however, is not alone sufficient to account for the decline, which began rather earlier than our change in practice.

Artificial pneumothorax is associated with a good many complications (some of them severe and occasionally fatal) such as air embolism, spontaneous pneumothorax, empyema, and bronchopleural fistula. Such complications can often be avoided—either by postponing induction or by re-expanding the lung if the pneumothorax is unsatisfactory, but even so we are not using pneumothorax more—even in the comparatively safe type of case—but a good deal less. Clearly, the risks are not to be ignored. While we may not get empyemata nowadays, we still get fluid, even with the most wary precautions; and atelectasis—even massive atelectasis—is not uncommon. Chemotherapy has made A.P. safer, but has not made it more widely used. Rather it has increased the popularity of *other* methods—particularly resection, but also the more permanent forms of collapse therapy, such as thoracoplasty and plombage, for which the patient can now be more adequately prepared.

The practice of collapsing the lung by pneumothorax only began to reach *large*-scale proportions in this country during the last ten or twelve years. Hence it is only in the last few years that we have been able to see what happens when the refills are stopped. We are thus beginning to develop a more proper appreciation of the late or ultimate results of pneumothorax therapy, and in some respects this has proved disturbing.

Thus a pneumothorax may force you to give it up because refilling it becomes increasingly difficult or even hazardous. Moreover, the best time to stop refills is still the subject of conjecture. Statistics suggest that it is best to terminate a pneumothorax after about three years, but not only may the doctors disagree about the time for its termination, but the patient may prove resistant to the suggestion, preferring to continue with refills more or less indefinitely: "I feel safer with it, doctor."

And even when it has been agreed that the best moment has been reached, the lung may not oblige by re-expanding in the desired way. Because of pleural thickening or old-standing bronchial stenosis, re-expansion may, in fact, be impossible; or possibly only at the cost of gross mediastinal distortion. The doctor is then faced with the problem of maintaining refills indefinitely or submitting the patient to some form of major surgery—either thoracoplasty, plombage, or decortication—which at this stage in the life-history of his illness he may not altogether welcome.

There is also the continual fear that the hazard of re-expansion may not be successfully overcome. We know that the overstretching of lung tissue which contains diseased foci does not favour healing—quite the reverse. There is also the risk of the unexpandable lobe, which is usually more dangerous than the unexpandable lung. Pneumothorax is usually done for upper-lobe disease, and sometimes this results in atelectasis of either the whole or part of the upper lobe which then rests like a little knob on the lobe below. If this collapse of the upper lobe is permanent, as it quite often is, when the pneumothorax is given up the lower lobe over-expands; and if there are foci—particularly in the *apex* of the lower lobe—breakdown with cavitation is quite possible. Even in the absence of relapse there may be considerable impairment of pulmonary function, due to thickened pleura, bronchial stenosis, pulmonary fibrosis, and compensatory emphysema.

All this adds up to uncertainty—which is the bugbear of pneumothorax therapy from the start, if not before. Other methods are not free from uncertainty, but with them it usually does not go on for such a long time. With pneumothorax the risk of major disaster is present for rather too long. In the early stages there is tuberculous pleural infection, and atelectasis. The pleura is extremely susceptible to the tubercle bacillus; it is also quite a large membrane (about $2^{2}/_{3}$ sq. ft. if laid out flat) and every square inch of it may become tuberculously infected. Pneumothorax, too, is a *temporary* form of collapse and some day the hazard of re-expansion has to be faced; this is always a period of uncertainty.

In recent years we have repeatedly tried to reduce its uncertainty. We kept the patient in bed for a longer time, to reduce his toxicity to a minimum; sometimes we added a phrenic crush to give relaxation without the risks attendant upon separating the pleural layers. Then we did pneumoperitoneum as a "cooler." Later on we made sure that the patient, if at all toxic, had an adequate course of chemotherapy beforehand. Next we started bronchoscoping the patient before induction to make sure he was free from tuberculous endobronchitis. Each of these steps had the effect of diminishing the field in which we felt pneumothorax could be safely applied, until now we are getting to the point where, in order to avoid all avoidable complications, we are quite likely not to do the pneumothorax at all. We have stopped doing it in the toxic patient; and we have stopped doing it in the emphysematous patient, to reduce the risks of "spontaneous" and air embolism. Or, having rested the patient and given him a pneumoperitoneum, perhaps with a phrenic crush as well, we sometimes find it scarcely necessary to proceed to pneumothorax. Or having given a thoroughly good course of chemotherapy, we again find A.P. unnecessary, or decide something else would be better. Or having bronchoscoped the patient and *found* tuberculous endobronchitis we are put off doing pneumothorax, whatever else we may or may not do. Unhappy experience has led us to regard some other things as contra-indications—for example, the presence of a large tension cavity, or a segmental lesion, or a thick-walled cavity which has resulted from the liquefaction of a solid focus. We hesitate to do a pneumothorax if there is too *much* caseation (tomograms incidentally have helped to reveal the size and extent of caseous foci) and, of course, we hesitate if there is too *little* disease. We won't do pneumothorax if the disease is too *new* or if the lesion is too *old* and fibrotic.

The positive indications for pneumothorax therapy, then, have been progressively disintegrating, and it has become increasingly difficult to pick out a patient and say with certainty: "This patient really must have an A.P. because it affords him the best chance of permanent recovery."

I have said that alternative methods appear to offer a better long-term result. But these methods, if they are to displace A.P. therapy, must not only be successful—they must also be available. We are fortunate here in having two full-time thoracic surgeons; but in the chest clinic even the most resection-minded of physicians could only get a limited number of his cases treated in this way and would be forced, willy-nilly, to use pneumothorax in a good many cases. Even here we still do more A.P.s than resections though the curve of the one is rising and of the other falling. There are centres, however, where pneumothorax has been shown the door: in Holland, I believe, it is now scarcely done at all, and even in this country we have resection-minded Liverpool and Sully.

We are, in fact, seeing a period of rapid change in the treatment of tuberculosis. Ten short years ago A.P. and thoracoplasty were the accepted standard forms of treatment with extrapleural causing a flurry in the dovecot. Chemotherapy was not used, resection was heresy, and pneumoperitoneum had scarcely begun. Now we are not only questioning the value of pneumothorax therapy, but thinking of replacing even the trusty thoracoplasty with an operation which will be less physically damaging. Already it is being suggested that chemotherapy and modified resection (segmental or wedge resection) will prove the most reliable long-term measures—thus displacing collapse therapy from its established position. In these circumstances it would be unwise to attempt a final pronouncement on any form of therapy. Pneumothorax, properly applied and properly managed can, of course, still give good results, and many patients have benefited from it in the past; but this does *not* necessarily prove that it is the *best* form of treatment. There is more than one way of treating tuberculosis successfully, and the ultimate test will be the long-term results. Until these become available there will be room, and to spare, for divergence of opinion.

PNEUMOPERITONEUM

Pneumoperitoneum is in a different position from pneumothorax. After a spell of what was probably over-application P.P. has settled down to a steady level which it appears to be maintaining. This position, *too*, is being held in spite of two factors which might have been thought to have affected it adversely.

First, chemotherapy has reduced its use as a "cooler" for the toxic case, and might have replaced it entirely. But in many of these cases we *still* find it *useful* to supplement chemotherapy, after a short interval, with pneumoperitoneum. This particular attribute of pneumoperitoneum—its ability to supplement other forms of treatment without interfering with them or *displacing* them—is one of its strong points. The good results of chemotherapy, we feel, can be improved and to some extent consolidated, by establishment of a pneumoperitoneum.

Secondly, its one-time trusty companion, phrenic paralysis, is now out of favour. We used to think that the results of P.P. were often enhanced by a phrenic crush on the appropriate side, but gradually have come to criticise this combined therapy. When the diaphragm is paralysed the position is not so readily reversible as with P.P. alone: the diaphragm needs time to recover its function. Sometimes, indeed, it does not recover, or recovers only partially; and almost always it remains high with diminished power of contraction. Hence respiratory function is limited, and this may prove a grave handicap when bilateral active treatment is needed later. Moreover, the surgeons dislike it because it may increase the chance of massive collapse at the time of thoracoplasty. For these reasons phrenic crush has gone quite out of favour, though the old combination of "P.P. and phrenic," is still useful to make good the space deficiency after removal of a lobe.

We find P.P. alone of particular value, in association with chemotherapy, for the treatment of a specific and readily recognisable type of case—pulmonary disease of hæmatogenous origin. Here the foci are usually in the upper zones of both lungs, and distributed symmetrically. Cavities are usually apical and thin-walled, and produce little sputum; and perhaps because of this, tuberculous endobronchitis is relatively uncommon. There is a strong tendency to fibrosis, the upper lobes shrinking and drawing up the hila, and the lower zones show compensatory emphysema. Such cases often respond well to chemotherapy; and a P.P., by raising the diaphragm, relieves the emphysema in the lower zones to some extent and encourages the apical lesions to contract further. The results are in the main so satisfactory that with many patients one is strongly tempted to leave well alone—particularly as the alternative is often bilateral pneumothorax or bilateral surgery. But I would emphasise that the pneumoperitoneum will probably have to be kept up more or less indefinitely, for there is a distinct risk of relapse when the diaphragm is allowed to descend.

On the whole pneumoperitoneum is perhaps most useful as a temporary procedure, used and recognised as such, in preparation for some more major and permanent form of surgical treatment. It has retained our confidence because we know more or less what to expect from it—not too much, but a useful contribution, nevertheless, towards the patient's recovery. Moreover, it is reasonably safe. Pneumothorax aims rather higher but is apt to fall down somewhat heavily; P.P. seldom o'erleaps itself.

CONCLUSION

The whole field of therapy is undergoing a rapid change, and our changing attitude to A.P. and P.P. is only one aspect of it. Chemotherapy has been mainly responsible. Besides consolidating the ground already held, it has driven a whole new salient—indeed a series of salients—into territory previously under the control of the tubercle bacillus. In this extended ground there is more room for us to manœuvre—to develop new ideas, new techniques, new lines of attack. We have moved forward: already the position is vastly changed. There is, of course, no need to cast away all the old ideas, all the old techniques; but it behoves us to re-examine them, to compare them as fairly as we can with the new—and where necessary be prepared to discard them, even if it hurts.

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SUPERFICIAL STAPHYLOCOCCAL INFECTION

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IN furunculosis and sycosis barbæ staphylococci are commonly carried from a lesion to infect the skin elsewhere. From the earliest stage of a boil until healing is complete, virulent staphylococci can readily be isolated from the overlying and surrounding skin; and, unless suitable precautions are taken, they are conveyed thence, by fingers or handkerchief, to other parts of the body—including sites where they are liable to persist, such as the nose, eyes, and external auditory meatus. Recurrent infection in the axilla—a warm, moist, dark, and hairy area, with apocrine glands—is readily understandable.

By eliminating the micro-organisms from the surface of the body, it should be possible to prevent this kind of spread and so bring the infection to an end. In a series of cases of sycosis barbæ, Burrows, Russell, and May (1945) used penicillin cream for this purpose, applying it both to the lesions and to the nose. The clinical response was usually good whenever the strain was sensitive to penicillin. Similar results were reported by Hobbs, Carruthers, and Gough (1947), who found that the strains from lesion and nose corresponded serologically in all the 17 cases tested. Penicillin cream usually cleared sensitive strains from the nares, though relapse might follow reinfection. Some cases showed evidence of sensitisation to penicillin, as would now be expected.

Dolman (1935) was the first to observe that in chronic furunculosis the anterior nares are often infected with *Staphylococcus pyogenes*. One of us (Valentine 1936) found that the production of hæmolytic and leucocidal toxins by strains derived from lesion and nose was usually comparable. Thereafter other workers, whose results are summarised by Miles et al. (1944), demonstrated a high rate of carriage in the general population, the figure varying from 22 to 47% in different investigations. Since the latent carriers greatly outnumber the cases of active infection, the significance of nasal carriage in the latter may have escaped notice, the more so because, with staphylococci, there is no recognised test for virulence as opposed to pathogenicity. It is reasonable, however, to assume that the strain isolated from a lesion is unusually virulent, at least in the particular patient concerned, and that the presence of the same strain in the nose may help to produce further lesions.

Miles et al. (1944), who obtained the highest figure (47%) in their sample of the population, also showed that in some people the swabs were constantly positive and in others negative, but that in most cases the results were inconstant, being sometimes positive and sometimes negative. Ability to get rid of pathogenic staphylococci from the nose varied, in fact, in different people. In our own investigation it has not been possible to show that the majority of the patients were constant carriers, firstly because the nasal infection, if constant, might have been maintained from lesions, and secondly because we were dealing with outpatients expecting active treatment. We were forced to assume that most of those with heavy nasal infection were constant carriers.

Rountree and Barbour (1951) investigated nasal infection in student nurses before and after entering the wards for training. Using bacteriophage typing of the strains isolated they found that, although the percentage of carriers rose after the nurses entered the wards, the permanent carriers usually kept their original strains, and that from 90% of positive swabs only one strain was isolated. We could therefore hope that, if the original strain were eliminated from the nose of a patient, permanent infection with a less virulent strain might follow.

PLAN OF INVESTIGATION AND TREATMENT

(1) At the first interview the usual history was taken, with special reference to previous lesions in the nose, eyes, or ears. It was then carefully explained to the patient that infection was due to minute living organisms in the discharge, which were readily carried to other parts of the body by the fingers and often settled in the nose or elsewhere. This explanation took little time and almost always gained the patient's coöperation.

(2) Swabs were then taken from the lesion and the probable sites of carriage; the nose and eyes should never be omitted. The number of colonies of pathogenic staphylococcus was roughly estimated, and the strains were kept for reference after tests for sensitivity.

(3) 1% cetrimide (' Cetavlon ') was prescribed for cleaning the skin round the lesions at each dressing, and 3% terramycin ointment was given to be applied after the cetrimide; lesions must receive treatment until completely healed. The ointment must also be used twice daily in the anterior nares (and, if necessary, at night on the margins of the eyelids) for four weeks without fail. After a rest of three or four weeks further cultures were taken.

(4) Patients were warned that sensitisation might develop, in which case treatment must stop at once. Some of those with a history of sensitisation to other agents were told to test an uninfected area exposed to light, such as the forehead, for two days before treating any region of infection.

(5) After shaving, patients with sycosis barbæ usually wash off the remaining lather. Water, with its low osmotic pressure, is somewhat irritating after the slight trauma of shaving, and in any case may not be free from infection. Such patients were therefore told to wipe off the lather and then to apply cetrimide and, finally, the ointment.

FINDINGS BEFORE TREATMENT

Table I shows that 53 cases of recurring furunculosis were seen. Only 16 of these were in women, of whom 8 were nurses. The nurses were all infected with penicillinase-producing staphylococci. It will be seen that there was a heavy infection of the nares in 64% of the cases and some degree of infection in 80%. These figures may be compared with a maximum of 47% in the general population (Miles et al. 1944) and with the results obtained from single swabbings of student nurses at the London Hospital (62% infected and 44% heavily infected). Since no previous record of the kind could be found in the literature, it was thought desirable that the strains from lesion and nose should be compared by bacteriophage typing. Dr. R. E. O. Williams, on consultation, agreed to do this, and we are deeply indebted to him and his colleagues for the typing of no less than 100 strains, including some isolated after treatment and some from other sites of carriage than the nose. The strains from lesion and nose were typed in 25 cases and were the same in 19, probably the same in 5, and different in only 1 case, in which the patient had had boils, mainly on the buttocks, for five years, and the strain from a boil on his wrist corresponded to one isolated from his anal region. For the criteria by which the results of phage-typing are judged, see Williams and Rippon (1952).

TABLE I—BACTERIOLOGICAL FINDINGS BEFORE TREATMENT

—	Boils and styes	Sycosis barbæ
Total	53	36
Nasal carriage :		
Heavy	34 (*64%*)	27 (*75%*)
Light	9	6
Negative	10	3
Penicillin-sensitive ..	38 (*72%*)	15 (*42%*)

The rate of nasal carriage appears to be even higher in sycosis than in furunculosis. In view of the work of Hobbs et al. (1947) the strains from lesions and nose were compared for pigment production and sensitivity to penicillin and terramycin, and in all cases they appeared to be similar; but they were not typed. The relatively small number of strains sensitive to penicillin suggests that our patients are in the main those who have failed to respond to penicillin.

In 1 case of boils and 2 of sycosis the eyes were more heavily infected than the nose, and it therefore seems advisable that the eyes should be included in the routine preliminary tests.

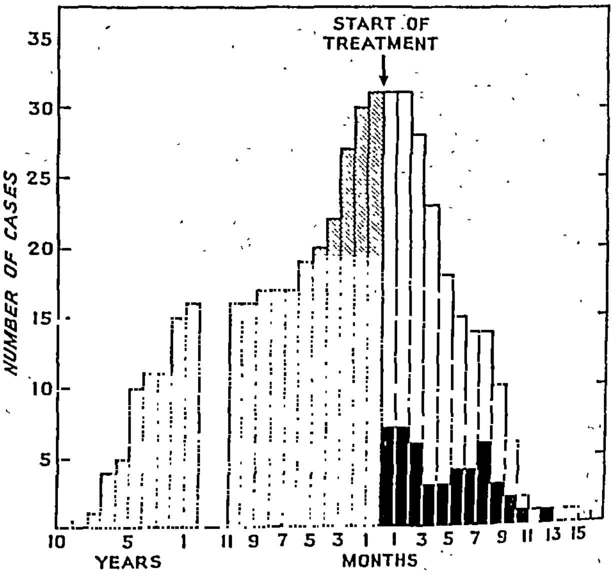

Fig. 1—Length of past history and follow-up of cases of furunculosis.

CLINICAL RESULTS

In 31 cases of boils and 24 of sycosis the course of treatment was completed and the follow-up period was long enough to give an indication of the immediate results.

Figs. 1 and 2 are designed to give a picture in bulk of the length of past history and of the follow-up, but do not portray the experiences of individual patients. Thus, in the series with boils (fig. 1) the history extended to one or more years in 16 cases and to months only in the rest. In the follow-up period the unit of area corresponds to one month per patient and is heavily shaded if lesions persisted but clear if they did not; thus in the first month of treatment fresh lesions appeared in 7 cases only. This is a form of presentation which is better suited to a continuous process, such as sycosis barbæ (fig. 2), than to furunculosis; in the latter, especially, a longer follow-up period is clearly necessary.

Tables II and III refer to furunculosis and sycosis respectively, and show the clinical results in relation to the bacteriological findings in the nose before and after treatment. The numbers in parentheses refer to cases requiring discussion.

Table II shows that in 23 cases the nares were heavily infected. After treatment nasal cultures were negative in 10 cases, with 1 case (case 40) of persisting active

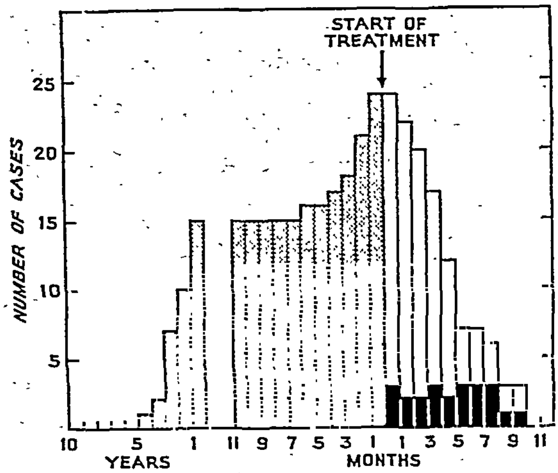

Fig. 2—Length of past history and follow-up of cases of sycosis barbæ.

infection; this man's boils were in the pelvic region and axillæ, where complete eradication of infection is difficult. Of the 7 patients in whom a new strain was isolated from the nose 4 have done well, 1 has had a minor recurrence in the nose, and in case 47 the original strain has persisted in the axillæ, although the nasal strain has changed. (This man is a poor attender and correspondent, and has not reported on his condition since told to shave his armpits three months ago.) The other case of minor recurrence (case 8) is of special interest; the patient gives eight years' history and has never attended with an active lesion, but the nasal strain has changed after treatment and is now moderately resistant to terramycin; it is not known which strain was present in a relapse after ten months' freedom. In the 6 patients with persisting nasal infection, 3 with the same type and 3 with probably the same, the clinical results have been less satisfactory, notably in case 24, a young lady who has not carried out the treatment, owing to irritation in the nose after using the ointment. 4 other patients in this group have shown a tendency to relapse when treatment of the nose stops, and cannot be regarded as cured; possibly in some there is a chronic sinusitis from which the nostrils are reinfected.

The remaining cases present a different problem in that the usual site of carriage was innocent. Case 45 during a recent relapse showed a heavy infection of the eye, which had not been tested earlier, and case 92, as has been described, showed infection in the anal region. In the others it is presumed that the skin around old lesions has retained the infection; in case 30, for instance, the boils are usually confined to the right arm. Case 53 is of interest in that the lesions, due to an *aureus* strain producing penicillinase, have recurred after an interval of seven months, during which the nose has been "occupied" by a sensitive *Staph. albus.*

TABLE II—FURUNCULOSIS: RESULTS OF TREATMENT IN RELATION TO NASAL INFECTION

Nasal swabs		Clinical results		
Before	After	Good	Recurred	Failed
Positive ..	Negative	9	..	1 (40)
	New strain	4	2 (8)	1 (47)
	Persisting	3	2	1 (24)
Scanty ..	Negative	1	..	..
Negative ..	Negative	3 (92)	2 (30, 45)	1 (4)
	New strain	..	1 (53)	..

TABLE III—SYCOSIS BARBÆ: RESULTS OF TREATMENT IN RELATION TO NASAL INFECTION

Nasal swabs		Clinical results		
Before	After	Good	Recurred	Failed
Positive ..	Negative	11	..	..
	New strain	3	1 (15)	1
	Scanty	2	..	1 (39)
	Persisting	..	..	1
Scanty ..	Negative	3	..	..
	Scanty	1	..	..

"Persisting," many colonies of *Staph. pyogenes.* "New strain," *Staph. pyogenes* of different phage-type. "Scanty," few colonies of *Staph. pyogenes.* Numerals in parentheses refer to individual cases.

We would again emphasise the importance, in sycosis barbæ, of discovering and treating sites of carriage, such as the nose and eyes, although one cannot say how often the nasal infection was merely maintained by transfer from the face. Our cases (table III) included 11 of deep folliculitis or sycosis vulgaris and 13 of superficial folliculitis; 7 cases had a decidedly seborrhœic background. The response to treatment was impressive and rapid, being at least comparable to that obtained by Solomons (1951) with 3% aureomycin ointment; 2 cases of severe lupoid sycosis have shown an immediate improvement but required a prolongation of the treatment to eight weeks in all. Of the cases shown as failed, 2 were in fact much improved, but the prognosis is far from satisfactory; the 4 patients with poor results were all psychologically somewhat abnormal, case 39 actually attending a psychiatric clinic. Case 15 is of interest in that relapse occurred four months after treatment began, and was associated with a resistant strain; most unfortunately the original organism was lost without being typed, but it was noted as producing penicillinase, whereas the later strain is sensitive to penicillin.

DRUG RESISTANCE

In addition to the simple agar-diffusion test for sensitivity to terramycin, samples from broth cultures have been streaked on agar plates containing the drug in different concentrations, in such a manner as to yield areas of single colonies on the control plate containing no terramycin. With two exceptions, all the strains tested in this manner showed delayed growth at a concentration of 0·4 µg. per ml. and complete inhibition of individual colonies at 1·6 µg. per ml. Latterly it has seemed enough to use plates containing 2 µg. per ml., which inhibited growth of the thinly spread inoculum from 115 strains, including 21 isolated after treatment. Two strains proved resistant to 25 µg. per ml.; they were isolated after treatment from cases 8 and 15, are probably both of them changelings, and may well have been resistant from the first. Since the development of resistance seems to be rare, we have been encouraged latterly to repeat the treatment where necessary or to treat for longer periods in old cases of sycosis associated with scarring. Clearly, however, casual intermittent treatment over long periods is to be condemned.

SKIN SENSITISATION

The development of sensitisation of the skin often follows the use of penicillin cream. Solomons (1951) reports a similar condition in 2 patients after the use of aureomycin ointment. In 1 of our cases of sycosis, sensitisation to terramycin ointment developed after eight days' treatment, by which time, most fortunately, the staphylococcal infection had been eradicated from both face and nose; the ultimate result was good. In another patient, a woman with thyroid disease with a history of sensitisation to thiouracil, terramycin ointment was given for treatment of facial pustules by a bacteriologist (F. C. O. V.) without dermatological advice, and led to an immediate and severe exacerbation of the condition. Though sensitisation seems to be uncommon, the testing of the preparation on uninfected skin seems to be a reasonable precaution when there is a history of reaction to other drugs.

DISCUSSION

In this series of cases of superficial staphylococcal infection, the nasal carriage of pathogenic cocci was commoner than in the general population. In furunculosis the strains from lesions and nose were nearly always of the same type, as has been shown by Hobbs et al. (1947) in sycosis barbæ. Since the possibility of constant reinfection of the nose from the lesions could not be excluded, there is no proof that these patients were permanent carriers like those described by Miles et al. (1944) and Rountree and Barbour (1951). But the presence of a considerable minority of cases in which pathogens were few or absent in the nose suggests that in the majority the nasal infestation was lasting and helped to maintain infection. Where the nose is innocent, other sites—e.g., eyes, ears, and axillæ—should be considered before concluding that infection is only being spread from one lesion to another.

The treatment which we have used has the disadvantage of being somewhat laborious, particularly for the patient, a fact which may well explain some of our failures. But we have been struck by the manner in which nearly all the patients responded when the problem was described to them. A simple explanation of the spread of staphylococcal infection is therefore essential in obtaining the patient's coöperation. Even so, it may sometimes be found that the nose is being treated while even more important areas around recent lesions are neglected. For the doctor's guidance the results of swabs taken from lesion, nose, and eyes are very desirable, and whenever possible these should be taken in the laboratory to avoid delay in culture. The need for further cultures will depend on the clinical results.

At first we intended to avoid using antibiotics suitable for systemic administration, for fear of breeding resistance in the staphylococci or hypersensitivity in the patient, and thus preventing the use of the drug in a future emergency. A few of the earlier patients were given 'Quinolor' ointment, to use in the nose for an indefinite period, with some degree of success; but the nasal infection persisted although its dissemination was largely prevented. As soon as it was found that terramycin ointment might sometimes eradicate the nasal infection its further trial seemed to be justified, provided that the course of treatment was limited in time and thoroughly carried out. Even so two resistant strains have been isolated after treatment—resistant also to aureomycin but not to chloramphenicol. These appear to be new strains, perhaps possessing intrinsic resistance; but the widespread use of terramycin might well encourage the dissemination of such strains, as has happened with penicillin (Barber and Rozwadowska-Dowzenko 1948). It would obviously be preferable therefore to use drugs which are not suitable for systemic administration.

The figures shown in the tables strongly suggest that, when pathogenic cocci can be extirpated from a nose which is heavily infected, the clinical result will usually be good. When reinfection with a fresh strain takes place, the results are more equivocal; but detailed study of the cases shows that only three of the twelve new strains isolated were definitely incriminated in the formation of fresh lesions.

SUMMARY

In most cases of persistent furunculosis and sycosis barbæ the anterior nares contain the same strain of staphylococcus as is found in the lesions. Occasionally, instead of the nose, the eye or some other region is the "site of carriage" or reservoir from which infection continues to be distributed. Infection also persists in the neighbourhood of a lesion until it is completely healed.

The scheme of treatment described is based on a simple explanation to the patient that infection is spread to other parts of the body, from lesion or nose, by fingers or handkerchief. All lesions are treated until healed, and terramycin ointment has been applied to the site of carriage twice daily for four weeks.

The clinical results are good, provided infection is eradicated from the site of carriage. Reinfection of the site of carriage with a fresh strain does not usually lead to clinical relapse.

Although no strain acquired resistance to terramycin, two resistant strains were isolated after treatment.

Sensitisation of the skin to terramycin ointment appears to be uncommon.

We wish to thank Dr. W. J. O'Donovan for his permission to study and treat so many of the patients under his care. Our great debt to Dr. R. E. O. Williams and his staff at the Staphylococcal Reference Laboratory, Colindale, has already been acknowledged in the text. We also want to thank Prof. S. P. Bedson and Dr. H. B. May for their advice and interest. For the supply of 3% terramycin ointment our thanks are due to the Antibiotics Clinical Trials (non-tuberculous conditions) Committee of the Medical Research Council.

ADDENDUM

Since this paper was written, the appearance and dissemination of staphylococci resistant to many or all of the newer antibiotics has been described (Lowbury et al. 1952, Clarke et al. 1952). The danger is greater in the case of inpatients since during bedmaking the nurses inhale dust and become nasal carriers of the resistant organisms. Our cases have been outpatients and the drug has usually been applied to relatively intact skin rather than to sloughing wounds in which resistance is readily bred; resistant strains have only appeared after treatment has been unduly prolonged, against instructions. None the less the widespread use in local treatment of drugs capable of systemic administration is clearly undesirable and we are investigating the use of other agents.

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COLLES FRACTURE OF THE RADIUS

A METHOD OF TREATMENT

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Colles fracture takes place about an inch from the carpal articular surface of the radius and presents a remarkably constant deformity, the small distal fragment being rotated so that the articular surface faces downwards and backwards, instead of downwards, or downwards and forwards. In addition there is usually some lateral rotation, carrying the carpus and hand to the radial side and rendering the head of the ulna more prominent. The proximal fragment is often driven into the distal one to a varying extent.

A recognised but insufficiently emphasised concomitant is the fragmentation of the dorsal and lateral aspects of the radial cortex at the *site of fracture*, which must occur to allow the classical deformity. This fact explains the common instability of this fracture after reduction, and the high incidence of recurrent displacement.

It appears to be tacitly accepted that, although the bones may unite in a position different from the normal anatomy, function may be, and commonly is, good. An investigation was therefore instituted to see to what extent this is true, and if a particular method of treatment produced satisfactory anatomical position of the bone and normal function.

MATERIAL

350 patients, treated by two methods, were selected at random from the records. All had uncomplicated Colles fractures with displacement. Of the number selected, 151 attended for interview and were examined personally. In all the fractures reduction and splintage had been effected within a few hours of injury, and all had united.

The average follow-up period since injury was 5 years, with a maximum of 7 years and a minimum of 2 years. The average age was $55^{1}/_{2}$ years.

PROCEDURE

Every patient was asked the following questions:

(1) Is your wrist as good as it was before your injury?

(2) If not, in what way does it now differ?

(3) Can you wring clothes normally?

(4) Can you turn a stiff door-handle?

(5) Can you carry weights in the affected hand without any trouble?

(6) Do you get pain?

Every wrist was next examined and classified under the following headings:

(1) Clinically indistinguishable from normal.

(2) Good—no obvious visible abnormality, but with a palpable bony deformity.

(3) Fair—a visible deformity of minor degree.

(4) Poor—a gross and obvious deformity.

RESULTS

The results in the 151 cases are shown in table I. The symptoms complained of by 73 patients were as follows: pain in 60 cases; weakness in 48 cases; inability to wring clothes normally in 32 cases; and difficulty in turning door-handles in 11 cases.

DISCUSSION

Table I shows that only 65 patients exhibited the normal wrist anatomy, and 74 showed visible deformity, classified as "fair" or "poor." Since all these fractures had been reduced, there was a very high rate of recurrent deformity of obvious degree. Furthermore, the symptomless patients were those who showed chiefly normal or good wrists, whereas the ones with symptoms were found chiefly in the fair and poor classes.

TABLE I—RESULTS IN 151 CASES OF COLLES FRACTURE

Result	Symptomless	With symptoms	Total
Normal	54	11	65
Good	9	3	12
Fair	11	38	49
Poor	4	21	25
Total	78	73	151

It seems reasonable to conclude that union in anatomical position is more likely to give a symptom-free wrist, and that, if the fracture unites in a position different from the normal, function is unlikely to be satisfactory.

As stated above, these patients had been treated by two methods:

Method A.—In the outpatient department the fracture was reduced under gas-and-oxygen anæsthesia (in a very few cases local anæsthesia was used), and a plaster slab encircling two-thirds of the wrist and forearm was applied from the metacarpal heads to the upper forearm. It was secured with a cotton bandage, which was adjusted later if it became loose. The wrist was held in the neutral position as regards rotation, flexion, and extension, and in slightly ulnar deviation. In all the cases X rays were used to confirm reduction. Splints were removed in the 5th or 6th week and, if union was present, active use was permitted.

Method B.—The patient was admitted, and reduction was effected under general anæsthesia. A posterior plaster slab was applied and secured with a cotton bandage. In all the cases X rays were used to confirm reduction. On the patient's return to bed the hand was kept elevated, and active exercises were started at once. When the swelling had subsided (usually after 4 or 5 days), and not until then, further radiographs were taken; and if, as happened in most cases, there was any recurrence of deformity, the bones were again manipulated into their correct position. After this, and also in cases showing no recurrence of displacement, a complete unpadded plaster cast was applied, from the metacarpal heads and proximal palmar crease to the upper forearm. The plaster was well moulded round the radial styloid and into the anterior concavity of the radius just above its lower end. The wrist was held in slight palmar flexion and moderate ulnar deviation, and in neutral rotation. The hand was elevated overnight to check reactionary swelling, and the patient was discharged next morning. The plaster was removed in the 6th week after injury and, if union was present, active use was permitted.

TABLE II—RESULTS ACCORDING TO METHOD OF TREATMENT

Method	No. of patients	Average age (yr.)	Result			
			Normal	Good	Fair	Poor
A	79	$55^{1}/_{2}$	19	7	37	15
B	72	$56^{1}/_{4}$	46	5	12	10

The results according to the method of treatment are shown in table II.

COMMENT

In method B insistence is placed on applying finally a skin-tight plaster cast to the limb after reduction (obtained by two or more manipulations if necessary) and after all swelling has subsided. The plaster is thus moulded to bones no longer masked by œdematous tissues. It seems clear that method B produces a substantially greater proportion of normal and good wrists than does method A.

CONCLUSION

The expectation of normal or good function after a Colles fracture has united in an abnormal position seems to be unjustified.

There is a strong tendency to recurrence of deformity after reduction, and the best hope of obtaining union in a normal position lies in applying a well-moulded plaster cast to the part after all swelling has subsided. Only in this way are the bones likely to be held in the correct relationship. This method often necessitates two (or even more) anæsthetics, but the result of this form of treatment appears to justify this.

SUMMARY

The anatomical position of wrists which have sustained a Colles fracture is correlated with symptoms.

It is suggested that union in anatomical position be aimed at in every case, since it gives the best chance of normal function.

A method of treatment embodying certain principles is described and its results are given.

I wish to thank Mr. J. C. R. Hindenach for his advice, and Dr. W. E. Evans for access to the case-records of the late Mr. George Stephen.

RECOGNITION OF FUNCTIONAL DISORDERS OF THE SMALL INTESTINE

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OF 1500 new patients attending the gastric clinic at the West London Hospital during a period of three years (1948–51), 8 had long-standing abdominal pain, obscure in origin and resistant to treatment, and on radiological examination were found to have an abnormality of the ileum.

Functional disorders of the colon have received attention in the past twenty-five years from Ryle (1928), Spriggs (1931), and Hardy (1945). But similar disorders of the small gut have had scant notice, although many agents (psychological, hormonal, reflex, chemical, physical, vascular, bacteriological, allergic) can affect intestinal movement and secretion. The importance of recognising such a condition was brought home to us by the following case:

Case 1.—Miss A, aged 34, a clerk in a responsible post, had for five years suffered from intermittent attacks of diarrhœa with aching lower abdominal pain radiating to the left sacro-iliac joint and down the front of both thighs, indifferent appetite, and a sense of fullness and belching after meals. She was subject to migraine and dysmenorrhœa, and in cold weather her extremities became blue and numb. She was of a shy and nervous disposition but well adjusted in spite of emotional immaturity. Her appendix had been removed in 1945. Apart from abdominal distension and an appendicectomy scar, nothing abnormal was found on physical examination, and early investigations (barium enema, sigmoidoscopy, bacteriology of stools, radiography of chest) were unhelpful. A barium meal, however, showed 6 inches of irregular narrowing in the distal ileum (fig. 1).

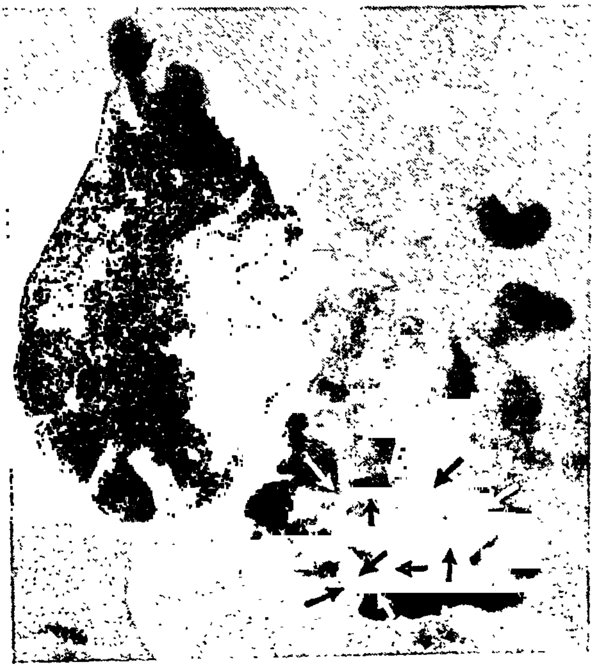
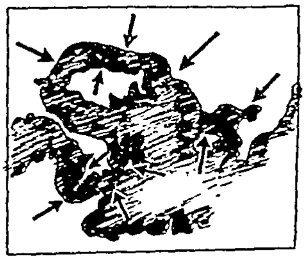


Fig. 1 (case 1)—Barium-meal radiograph showing 6 in. of irregular narrowing in distal ileum.



Tracing of spastic area in distal ileum.

Crohn's disease was diagnosed and laparotomy was done, but no abnormality whatsoever was found.

This case taught us that ileal spasm associated with abdominal symptoms could be sufficiently prolonged and severe as to mimic organic disease; and as a result other cases came to light. In these cases we had previously failed to recognise that the disorder lay in the small gut. Some of these patients had diarrhœa, others were constipated, none had normal defæcation.

CASES WITH DIARRHŒA

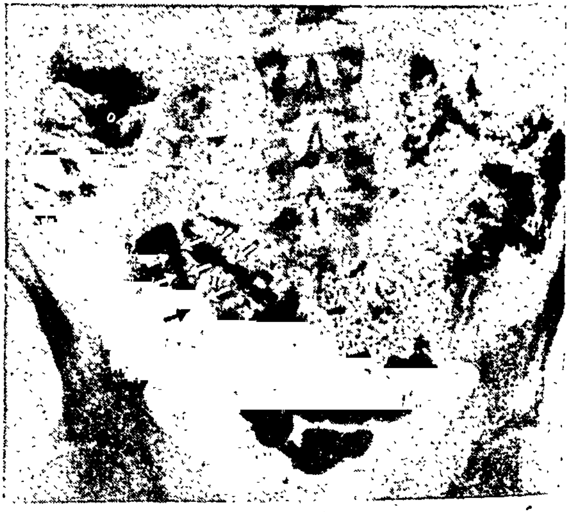
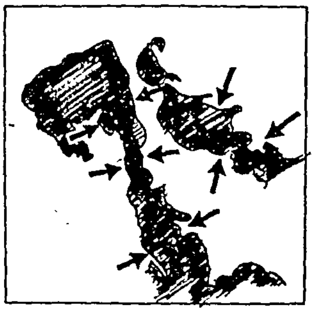


Fig. 2 (case 2)—Irritable loop in upper ileum with thickening of the mucosa.



Tracing of irritable loop.

Case 2.—Miss B, a Civil Servant, aged 36, had had an appendicectomy at 16, jaundice at 30, and bacillary dysentery at 31 and again at 35. She had suffered from asthma and hay-fever since the age of 16. For two and a half years she had been troubled with intermittent lower abdominal and right sacro-iliac pain, radiating down the front of her right thigh, aggravated by walking and by defæcation, and relieved by sitting and while menstruating. These symptoms were accompanied by diarrhœa, with loose pale stools, anorexia, frequency and urgency of micturition, and a variable pyrexia. Two laparotomies, one in 1949 and the other in 1950, had failed to relieve her or to discover the cause of her symptoms. At the first laparotomy a broad-ligament fibromyoma was excised. At the second, endometrial cysts were removed from both ovaries.

When we saw her she was rather tense; she had hay-fever, a tender spastic sigmoid colon, and a ballooned cæcum. The erythrocyte-sedimentation rate (E.S.R.), a complete blood-count, examination of the urine, and radiography of stomach and duodenum, gall-bladder, and chest, and an intravenous pyelogram, were all normal. The Wassermann reaction of the blood and a gonococcal complement-fixation test were negative. Skin sensitivity tests were positive to mixed pollens and grasses and negative to intradermal histamine 1 : 10,000. Radiography of the small intestine, however, showed in the upper ileum an irritable tender loop

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* Working with a grant from the Dan Mason Research Foundation, West London Hospital Medical School.

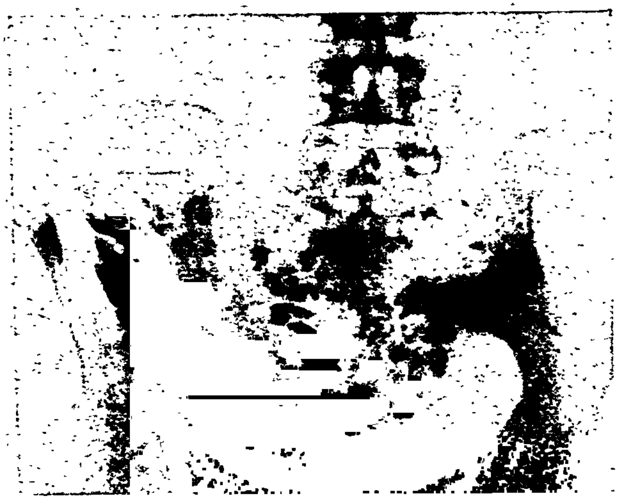


Fig. 3 (case 3)—Clumping and segmentation in small intestine (patient erect).

with evident thickening of the mucosa (fig. 2). The hay-fever responded to anti-histamines, but there was no improvement in the abdominal symptoms, nor were these affected by antispasmodics and sedatives.

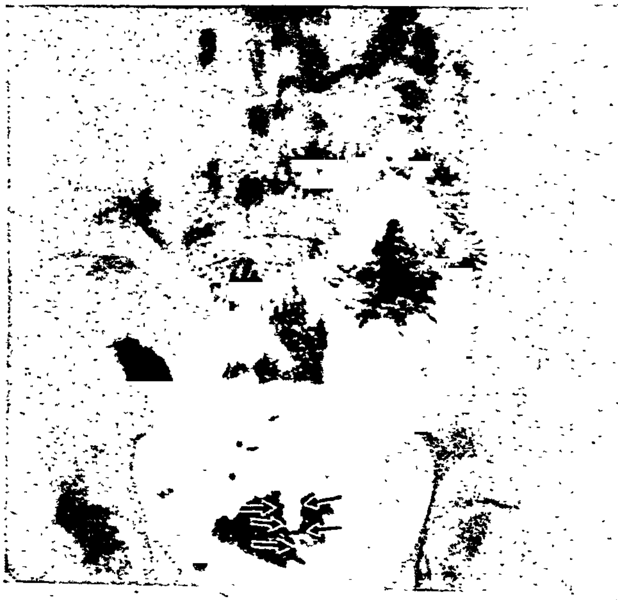
In endometriosis the intestines may become involved by the growth of endometrium on their walls or by incorporation of loops in a pelvic mass, the end-result being intestinal obstruction. This patient's intestines were not affected, and her symptoms remained unrelieved after removal of the diseased tissue.

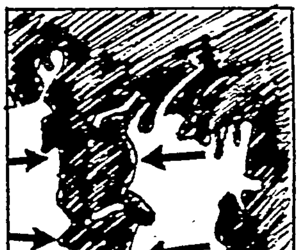
Case 3.—Mrs. C, divorced, aged 33, a packer in a factory, began at the age of 29 to have attacks, usually of sudden onset and lasting about eight hours, characterised by diffuse abdominal cramping pain, doubling her up and accompanied by malaise, sweating, nausea, vomiting, distension, and flatulence. Her stools, which were normally frequent and pale, became watery and more frequent. Apart from these bouts she had frequency of micturition, dysmenorrhœa, and attacks of urticaria, and her extremities became very cold in winter. She had never been pregnant. Appendicectomy in 1948 had failed to improve her health.

Seen by us in an attack her face was flushed, weals were visible on her chest and back, her abdomen was soft, distended, and diffusely tender, and her temperature was 99°F. Her personality was somewhat immature, her intelligence average. A barium meal showed small-gut hurry, clumping, and segmentation (fig. 3), but the fat-content of the stools was 26·3 g. per 100 ml., of which 16 g. was split, and fat-balance (Cooke et al. 1946) showed that 97% of ingested fat was absorbed. There was no response to folic acid. A complete blood-count, estimation of the plasma-protein level, a histamine test-meal, and bacteriological examination of the stools gave normal results. Skin sensitivity tests were positive to mixed inhalants, mixed grasses, pollens, and intradermal histamine 1 : 10,000. Histamine desensitisation, and anti-histamines, antispasmodics, and sedatives were all without effect.

A year later a further barium meal showed persistence of the abnormal pattern, and passage through the gut was so rapid that the head of the meal was at the splenic flexure ten minutes after ingestion.

Fig. 4 (case 4)—Ileal spasm.





Tracing of spastic area of ileum.

Idiopathic steatorrhœa, suggested by the small-gut pattern, was excluded by the normal fat-balance and lack of response to folic acid. We favoured a diagnosis of intestinal allergy but were disappointed by the failure of appropriate therapy.

CASES WITH CONSTIPATION

Case 4.—Miss D, aged 33, buyer for a large business concern, said that for five years she had been subject to attacks of epigastric or lower abdominal pain, sometimes radiating to the sacrum and down the front of both thighs. This was accompanied by anorexia, nausea, headache, sweating, malaise, abdominal distension, and dysuria. These attacks often, but not invariably, coincided with her menses, which were very irregular. Each attack had lasted from one to three weeks; they were lasting longer and becoming more severe. At first she had had diarrhœa with pale stools, but obstinate constipation had gradually become a feature of the attacks, and any bowel action enhanced the pain. She had had a ventrisuspension and appendicectomy in 1946.

Under observation by us during an attack she had pyrexia of 99°–101°F, blotchy erythema of her face, and distension and tenderness of the lower abdomen, particularly at McBurney's point. At times portions of her transverse, descending, or sigmoid colon became spastic and tender. The following investigations were normal or negative: complete blood-count, E.S.R., skin tests for allergy, intradermal histamine sensitivity test, catheter specimen of urine, twenty-four-hour specimen of urine for tubercle bacilli, bacteriology of stools, gynæcological examination under anæsthesia, plasma-proteins, serum colloidal gold, serum alkaline phosphatase, urinary 17-ketosteroids, blood agglutinations, chest radiography, intravenous pyelogram, barium enema, Wassermann reaction and Kahn test of blood, and examination of cerebrospinal fluid. A barium meal showed clumping, stasis, and spasm in the upper ileum (fig. 4), and this spasm was still present six months later.

Her personality was immature, and one attack was complicated by hysterical paralysis of the left lower limb. This disappeared under psychotherapy, but her attacks continued to get worse. Finally, after an especially long attack when she had lost over 1 stone in weight and her condition was deteriorating and giving rise to anxiety, laparotomy was done; but no organic disease was found and the attacks have continued.

In this case constipation has superseded diarrhœa as the attacks have become longer and more severe. These may be associated with menstruation, and it is noteworthy that a bad attack tends to be followed by a period of about three months during which there is a spontaneous remission, together with amenorrhœa.

Case 5.—Miss E, aged 24, holding a responsible secretarial post, had had acute gastro-enteritis in 1947. Ever since

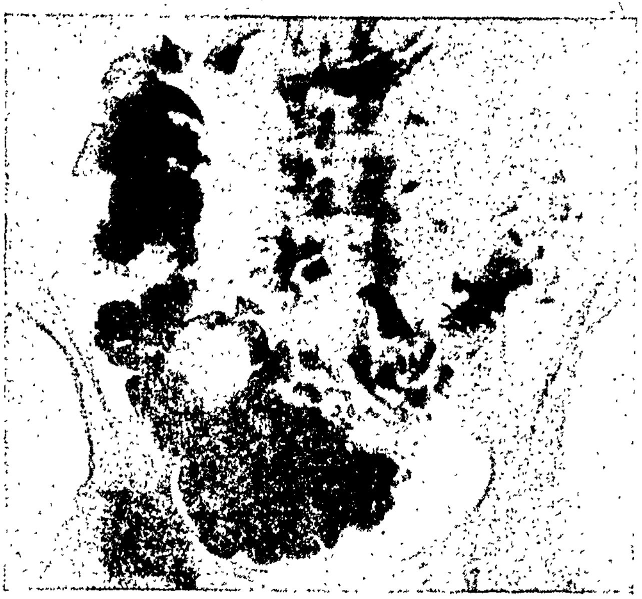


Fig. 5 (case 5)—Clumping and mucosal thickening in small intestine.

then she had had recurrent attacks of dull peri-umbilical *pain radiating to her back, worse during menstrual periods* and accompanied by nausea and flatulence. She had always been constipated.

On examination the only abnormal finding was a loud intestinal splash on movement, a phenomenon which the patient herself had observed and which she stated was always more noticeable after taking liquids. She was an intelligent girl with a bright and cheerful outlook. A barium meal showed what appeared to be a large duodenal polyp, and the meal was still present in the transverse colon one hundred and ten hours after ingestion. Treatment to relieve her *constipation failed to improve her pain.*

When a second barium meal three months later indicated that the "polyp" had become larger, a laparotomy was performed. There was no polyp, the radiological appearances being due to a diverticulum, with a raised margin, arising posteriorly from the first part of the duodenum. This was not considered responsible for her symptoms; so the abdomen was closed.

A year later the symptoms remained unchanged. Skin sensitivity tests were positive to mixed inhalants, and negative to intradermal histamine 1 : 10,000. A histamine test-meal, bacteriological examination of stools, and glucose tolerance were all normal. It was thought that the symptoms might be due to appendicitis; so appendicectomy was performed. *The appendix was normal, and the operation produced no improvement.*

Eighteen months after she had first consulted us, radiological *examination of the small intestine showed clumping and mucosal thickening* (fig. 5), and a reasonable basis for her symptoms had at last been established.

Diverticula are rare in the first part of the duodenum (Golden 1949) and only occasionally produce symptoms (Spriggs and Marxer 1925, Bockus 1944). Apart from the diagnostic difficulties, this case is of interest as being the only one in our series where constipation was associated with demonstrable intestinal delay.

Case 6.—Miss F, aged 42, a Civil Servant, was well adjusted despite a rigid immature personality and chequered history. Abdominal pain had been persistent since she was 23, when appendicectomy had afforded no relief. A second laparotomy at 37 showed no abnormality. At 40 a third laparotomy had revealed tuberculous glands in the ileocæcal region. The abdominal pain was generalised, subject to spontaneous exacerbations and remissions, and was aggravated by defæcation. Constipation was marked. Other symptoms included sacral backache, frequency of micturition, indifferent appetite, nausea, flatulence, and severe abdominal distension. In addition she had asthma, urticaria, and allergic rhinitis; *she was subject to dysmenorrhœa, and in winter her peripheral circulation was poor.*

Under observation she ran an intermittent temperature up to 99°F. Her abdomen was extensively scarred, distended, and tender. E.S.R., complete blood-count, basal metabolic rate, plasma-cholesterol, catheter urine, barium enema, radiography of spine, and fat-balance were all normal. Skin sensitivity tests were positive to mixed inhalants. Although the small-gut pattern was normal, barium reached the cæcum twenty-five minutes after ingestion; follow-through examination of the colon was normal. *Anti-histamines, though very effective for her allergy,* did not help her abdominal pain, and there has been no response to measures designed to relieve the constipation.

This is the only patient in the series with a normal small-gut pattern. *It is interesting and unexpected to find constipation associated with hypermotility* of the small intestine, the time of passage of barium here being less than half the normal minimum of 1 hour (Golden 1945, Shanks and Kerley 1950).

Once the significance of the symptoms was appreciated, it became possible, on clinical grounds alone, to pick out cases from the general mass of dyspeptics attending the clinic, as in the following case:

Case 7.—Mrs. G, aged 36, had had intermittent attacks of abdominal pain, lasting four or five days, since the age of 14. She had never been pregnant and at 32 she had had bilateral tubo-ovarian masses and her appendix removed. The pain was lower abdominal, cramping, and radiating into either groin, to the sacrum, or down the left thigh. It was accompanied by flatulence, distension, frequency of micturition, and constipation, and was sometimes relieved by the passage of a loose stool. The patient had dysmenorrhœa. Clinical examination was unremarkable. A tentative diagnosis of ileal dysfunction was made, and a barium meal showed some 2 inches of severe spasm in the distal ileum (figs. 6 and 7).

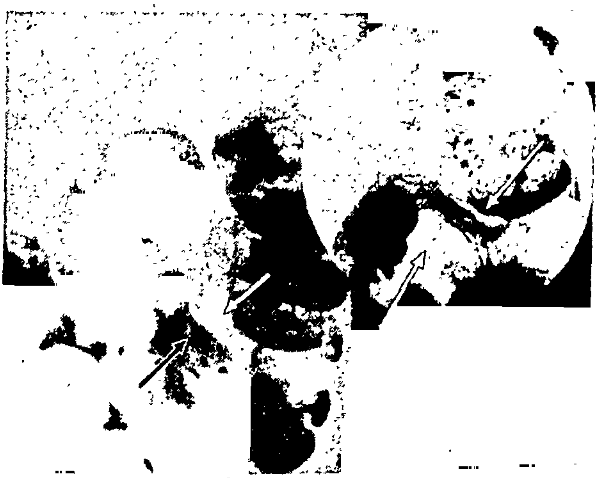


Fig. 6 (case 7)—Intense spasm for 2 in. in distal ileum.

DIAGNOSIS

The main features of the 7 cases reported are:

(1) All were in women who had never been pregnant and whose symptoms had begun during the childbearing period, the length of history averaging *more* than nine years. Dysmenorrhœa was usual.

(2) All the patients had abdominal pain, poorly localised, often radiating to the sacrum, groins, or down the front of the thighs. The pain tended to be aggravated by menstruation and defæcation, but was unaffected by food, holidays, antispasmodics, or rest in hospital.

(3) All had disordered bowel action, abdominal distension was commonly severe, and nausea was frequent.

(4) All were energetic and over-conscientious, with average to good intelligence. They held fairly responsible jobs. Their personalities were immature but they had adapted well to their life situations.

(5) All had had laparotomies for their symptoms, and in none had any organic change been found in small or large bowel.

(6) Clinical examination revealed abdominal distension and tenderness with variable spasticity of the colon. Radiography of the intestines showed spasm, mucosal thickening, hypermotility, or a deficiency pattern, the ileum being consistently affected.

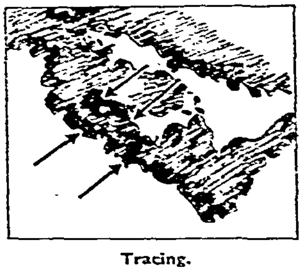
(7) Inconstant features included: pyrexia (4 cases during the attacks), bladder disturbances (5 cases), evidence of poor peripheral circulation (3 cases), and allergic manifestations (3 cases).

Many of these points have been made by Ryle (1928), Spriggs (1931), Hardy (1945), or Bockus (1944) in their writings on colon spasm: and, although Bockus states that colon spasm is often accompanied by motor disturbances of the small intestine, the part played by the small intestine has not been defined further. The points which are significant in the diagnosis of ileal dysfunction and which have not previously been emphasised are the diffuseness of the abdominal pain, the pain in the groin, the distension, the radiological appearances in the small intestine, and the failure of holidays, rest in hospital, psychotherapy, or antispasmodics to have any effect. So far we have found this syndrome only in single, barren, or unhappily married women.

In our experience these cases do not fall into the pattern we have come to recognise as typical of colon spasm. In the same three years 5·5% of the new cases attending the clinic were diagnosed as colon spasm. Males and females, average age 36, were affected in the proportion 6 : 5. These patients had intermittent pain, often mimicking a peptic ulcer in its behaviour, localised to a palpably spastic segment of colon, sometimes associated with constipation, rarely with diarrhœa. They had no allergic manifestations, but overwork and anxiety were often precipitating factors. Relief with a holiday was usual, and the patients responded almost invariably, after reassurance, to antispasmodics and sedatives.

It seems likely that some degree of colon spasm is present in the cases under discussion, but that, when the ileum is involved, the ileal dysfunction tends to dominate both the clinical picture and the response to treatment.

Fig. 8 (case 8)—Abnormal mucosal pattern at junction of proximal two-thirds with distal third of ileum, site of tenderness.



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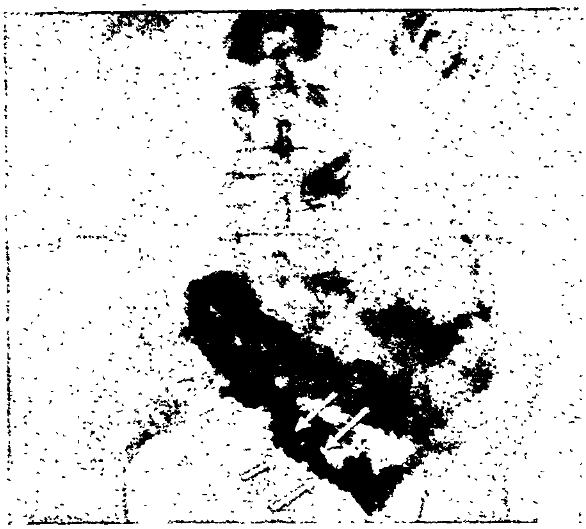


Thus the two syndromes are generally distinct. We have, however, seen one patient presenting the features of small intestinal dysfunction at the same time as those of colon spasm:

Case 8.—Mrs. H, divorced, aged 52, departmental secretary in a large hospital, had had intermittent lower abdominal pain for nineteen years, ever since acute gastro-enteritis. Other symptoms included anorexia, distension, flatulence, nausea, and a worsening of her habitual constipation during the attacks. The attacks were less frequent on holiday and were sometimes precipitated by worry and fatigue. She had had dysmenorrhœa until a subtotal hysterectomy for fibroids in 1945. Her extremities became cold and numb in winter. She was of a highly strung and anxious disposition.

On examination, parts of the ascending and descending colon were distended, and a barium enema showed mild colon spasm. A complete blood-count, E.S.R., and bacteriological examination of stools were all normal. A barium meal showed mucosal thickening of the ileum and an abnormal pattern (fig. 8) at the site of the tenderness. With psychotherapy, antispasmodics, and sedatives the attacks, although still troublesome, have become shorter and less frequent.

This case illustrates very well how the pattern of ileal dysfunction may occasionally overlap that of colonic dysfunction to produce a mixed clinical picture. On the one hand, the patient had a mild anxiety state, her symptoms were aggravated by worry and fatigue, and a barium enema showed colon spasm: she had no allergic manifestations or pyrexia. On the other hand, her pain and tenderness were not localised to the colon, which was not palpably spastic she had radiological changes in the small intestine, and her symptoms were only partially relieved by a holiday, reassurance, and antispasmodics.

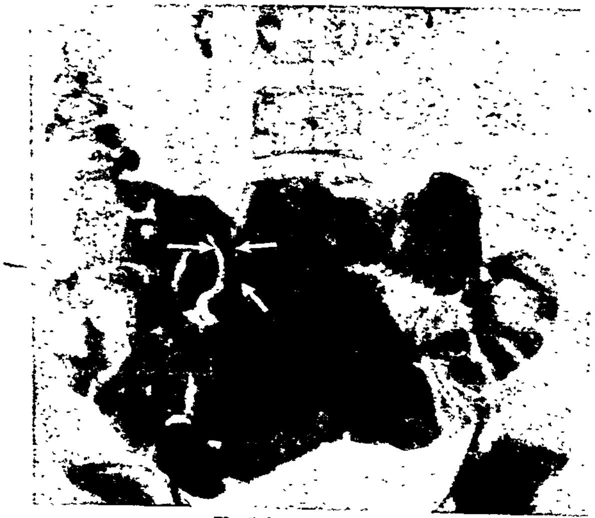
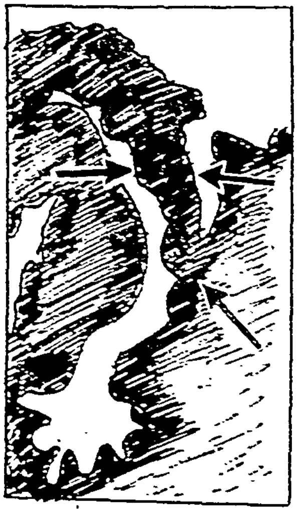


Fig. 7 (case 7)—As fig. 6.



Tracing of spastic area of ileum.

SUMMARY

Functional disorders of the intestine are ill recognised in this country, and, when recognised, the dysfunction has been attributed solely to the colon (colon spasm, irritable colon, functional or motor disorder of the colon).

In our experience many of the features previously described under the heading of

colon spasm are found when the small intestine is involved.

Eight cases (0·53% of 1500 new patients with gastro-intestinal complaints attending a gastric clinic in three years) are described here. They are examples of intestinal dysfunction affecting the ileum in particular.

Colon spasm alone is ten times more common. It is closely related to manifest anxiety, has a well-defined clinical picture, and responds well to reassurance, belladonna, and phenobarbitone.

The ileal syndrome is less obviously psychosomatic in origin, has a more complex symptomatology, and has proved very resistant to treatment.

Although the two syndromes are usually distinct, a case is occasionally seen (case 8) showing some features of both syndromes at the same time.

We wish to thank Dr. Horace Post and Dr. Hector Jones for the radiological investigations, Dr. Arthur Conachy for his psychiatric reports, Mr. Harold Burge for the surgery, and Dr. W. M. Politzer for carrying out the fat-balance tests.

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LEAD PAINT: A HAZARD TO CHILDREN

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IN this country the commonest cause of lead poisoning in children is the ingestion of paint on woodwork in the home, particularly on cots.

The danger of lead paint to children, well known by manufacturers of nursery furniture, is less well appreciated by the general public. Fathers in particular should be warned; in 4 of the following 5 cases they were unwittingly responsible for the poisoning of their own offspring by applying lead paint to cots.

Titanium, antimony, and zinc oxides have superseded white lead in many pale-coloured gloss paints and enamels used today. It should be noted, however, that some yellow and green varieties still contain 20% of lead chromate.

Compared with other countries, Great Britain is strangely lacking in reports of lead as a hazard to children. Reporting 5 cases Burrows et al. (1951) referred to only 7 other reports during the past sixty years. In addition, 1 due to lead nipple-shields was described by Gordon and Whitehead (1949), and 1 in which the diagnosis was suspected only after death has recently reached the public press: a child, aged 21 months, had chewed lead paint on his cot.

The present 5 cases of plumbism in children bring the number of reports published in this country, during more than half a century, to 19, in which the sources of lead were as follows: painted woodwork (9), nipple-shields (4), toy soldiers (2), fumes inhaled from burning battery casings (2), drinking-water (1), and toilet powder (1).

CASE-RECORDS

Case 1.—A girl, aged 2 years, was admitted to St. Bartholomew's Hospital on July 17, 1951, having been irritable and constipated for three weeks, during which time her face had become thin and pale.

On admission she was drowsy and slightly jaundiced. Respiratory embarrassment was remarkable, with paradoxical inspiratory recession of the epigastrium. Her temperature was 100°F, pulse-rate 140 per minute, and respirations 30 per minute. Her breath was fœtid from ulcerative stomatitis, and her tongue was furred. Apart from the apparent diaphragmatic paralysis no abnormal signs were elicited on examination of the chest. The abdomen was tender to palpation but otherwise normal. There were pain and unequivocal tenderness of the lower limbs, which were held flexed and abducted at the hips. All reflexes were exaggerated and the plantar responses were flexor. The functions of the cranial nerves were unaffected and the ocular fundi normal.

Investigations.—A catheter specimen of urine was pink and contained uroerythrin and urobilin, but no protein or sugar. A moderate excess of white cells was noted in the deposit; there were no red cells or casts, and culture was sterile. A blood-count showed Hb 52%; red cells 3,100,000 per c.mm.; reticulocytes 6%; white cells 18,000 per c.mm. (neutrophils 71%). A blood smear showed punctate basophilia. The red-cell fragility was normal. A blood-culture was sterile. The blood-serum contained total protein 8 g. per 100 ml. (albumin 5·2 g. per 100 ml., globulin 2·8 g. per 100 ml.), blood-urea 58 mg. per 100 ml. The alkali reserve was 70 vols of CO_2%. An indirect van den Bergh test showed bilirubin 1·3 mg. per 100 ml. Thymol turbidity was 3 units. The Takata Ara, Wassermann, Kahn, and direct Coombs tests were negative. The stools contained blood when examined by the benzidine and aminopyrine tests. In the chest radiograph no abnormality was detected, but screening confirmed the clinical diagnosis of diaphragmatic paralysis.

Lumbar puncture produced clear colourless cerebrospinal fluid (C.S.F.) under normal pressure containing 300 red cells, 5 lymphocytes, and 3 polymorphs per c.mm.; protein 45 mg. per 100 ml.; globulin in slight excess; and sugar 90 mg. per 100 ml. The Wassermann reaction was negative.

Lead in bones.—The presence of punctate basophilia prompted a radiographic examination of the bones for lead deposits; bands of increased density were revealed at the growing ends of the shafts of long bones and along the growing margins of flat bones—appearances consistent with lead poisoning. The blood-lead level was 4 µg. per ml. (normal <0·5 µg. per ml.); lead in the urine was slightly in excess of 0·1 mg. per litre (normal <0·1 mg. per litre) (Dr. W. G. Dangerfield).

It was discovered on further inquiry that, for a year, the patient had regularly gnawed her cot, and that her twin sister (case 2) had also acquired this habit but not to the same degree. A history was obtained of other manifestations of pica. The paint, applied to the cot by the father, was examined and found to contain lead.

Treatment, consisting of milk feeds, calcium lactate, and vitamin D, aimed at immobilisation of lead in the bones.

Progress.—Despite penicillin given for the ulcerative stomatitis, and a transfusion of 350 ml. of group O Rh+ blood, pyrexia and tachycardia persisted. Eight days after admission bilateral foot-drop with spasm of the gastrocnemii was evident. Improvement began a week later, the appetite returned, and the child took an interest in her surroundings. At three weeks she weighed 21 lb., having gained more than 1 lb. since admission; her temperature was normal, and repeat screening of the chest showed diaphragmatic contraction. There was now no tenderness of the calf muscles, though wasting was apparent; limitation of dorsiflexion of the foot persisted. Electrical reactions revealed complete degeneration in the extensor hallucis and digitorum longus muscles of both legs; partial degeneration was present in the tibialis anterior and peronei muscles. The upper limbs were unaffected. Physiotherapy, continued for six months, achieved a slow but complete recovery of the affected muscles. On Feb. 19, 1952, a blood-count showed Hb 68%, red cells 3,510,000 per c.mm., and reticulocytes 7·2%; and a blood smear showed mild punctate basophilia. Notwithstanding this evidence of continued toxicity the lead lines in radiographs of the bones were less dense than formerly.

Case 2.—The twin sister of case 1 was admitted to St. Bartholomew's Hospital on July 24, 1951. Other than pica, there was no history of illness. The patient was in the habit of chewing the paint on her sister's cot, and for this reason she was brought to hospital for examination.

On admission she was pale and quiet and looked ill. Her temperature, pulse-rate, and respiration-rate were normal, and no abnormality was detected in the central nervous system. Her urine contained no protein or sugar. A blood-count showed Hb 52%; red cells 3,240,000 per c.mm.; white cells 5700 per c.mm. (neutrophils 46%, lymphocytes 44%, monocytes 10%). Punctate basophilia was seen in a stained blood smear. Similar changes to those found in case 1 were revealed in radiographs of the bones; the inner and outer tables of the skull were involved. The blood-lead level was 2 µg. per ml., and the urinary excretion of lead $<0{\cdot}1$ mg. per litre.

Treatment and progress.—Milk feeds, calcium lactate, and vitamin D were administered; a blood-transfusion increased the hæmoglobin to 68%. The appetite, at first capricious, improved, and when discharged from hospital on Aug. 18, 1951, the patient had gained 2 lb. in weight.

Follow-up.—Six months later the hæmoglobin was 66%, red cells 3,990,000 per c.mm., and reticulocytes 3·1%. Punctate basophilia, though now mild, persisted.

Case 3.—A boy, aged 1 year 8 months, was admitted to the Westminster Children's Hospital on April 22, 1951. For three months previous to admission he had gnawed the paint on his cot and exhibited other manifestations of pica. He had been irritable and constipated for three weeks. Vomiting, at first intermittent, had become copious and projectile.

On examination he was pale, dehydrated, and drowsy. The ocular fundi showed papillœdema, tendon-reflexes were exaggerated, and the plantar responses were extensor.

Lumbar puncture produced clear colourless C.S.F. under increased pressure and containing 4 lymphocytes per c.mm. and 120 mg. of protein per 100 ml.

Other investigations.—The hæmoglobin was 58%, and a blood smear showed a few examples of punctate basophilia. A radiograph of the chest was remarkable in that the angles of the scapulæ were demarcated by dense lines; the growing ends of the long bones also revealed lead lines. The urine contained sugar and 0·9 mg. of lead per litre. The blood-lead level was 6 µg. per ml. On inquiry it was found that the child had ingested paint from his cot and from an outside window-sill, the lead contents of which were 0·85% and 3% respectively; a possible source, which appeared untouched, was red-lead putty containing 7% of lead.

Treatment.—Hydration was maintained with glucose-saline solution, and 10 ml. of 10% calcium gluconate was added to each pint infused. To eliminate the lead remaining in the alimentary canal magnesium sulphate was administered by Ryle's tube; an enema was also given.

Progress.—After two days small milk feeds were taken, the patient becoming more alert. On the advice of the Medical Research Council dimercaprol injections, begun with the object of producing a less toxic lead-dimercaprol compound, were discontinued. Convincing evidence that the compound was less toxic than the lead itself was wanting. Further, the acidosis produced by dimercaprol liberated lead from the bones. It was also suggested that lead in the colon was unlikely to be absorbed in significant degree, and that purgation with magnesium sulphate would again tend to produce a deleterious acidosis. Therapy thereafter consisted of a milk diet, a single dose of 90,000 units of calciferol, and gr. 10 of calcium gluconate with each feed.

Recovery.—Apart from glycosuria, which persisted up to the date of discharge on May 31, 1951, recovery was rapid and uneventful. Two months later the child was healthy; his blood picture was normal, and the radiographic changes in the bones were less evident.

Case 4.—A girl, aged 2 years, was admitted to the Westminster Children's Hospital on Feb. 9, 1952, having been well until five days previous to admission, when cough and coryza developed together with loss of appetite and occasional vomiting. After a transitory remission of her symptoms she was admitted with convulsions, which continued as status epilepticus for twenty-four hours despite repeated intramuscular injections of paraldehyde.

Lumbar puncture produced a clear colourless C.S.F. containing 860 red cells, 15 lymphocytes, and 4 polymorphs per c.mm.; protein 150 mg. per 100 ml.; and sugar 110 mg. per 100 ml. The hæmoglobin was 68%, the white cells numbered 11,000 per c.mm., and the reticulocytes were 0·5%. Punctate basophilia was not reported.

Treatment and progress.—Control having been effected with intramuscular phenobarbitone, on Feb. 12 the convulsions ceased. The child was drowsy and vomited after several feeds, and early papillœdema was detected. A second lumbar puncture produced clear colourless C.S.F. containing 5 lymphocytes per c.mm.; protein 110 mg. per 100 ml.; sugar 84 mg. per 100 ml.; and chloride 730 mg. per 100 ml. The urinary excretion of lead was 0·27 mg. per litre, and radiography of the long bones accorded with a diagnosis of plumbism. A history of pica was elicited on further inquiry, the patient having stripped and eaten the paint off a wall during the past month. A sample of this paint contained lead in high concentration.

Improvement followed treatment with a high-calcium diet and vitamin D; and the excretion of lead in the urine fell to 0·08 mg. per litre in nine days. On discharge on March 14, the patient appeared healthy, with no evidence of cerebral damage ensuing from the encephalopathy. The hæmoglobin was 78%, and slight increase in density of lead lines was shown on repeated radiography of the bones.

Case 5.—A girl, aged 3 years, was admitted to the Westminster Children's Hospital on July 22, 1952. She had been pale and generally unwell for ten months. Her appetite was poor, she had lost weight, and had vomited repeatedly during the week before admission.

On examination she was pale, irritable, and drowsy. Apart from a moderate degree of papillœdema, no abnormality was detected in the nervous system. A radiograph of the skull revealed early separation of the sutures.

Investigations.—Lumbar puncture produced clear, colourless C.S.F. under more than 300 mm. pressure and containing 3 cells per c.mm.; protein 30 mg., sugar 75 mg., and chlorides 720 mg. per 100 ml. The Mantoux 1/1000 was negative. A blood-count showed Hb 50%, and 17,000 white cells per c.mm. with an absolute lymphocytosis. Anisocytosis, poikilocytosis, and hypochromia, but no punctate basophilia, were reported on blood smears. The bone-marrow was normal. Traces of protein and sugar were present in the urine, the deposit contained a few white cells, and the culture was sterile. X-ray examination showed dense lines at the ends of all long bones, and at the angles of the scapulæ. Five days after admission the urinary excretion of lead was 0·29 mg. per litre.

On further inquiry a history of pica was obtained; from the age of ten months she had gnawed her cot which had been repainted four months before admission. The paint was found to contain lead.

Progress.—After lumbar puncture vomiting ceased dramatically, papillœdema subsided slowly, and the patient has since been free from symptoms.

DISCUSSION

Polyneuritis

As a manifestation of lead poisoning in children, polyneuritis, observed in case 1, is much less common than encephalopathy and may occur without any cerebral symptoms whatever.

Ford (1945) states that the legs are usually more severely affected than the arms, and the distal muscles more than the proximal ones. Moreover, there is often definite tenderness of the muscles and even some degree of anæsthesia of peripheral type. Muscular cramps are very common.

Muscle pain and tenderness were undoubtedly present in case 1; but areas of anæsthesia to pinprick were not apparent, though the age of the patient precluded a critical evaluation of sensory changes.

Polyneuritis affecting the diaphragm has been recorded in children by Ford (1945) and Goodwin (1934). The extremities were completely paralysed, and the bulbar muscles involved; a fatal outcome resulted.

The diaphragmatic paralysis in case 1, with recovery after three weeks, seems to be unique.

Radiography in Diagnosis

The importance of radiography in the diagnosis of lead poisoning in children is emphasised by many workers. Heavy transverse bands at the growing ends of long bones may be found, however, in apparently healthy children, especially from the second to the fourth years of age, and these are identical radiographically with the lines which appear during chronic lead poisoning (Caffey 1950).

Endocrine disturbance, particularly hypothyroidism; healing rickets; scurvy; congenital syphilis; Albers-Schönberg disease; poisoning by phosphorus, bismuth, arsenic, and strontium; and excessive medication with vitamin P may all give rise to somewhat similar bands (Stammel 1941).

Evidence of toxicity may persist, notwithstanding regression, as in case 1, or even disappearance of radiological changes in the bones.

Radiographic appearances consistent with the diagnosis of plumbism were present in all five cases; the dense lines at the angles of the scapulæ of cases 3 and 5 were perhaps the most remarkable.

Punctate Basophilia

An increase of stippled cells in the blood, often regarded as the earliest sign of chronic lead poisoning, was minimal in case 3 and absent in cases 4 and 5. It prompted us, however, to suspect the diagnosis in case 1 and to elicit a history of ingestion of lead.

Though not a constant feature, punctate basophilia may also be found in leukæmia and in any severe anæmia (Whitby and Britton 1946).

Diagnosis

That radiographic findings and punctate basophilia alone cannot be recognised as pathognomonic of lead poisoning is evident from the foregoing remarks. The definitive diagnosis must be based on a history of ingestion or inhalation of lead and its demonstration in excessive amounts in the blood and urine.

Pica, a common prelude to plumbism, was exhibited by all five patients. Its diagnostic significance is emphasised by Burrows et al. (1951) and has been mentioned by other workers.

Apart from this symptom, no history of illness was elicited in case 2. The parents considered the patient healthy, and without the knowledge of a case of poisoning in the family admission to hospital and treatment of this child might have been long delayed.

It therefore appears permissible to suggest that, in this country, many similar cryptic cases of lead poisoning probably exist; the paucity of published reports does not reflect the potential danger to children of paint containing lead.

Serious complications, such as encephalopathy, can be averted only by early diagnosis and removal of the source of lead, and by education of the general public to this hazard.

SUMMARY

The potential danger of lead paint to children is emphasised, and 5 cases of poisoning are presented. In 1 complete recovery from diaphragmatic paralysis and bilateral foot-drop was observed. Fits were absent in 2 cases of encephalopathy, and in 1 the C.S.F. was normal.

Polyneuritis, an uncommon manifestation of plumbism in children, is briefly discussed.

Radiography in diagnosis is of value, but more definitive are the history of ingestion of lead and the blood-lead level.

Despite the paucity of published reports it is suggested that many cryptic cases of lead poisoning are probably in existence in this country, most of them arising from the ingestion of lead paint on cots.

We wish to thank Dr. Charles F. Harris for his encouragement and permission to publish cases 1, 2, 3 and 5; Dr. N. O. Richards for allowing us to report case 4; Dr. D. Graham Harvey for the blood-lead estimations; and Dr. D. Hunter for helpful advice.

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MANAGEMENT OF HYPOTENSION DURING ANÆSTHESIA

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THOUGH in the modern practice of anæsthetics the combinations of agents, the methods of administration, and the surgical procedures are numerous and often elaborate, there is a strong case for systematising the treatment of hypotension developing under anæsthesia. This is true especially where the onset is sudden; but, whether the onset is sudden or not, it is generally agreed that such hypotension must be counteracted. Sometimes, indeed, this treatment is more important than continuation of the operation; for without it the patient's cardiovascular system will fail and the operation become pointless.

The two features of the cardiovascular state which are readily and commonly measured are, of course, the blood-pressure (systolic and diastolic) and the pulse-rate.

A rise of blood-pressure during anæsthesia usually indicates maladministration of the anæsthetic rather than a cardiovascular response to physiological disturbances induced by the operation. The progressive hypertensions associated with raised carbon dioxide levels or those associated with anoxia are of this type. They should never occur; but, if they do, the treatment is never empirical but always directed towards removing the precipitating cause. Rare conditions such as phæochromocytoma and pituitary tumours, which may lead to a sudden rise of the blood-pressure, must be borne in mind.

A falling blood-pressure during anæsthesia is, however, a matter of extreme importance, and it is on this response that attention will here be focused. The condition may present in one of three ways:

I. Hypotension with a raised pulse-rate.
II. Hypotension with an unchanged pulse-rate.
III. Hypotension with a slowed pulse-rate.

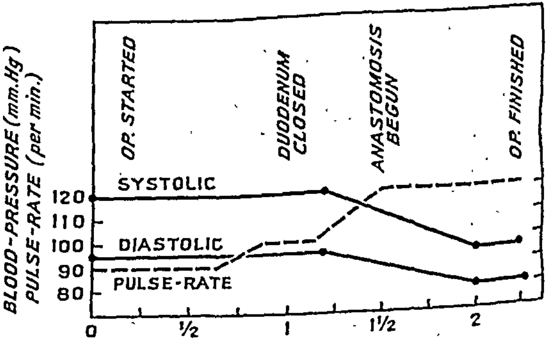

Fig. I—Hypotension with raised pulse-rate (group I) in patient, aged 51, anæsthetised with thiopentone, curare, and oxygen and ether, and undergoing partial gastrectomy. Note pulse-rate began to rise before blood-pressure began to fall. No undue hæmorrhage or trauma was present. No treatment was given for hypotension.

Where the blood-pressure falls suddenly during anæsthesia the pulse-rate at the time will indicate the immediate treatment.

PHYSIOLOGY

The blood-pressure in a normal person is the product of two variables, the cardiac output and the peripheral resistance:

B.P. = C.O. × P.R.

The peripheral resistance is determined by the degree of vasomotor tone, and the cardiac output by a further three variables—namely, the venous return, the force of contraction, and the heart-rate.

From the relationship B.P. = C.O. × P.R. it follows that a sudden fall in blood-pressure must be due either to a sudden falling-off of cardiac output or to a sudden relaxation of vasomotor tone in the peripheral circulation, or to both. There are therefore four physiological disturbances which may lead to acute hypotension:

(1) Reduction in vasomotor tone (peripheral resistance).
(2) Reduction in venous return
(3) Reduction in force of contraction } (cardiac output).
(4) Changes in heart-rate

In the normal person a slight alteration in either the cardiac output or the peripheral resistance will be met by some reflex compensatory mechanism, and no recordable change in the blood-pressure will be seen. It is only when these compensatory mechanisms either break down or become fully expended that the signs of circulatory collapse become evident. The compensatory mechanisms which play the greatest part in maintaining a normal blood-pressure in the face of impending hypotension are increasing heart-rate and increasing peripheral vasoconstriction.

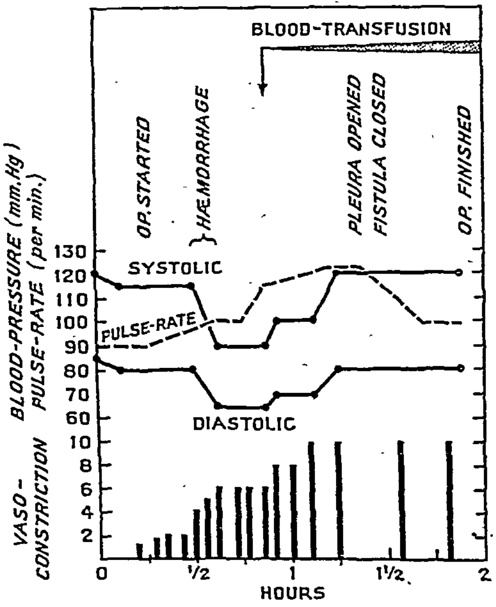

Fig. 2—Hypotension with raised pulse-rate (group I) in patient, aged 37, anæsthetised with thiopentone, gas-and-oxygen, and curare, and undergoing postpneumonectomy thoracoplasty and closure of fistula. Hæmorrhage occurred after $^1/_2$ hr. and accentuated fall of blood-pressure. Note response to blood-transfusion. Vasoconstriction was measured with a digital plethysmograph.

HYPOTENSION WITH A RAISED PULSE-RATE
(Group I)

Figs. 1 and 2 show changes in pulse-rate and in blood-pressure during two operations.

In fig. 1 it is seen that after 40 minutes there was a rise in pulse-rate, followed some 30 minutes later by a progressive decline in blood-pressure. This is a well-known and characteristic response, which may occur where there is no undue anæsthetic depression or maladministration, and where there is no great surgical trauma or hæmorrhage—though its onset may be hastened or precipitated by such factors.

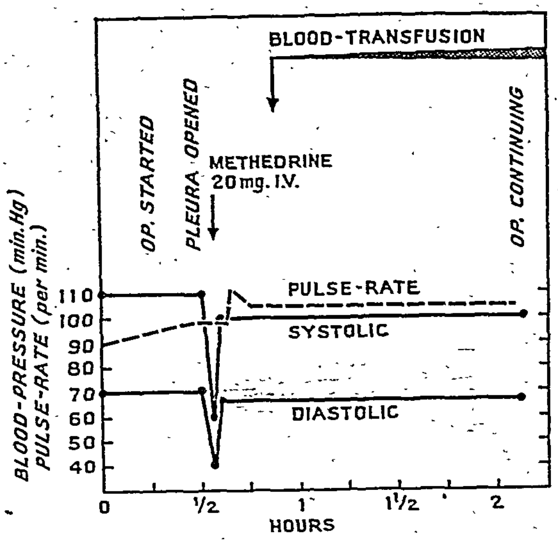

Fig. 3—Hypotension with unchanged pulse-rate (group II) in patient, aged 58, anæsthetised with thiopentone, curare, and gas-and-oxygen, and undergoing transthoracic gastrectomy. Note response to intravenous methedrine 20 mg. Blood-transfusion was begun after 50 minutes in anticipation of group-I response, because pulse-rate had begun to rise.

Fig. 2 shows a similar type of response with the vasoconstriction recorded by means of a digital plethysmograph. Vasoconstriction began before the pulse-rate started to rise, and after 30 minutes the blood-pressure fell sharply as hæmorrhage took place. The heart-rate increased progressively, and so did the degree of vasoconstriction; but these two mechanisms, although they prevented further fall in the blood-pressure, did not restore it to normal. Blood-transfusion was instituted after 15 minutes' hypotension, and gradually the blood-pressure returned to normal, while the pulse-rate eventually decreased. The vasoconstrictor tone was maintained but did not increase further, once the transfusion became effective.

The explanation of this group-I response is physiological. Refer to the complex B.P. = C.O. × P.R. The cardiac output becomes reduced, largely because of the reduction in venous return, which occurs in any curarised or otherwise relaxed person whose active respiratory movement is depressed. There is a compensatory increase in heart-rate together with a compensatory increase in vasoconstriction. These two factors combined suffice, for a time, to maintain a normal blood-pressure. After a variable period, however, the compensatory mechanisms become fully expended and the blood-pressure begins to fall.

The venous return during anæsthesia has in the past received less than its share of attention. In modern anæsthetic practice the use of relaxant drugs produces a person whose muscle tone is, on occasion, virtually nil and whose respiratory excursion and efforts are minimal, being often manually assisted by some degree of positive pressure during inspiration. The venous return depends largely on muscle tone and the intrathoracic negative pressure during inspiration, and under such conditions it will inevitably decrease, with consequent reduction in cardiac output.

One other point should be emphasised. Among the general pharmacological effects of anæsthetic drugs is the decrease of peripheral vasomotor tone, either by direct peripheral action or by medullary depression. In the deeper planes of anæsthesia, therefore, the compensatory vasoconstriction discussed above may not occur, and hypotension will therefore come on earlier. On the other hand, if active vasodilatation occurs as a result of anæsthesia, it may happen that the peripheral blood-flow, and therefore the venous return, is enhanced, with the result that there is less tendency for the cardiac output to fall off. The physiological balance is at all times the deciding factor. If the relaxant drugs are used, *and only light anæsthesia is maintained,* this effect will not become evident so readily.

Whatever the exact mechanism of this response, the treatment is always to improve the cardiac output. The most physiological means of doing this is to increase the venous return by posture or by infusion of whole blood or whatever blood substitute is favoured. The response to blood-transfusion is shown in fig. 2.

This type of response is well known to all clinical anæsthetists, and its mode of onset is only rarely as acute as that of the hypotensions to be described below *(groups II and III). Such an acute onset may, however,* be seen. Immediately after induction of anæsthesia there may be acute cardiovascular collapse, with severe hypotension and tachycardia. The basic physiological explanation is the same as before: the falling blood-pressure is the direct result of a lowered cardiac output. The only difference in this instance is that the precipitating cause of the lowered output is different. Instead of the decreased venous return we now have a diminished force of contraction, perhaps due to overdosage with or without medullary depression, or perhaps due to disease of the myocardium. The exact mechanism is of less consequence than the immediate treatment. This treatment is, in principle, the same as before—namely, to improve the cardiac output. In such an emergency intravenous therapy may be too slow a remedy, and it is in such instances that cardiac analeptics and medullary stimulants, such as adrenaline and nikethamide, have their place in anæsthesia.

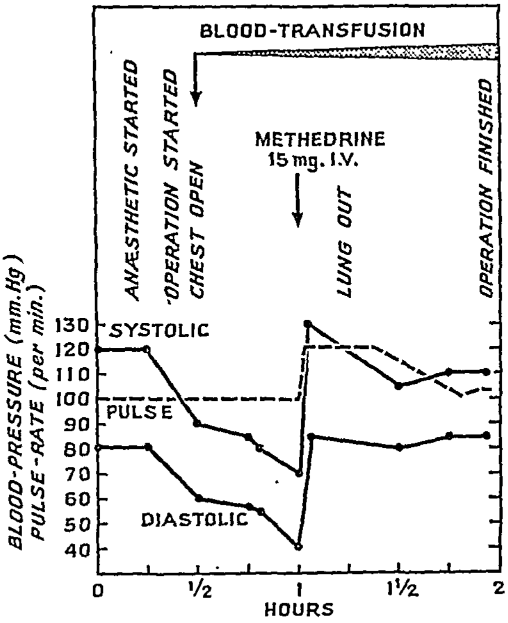

Fig. 4—Hypotension (less acute than in fig. 3) with unchanged pulse-rate (group II) in patient, aged 48, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, and undergoing pneumonectomy. Note absence of response to blood-transfusion and good response to intravenous methedrine 15 mg.

The group just described is an extensive one, with many factors at work. The treatment, however, rests on a single physiological factor—the cardiac output. We may, in fact, say:

> Where anæsthetic hypotension is associated with an increase in pulse-rate, the treatment should be directed towards increasing the cardiac output.

In this type of response the use of vasopressor agents, such as 'Methedrine' and *l*-noradrenaline, is unsound. Compensatory vasoconstriction takes place quite automatically, and it is only when this mechanism becomes exhausted that the hypotension appears as a clinical sign of failure. The degree of vasoconstriction present in the patient at this time will already be high, and pure vasoconstrictor drugs will do little to increase it.

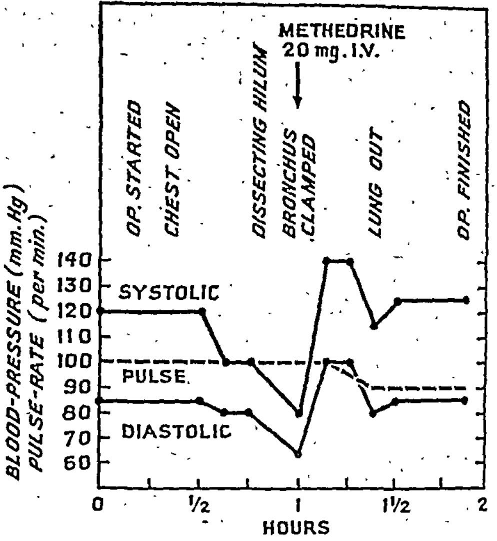

Fig. 5—Hypotension with unchanged pulse-rate (group II) in patient, aged 54, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, and undergoing pneumonectomy. Note hypotension took 30 minutes to become fully developed and steady pulse-rate fell when vasoconstriction, effected with intravenous methedrine, improved venous return.

HYPOTENSION WITH AN UNCHANGED PULSE-RATE
(Group II)

Increasing the heart-rate will not improve cardiac output unless the venous return to the right side of the heart is increased sufficiently to keep the myocardium adequately stretched during the shortened diastole.

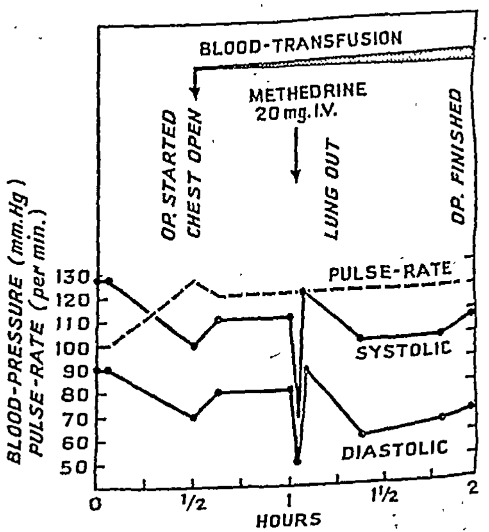

Fig. 6—Hypotension of both group I and group II in patient, aged 47, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, and undergoing pneumonectomy.

The venous return is, as already mentioned, maintained by muscle tone and respiratory movement, and improved by vasoconstriction. In the normal person the degree of vasomotor tone in the arteriolar bed will therefore influence the venous return.

Reduction in vasoconstrictor tone will lead to a lowering of the pressure within the peripheral circulation and hence to a reduced pressure head behind the venous flow. The venous return will therefore decrease, and so, in consequence, will the cardiac output. Increase of heart-rate is therefore not seen, for without adequate venous filling it will not improve output.

Fig. 3 is the record of cardiovascular changes in a man, aged 58, undergoing thoracotomy for total resection of the stomach. After the pleura was opened, the systolic and diastolic blood-pressures fell sharply, but the pulse-rate remained at its previous level. This hypotension could not be due to a primary falling off of cardiac output, since compensatory vasoconstriction would have occurred, and the resulting improvement in venous return would have led to an increase in heart-rate. Administration of a vasoconstrictor drug (in this instance intravenous methedrine 20 mg.), produced the necessary increase in vasomotor tone, and the blood-pressure returned to a more normal level. Some tachycardia was seen and was perhaps due to the slight cardio-stimulant action of the methedrine.

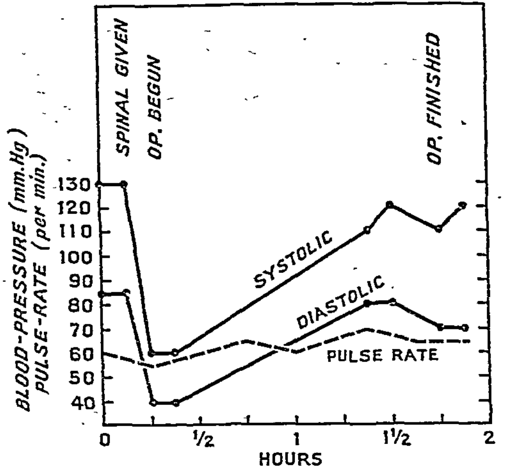

Fig. 7—Severe hypotension induced by spinal anæsthetic (heavy 'Nupercaine' 2 ml.) in patient, aged 69, anæsthetised with thiopentone, gas-and-oxygen, and spinal nupercaine, and undergoing herniorrhaphy. No vasoconstrictor was used.

Fig. 4 illustrates the effect of treating this type of response with blood-transfusion. The blood-pressure began to fall shortly after the induction of the anæsthetic, but intravenous blood did little to combat it. The pulse remained steady. After 50 minutes a vasoconstrictor drug was given with an immediate response, which was maintained for the remainder of the operation.

In the first example the sudden fall in blood-pressure may have been due to the opening of the pleura with its possible attendant complications. In the second example the anæsthetic or its method of administration may be suspect. Figs. 5 and 6, however, show how this response may appear either suddenly or less acutely during an operation without any apparent precipitating factor.

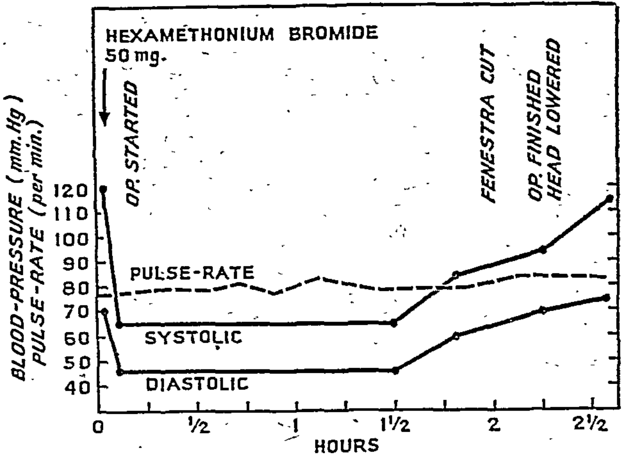

Fig. 8—Hypotension artificially induced with hexamethonium bromide in patient, aged 46, anæsthetised with thiopentone, gas-and-oxygen, and 'Trilene,' and undergoing fenestration. Note pulse-rate reasonably steady.

Other examples of this type of response are seen with high spinal block, or when "controlled circulation" is used with the aid of hexamethonium or similar hypotensive agents.

Fig. 7 illustrates the response to spinal block where no vasopressor is used. The blood-pressure was considerably reduced by sympathetic paralysis, but carbon dioxide retention and anoxia were avoided and little hæmorrhage took place; hence the pulse-rate did not increase. Clearly the use of a vasopressor in this instance would have restored the blood-pressure to a more reasonable level.

Fig. 8 shows hypotension caused by hexamethonium bromide. The blood-pressure was considerably lowered but again the pulse-rate remained steady.

Both spinal block and hexamethonium lead to either a localised or a generalised vasodilatation. In both cases the peripheral resistance *and* the cardiac output are reduced and hypotension results. Restoration of the vasomotor tone restores normal vascular tone, and circulatory efficiency is once more produced. Hence:

> Where anæsthetic hypotension is unaccompanied by any alteration in heart-rate the initial treatment should be directed towards improving vasoconstrictor tone.

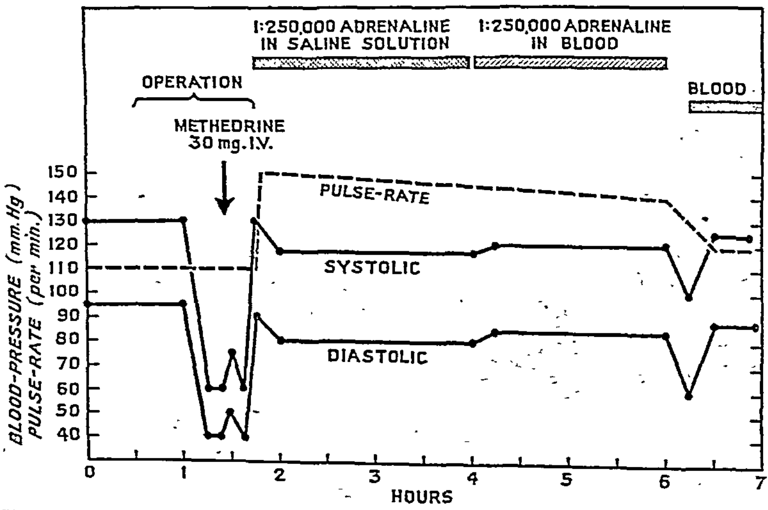

Fig. 9—Treatment of peripheral circulatory collapse with adrenaline drip in patient, aged 42, anæsthetised with heavy nupercaine (spinal) 1·8 ml., thiopentone, and gas-and-oxygen, and undergoing laparotomy and colostomy. In spite of severe fall in blood-pressure towards end of operation, pulse-rate remains steady until adrenaline produces tachycardia.

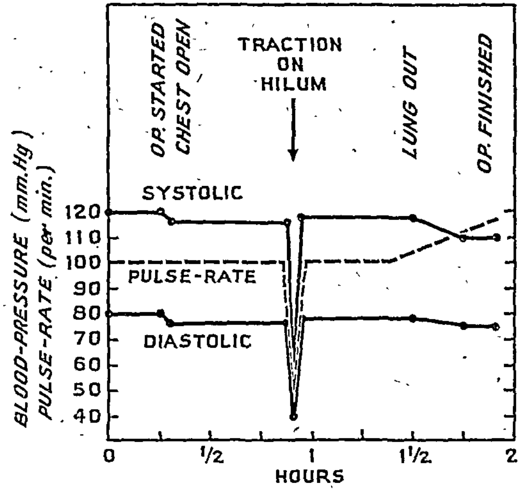

Fig. 10—Transient hypotension with slowed pulse-rate (group III) caused by traction on hilum of lung during pneumonectomy in patient, aged 24, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare. No treatment necessary.

Sometimes it does seem necessary to maintain the vasoconstrictor therapy for a long time. The term "peripheral circulatory failure" has been applied to this same picture when the hypotension is prolonged. Repeated injections of methedrine or adrenaline or *l*-noradrenaline by intravenous drip may be required. Fig. 9 illustrates this type, a case of this kind in which adrenaline was used. *l*-Noradrenaline appears to be more effective and to lead to less tachycardia.

HYPOTENSION WITH A SLOWED PULSE-RATE
(Group III)

This is the so-called "vagal overaction" group.

Since the vagus is the cardio-inhibitory nerve, stimulation of the efferent motor side, or of the afferent sensory one, may lead to slowing of the heart or even to actual inhibition. Hypotension associated with bradycardia may result from vagal stimulation from any cause.

The physiological mechanism is threefold. Vagal stimulation may lead to bradycardia, lessened force of contraction, or peripheral vasodilatation due to inhibition of the vasomotor centre. The fact that any one of these factors can by itself lead to hypotension by disturbance of the B.P. = C.O. × P.R. complex will be appreciated from what has been said before. The combination of all of them acting together, or of the first two only, will on occasion make treatment necessary.

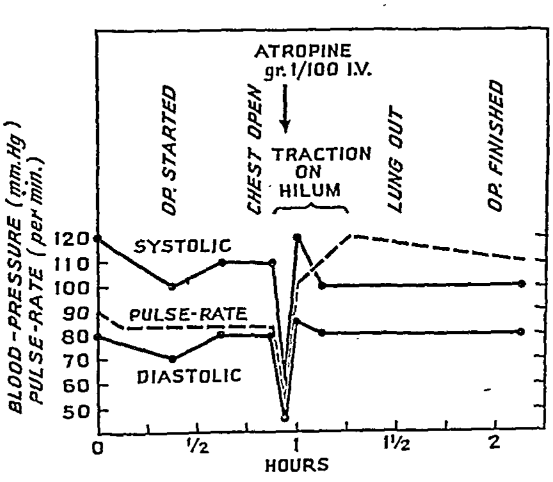

Fig. 11—Hypotension with slowed pulse-rate (group III) caused by traction on hilum of lung during pneumonectomy in patient, aged 37, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, showing response to atropine.

Figs. 10 and 11 illustrate this vagal overaction where the precipitating cause was traction on the hilum of a lung. Fig. 12 illustrates the same phenomenon where the initial trauma was dissection of the œsophagus.

In the case illustrated in fig. 10 the traction was transient and cessation of the stimulus led to a return of the pulse-rate and blood-pressure to normal. In the case illustrated in fig. 11 the traction was maintained longer, but pharmacological vagal block with intravenous atropine restored the picture to normality very rapidly, and indeed there was tachycardia when the vagal influences were removed. An intravenous dose of gr. $^1/_{100}$ seems to be sufficient to inhibit the vagal influence in such instances.

The existence of a slow heart-rate from the beginning, either before induction or during the progress of the operation, suggests that the patient may be more likely to exhibit these vagal responses. Moreover this vagal overaction is seen mostly in lightly anæsthetised patients; and, since it is common practice today to maintain these light planes of anæsthetic depression when relaxant drugs are being used, it will develop more often than in the past.

The stimulus which precipitates these vagal manifestations need not, of course, be intrathoracic: indeed direct mechanical stimulation of the vagus nerve rarely leads to this response. It is usually the afferent nerves which bring about reflex vagal hypotensions. The afferents may be direct vagal ones—e.g., from the lung hilum—or they may be visceral afferents from the abdomen and pelvis, and this response has been seen as a result of cutaneous stimulation in a highly susceptible person. Hence:

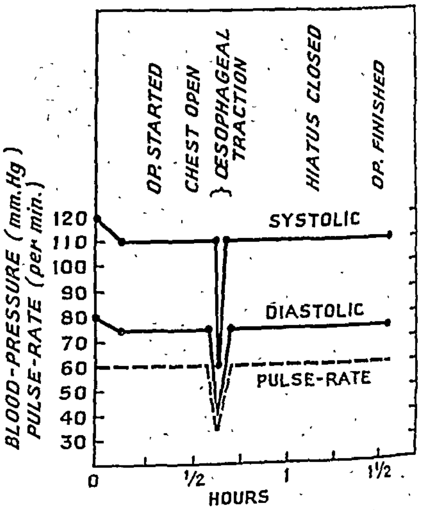

Fig. 12—Transient hypotension with slowed pulse-rate (group III) in patient, aged 41, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, and undergoing repair of hiatus hernia. Note initial bradycardia typical of patients who develop this type of hypotension.

> When anæsthetic hypotension is accompanied by a slowing of the pulse-rate, the most effective treatment is pharmacological vagal block.

DISCUSSION

The management of anæsthetic hypotension may be an emergency problem. For this reason I have classified it in the three above-mentioned groups together with the appropriate treatment. Occasionally, however, there is difficulty in allotting a particular response to its correct group. In such cases the most effective line of treatment can only be decided on clinical judgment.

As is to be expected, the picture is sometimes clouded by tachycardia from other causes, but it is not the *absolute* pulse-rate which is important. It is of no great consequence whether the pulse-rate is 80 or 110 at the outset of the operation. What does matter is the fluctuation from the original rate, if and when the

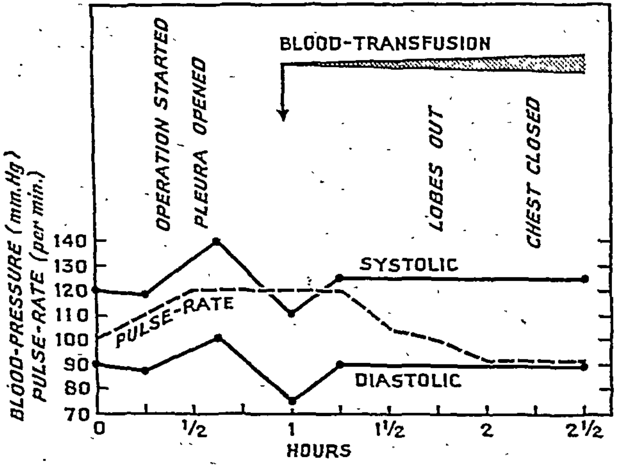

Fig. 13—Atypical form of group-I hypotension in patient, aged 23, anæsthetised with thiopentone, pethidine, gas-and-oxygen, and curare, and undergoing lobectomy. Fall in blood-pressure is preceded by a rise associated with raised pulse-rate. There was no accumulation of carbon dioxide.

blood-pressure begins to fall. It is this *alteration* in rate which gives the clue to the precipitating mechanism and therefore to the best form of treatment.

Some of these responses may be so transient as to be overlooked—as with the vagal traction reflexes. They may appear and pass off and not be noticed unless the pulse-rate is closely observed throughout.

The expression "shock" has not been used. It has been avoided deliberately. The word is confusing and gives no indication of the mechanism of the disturbance. Moreover, it has led in the past, and unfortunately sometimes still leads, to the treatment of all hypotension during operation by blood-transfusion. Such treatment is appropriate only for hypotension resulting from lowered venous return (group I).

Some still believe that, unless bleeding has taken place, transfusion is not called for; but nothing could be further from the truth. There can be few operations necessitating extreme muscular relaxation and lasting an hour and a half or more which do not tax the compensatory vasoconstrictor mechanism of the patient very considerably.

Where there is accumulation of carbon dioxide within the circulation, the blood-pressure may be artificially maintained, and there may even be a rise in blood-pressure. The so-called cyclopropane shock may be explained upon this basis: a raised blood-carbon dioxide level (due to respiratory depression, and perhaps to inefficient absorption in a closed circuit) maintains the patient's blood-pressure until administration is discontinued, but as soon as carbon dioxide is eliminated the patient develops hypotension. Carbon dioxide build-up may also be the cause of the somewhat atypical group-I responses which are sometimes seen (fig. 13).

An alternative explanation of this picture is, however, suggested by the possibility of overcompensation due to excessive vasoconstriction. Whatever the reason, this example serves to emphasise the final point: however many generalisations are made from clinical observation, there is always the need for individual assessment of each case. It may prove the exception to the rule.

SUMMARY

The development of hypotension during an operation under anæsthesia should be regarded as an emergency.

Such hypotension can be divided into three groups: (1) with a raised pulse-rate; (2) with an unchanged pulse-rate; and (3) with a slowed pulse-rate. If the blood-pressure falls suddenly, the patient's pulse-rate at that time indicates the immediate treatment.

Hypotension with a raised pulse-rate is due to reduction of the cardiac output, largely because of reduction of the venous return. So the treatment aims at increasing the venous return by posture or by blood-transfusion. Sometimes the cardiac output is reduced owing to insufficient contraction of the heart, perhaps due to overdosage with anæsthetic. Blood-transfusion would then act too slowly, and treatment should be with cardiac analeptics and medullary stimulants. In both these forms of hypotension the treatment aims at increasing the cardiac output.

Hypotension with unchanged pulse-rate is due to reduction of vasoconstrictor tone. Therefore treatment should be directed towards improving that tone with such drugs as methedrine and adrenaline.

Hypotension with slowed pulse-rate is due to overstimulation of the vagus nerve, when the most effective treatment is pharmacological vagal block with atropine.

I am indebted to Dr. B. L. S. Murtagh for his encouragement and helpful criticism in the preparation of this paper.

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PRIMARY CLOSTRIDIAL PNEUMONIA

REPORT OF A CASE

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Clostridial infection of the lungs and pleural cavity is common in war surgery (it accounted for 10% of all infected hæmothoraces in the 1914–18 war) and not uncommon in civilian practice, when it occurs either as a secondary infection in chronic pulmonary disease or as an intrapleural infection following lobectomy. But I have not been able to find any record of a primary clostridial pneumonia which behaved as a lobar pneumonia, without lung gangrene, followed by clostridial empyema.

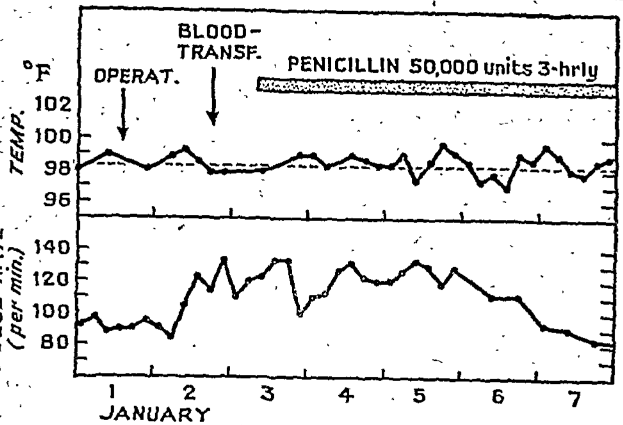
CASE-RECORD

Miss A, aged 52, was admitted to Bromley and District Hospital on Dec. 8, 1947, with duodenal ulcer of 15 years' duration, for which she had had previous medical treatment. She had also had nasal catarrh for some years, for which she had undergone submucous resection of the nasal septum, with poor result. In the past year she had vomited frequently, sometimes once or twice a day, and radiography after a barium meal on Oct. 28, 1947, suggested that there was an old duodenal ulcer with pylorospasm or stenosis. It was thought that partial gastrectomy would be necessary; but, owing to the nasal infection, medical treatment was continued for three weeks. The vomiting became less, but the pain increased in intensity, and it was decided to operate.

A blood-count on Dec. 30, 1947, showed red cells 4,850,000 per c.mm., Hb 93%, and colour-index 0·96.

Operation and Postoperative Course

On Jan. 1, 1948, a Polya type partial gastrectomy with antecolic anastomosis was done. At the end of the operation and throughout the following night the patient's condition was excellent, and at 8.30 A.M. on Jan. 2 her pulse-rate was steady at about 86. She then began to look ill, and her pulse-rate rose rapidly, reaching 120 by noon. Since only a little blood had been aspirated through the Ryle's tube, intra-abdominal hæmorrhage was suspected, and a pint of group-O4 blood was transfused, but a blood-count later on the same day showed red cells 4,789,000 per c.mm., Hb 88%, and colour-index 0·92. The blood was Rh-positive.



Association of rapid pulse-rate with low temperature.

By the morning of Jan. 4 the patient had a fulminating pneumonia at the left base. Parenteral penicillin 50,000 units three-hourly was prescribed, with sulphamerazine gr. 2 four-hourly for twelve hours and then gr. 1 four-hourly.

Course of Pneumonia

The temperature at this stage rarely rose above 99°F, and the patient's general condition was regarded as very grave. The accompanying figure shows the disparity between the pulse-rate and the temperature.

Jan. 8.—A blood-count showed red cells 3,000,000 per c.mm., and Hb 62%, but the general condition was improving steadily.

Jan. 11.—Penicillin discontinued.

Jan. 12.—A blood-count showed red cells 1,480,000 per c.mm., and Hb 34%. Two pints of group-*O4* blood was transfused; but two days later a blood-count showed only moderate improvement: red cells 2,500,000 per c.mm., Hb 50%, and white cells 45,000 (polymorphs 88%). A further two pints of blood was given.

Jan. 18.—The pulse-rate, which had fallen to about 100 on the fifth postoperative day, now rose again and the temperature began to swing. There was bronchial breathing at the left base, with stony dullness and tenderness over the ribs. Treatment with parenteral penicillin 100,000 units three-hourly was begun again.

Jan. 24.—Aspiration produced 20 ml. of opalescent straw-coloured fluid, for which was substituted 100,000 units of penicillin. Culture of the fluid yielded a scanty growth of *Clostridium welchii* sensitive to penicillin.

Jan. 26.—About 150 ml. of stinking pus was aspirated, for which was substituted 350,000 units of penicillin. Culture yielded a profuse growth of *Cl. welchii*. By this time considerable œdema and tenderness had developed in the left chest wall posteriorly, and the patient complained of a good deal of pain.

Jan. 27.—A blood-count showed red cells 3,900,000 per c.mm., and Hb 70%. A fourth transfusion (2 pints) was given. Treatment with anti-gas-gangrene serum, 10,000 units twice daily, was started and continued until Feb. 5. The patient began to cough up thick offensive mucopurulent yellowish sputum. A direct stained film showed many pus cells, gram-positive cocci, and a few gram-positive bacilli. Cultures yielded a fair growth of coliform organisms, hæmolytic streptococci of Lancefield group C, and a scanty growth of *Cl. welchii*.

Jan. 31.—Her condition was deteriorating, the œdema of the chest wall was spreading, and she again complained of pain. A third aspiration produced 150 ml. of similar pus. No penicillin was substituted.

Feb. 1.—There was localised subcutaneous emphysema of the chest wall at the site of the aspiration, and it was feared that the infection had spread to the chest wall, but this disappeared in a few hours, and did not recur.

Feb. 3.—A fourth aspiration produced 40 ml. of pus and 350,000 units of penicillin was introduced. In a search for the original focus of infection a nasal swab was taken which on culture yielded a heavy growth of *Cl. welchii* and a fair growth of coagulase-positive *Staph. aureus* and fæcal streptococci.

Feb. 6.—Despite several attempts at aspiration, no pus was located. Henceforth the patient began to improve rapidly; the pain in her chest disappeared, and her appetite returned. The anti-gas-gangrene serum was discontinued on Feb. 5, and the penicillin on Feb. 13.

Feb. 25.—Patient was discharged to her home.

Follow-up

On March 8 she felt well but "shaky." There was still some discomfort in the left chest which prevented her from inhaling deeply. She could take a normal diet without discomfort, so long as she avoided a heavy meal. Radiography showed that the left lung was mainly clear, with overlying residual pleural thickening and an obscured left costophrenic angle. A nasal swab was negative for *Cl. welchii.*

COMMENTS

It is fairly evident from the bacteriological findings that in this case of clostridial pneumonia the infection came from the nose.

The sudden increase of pulse-rate to 120, accompanied by low temperature (97°–99°F) and intense toxicity, caused some confusion until *Cl. welchii* was identified. It was then seen that the infection followed the general pattern of other clostridial infections.

In eleven days the amounts of hæmoglobin decreased from 93 to 34% and the erythrocyte-count from 4,850,000 to 1,480,000 per c.mm.

Two courses of parenteral penicillin, to a total of 18,500,000 units, and one course of anti-gas-gangrene serum, to a total of 140,000 units, were given. In addition, penicillin 800,000 units was injected into the abscess cavity, and a nasal spray containing 30,000 units per ml. was used four or five times daily from Feb. 4 until the day before discharge from hospital.

Throughout this illness, the partial gastrectomy gave no trouble whatsoever. The patient vomited once only, at the end of four days' sulphamerazine therapy, which was immediately discontinued.

Much suffering to the patient, and anxiety of the doctors and nurses could, I believe, have been avoided if her nose had been swabbed before the operation. The penicillin spray succeeded in eliminating the infecting organism from the nasal discharge at least temporarily. Had this been done preoperatively and supplemented by a prophylactic course of parenteral penicillin, continued through the early postoperative period, she would probably have had an uneventful convalescence.

My thanks are due to Dr. John Keall and Dr. A. C. Glendinning for their keen interest and the considerable amount of work done in the pathological and radiological departments respectively. Also to Mr. W. P. Greening for his persistent advice to avoid, at all costs, open drainage of the empyema cavity.

Preliminary Communication

EXPERIMENTAL DEPLETION OF POTASSIUM IN MAN

More than 97% of the body potassium is intracellular, and deficiency of potassium affects mainly the intracellular compartment. It may result from excessive *loss, deficient intake, or increased need.* An increased need arises when the volume of intracellular fluid is expanded, as with the laying down of glycogen. In this instance there is an increased need for other constituents of intracellular fluid as well, such as phosphate. But when deficiency of potassium arises from simple loss or lack of the ion, it is not clear whether other constituents of intracellular fluid, such as phosphate and water, are lost, to preserve the composition of intracellular fluid at the expense of its volume. Potassium deficiency is usually compensated by entry of sodium into cells and accompanied by alkalosis.

Potassium deficiency has not been much studied by experiment in man. Its clinical significance and the nature and importance of compensatory mechanisms remain ill defined. Black and Milne[1] induced moderate deficiency of potassium by removing potassium from their fluid diet with an exchange resin ('Zeo-Karb 225 Na'). The place of potassium in the diet was taken by sodium. The experiments were perforce of short duration; the deficiency of potassium was largely due to renal losses while the kidney adjusted to the low intake; the intake of sodium was liberal (about 300 mEq. per day).

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[1] Black, D. A. K., Milne, M. D. *Lancet*, 1952, i, 244.

We have induced deficiency of potassium by eating the resin in H or NH_4 form for 12 or 16 days while taking a normal and constant diet. The deficiency of potassium was largely due to fæcal losses, which exceeded the dietary intake. The intake of sodium was about 200 mEq. daily, and absorption of sodium was partly prevented by the resin.

There were three experiments (F1, W, and F2). The procedure has previously been described.[2]

RESULTS

The results are based on the differences between balances in the control periods and those in the treatment and recovery periods. They are presented cumulatively in the accompanying table. The deficiency of potassium calculated in this way amounted to 338 mEq. in F1, 674 mEq. in W, and 839 mEq. in F2. In W and F2 this would correspond to some 28% of the exchangeable potassium in the body. Although the resin took up some sodium, sodium balance was maintained, because renal conservation of sodium was efficient. On the other hand, an excess of sodium was not available to take the place of potassium. The loss of potassium was accompanied by a moderate acidosis, and the plasma CO_2 fell to 17, 12, and 15 mEq. per litre in F1, W, and F2. The acidosis was possibly due to the loss of cation—i.e., potassium—rather than to a gain of anion resulting from any failure of the kidneys to excrete the excess of anion over cation absorbed from the gut. It was accompanied by the loss of 2 or 3 litres of fluid. Most of this was from cells, as calculated from the chloride balance, the serum-chloride, and the changes in water excretion. There was also some loss of phosphate and of nitrogen. The loss of nitrogen, representing breakdown of protoplasm, accounted for some of the loss of phosphate (see table). In proportion to the composition of intracellular fluid these losses were not of the same order as the loss of potassium; they were of the magnitude seen in acidosis without depletion of potassium. The subjects felt and looked very ill, took their diet with extreme difficulty, and became absent-minded and then confused. Some features, such as thirst, hæmoconcentration, and a raised serum-sodium level, suggested a state of water deprivation, but the changes were not corrected by a free intake of water.

CUMULATIVE BALANCES OF K, N, P, Na, Cl, AND WATER

	At end of resin period			At end of recovery period	
Experiment	F1	W	F2	F1	F2
Duration of period (days)	16	12	16	8	12
K (mEq.)	−338	−674	−839	−122	−692
N (g.)	−18·7	−13·1	−27·1	−18·0	−36
P (g.)	−2·6	−5·1	−3·2	−0·8	−1·3
Na (mEq.)	+346	−98	−28	+748	+855
Cl (mEq.)	+238	−48	−144	+308	+252
Water (litres)	+0·5	−3·0	−3·1	+3·6	+1·8

In protoplasm K (mEq.) : N (g.) : P (g.) :: 2·7 : 1 : 1/15.

When the administration of resin was stopped, sodium and potassium were again available for absorption. Retention of potassium was maximal but limited by the amount available in the diet (38, 36, and 31 mEq. daily); hence deficiency of potassium was present for the duration of the observations. Retention of sodium was maximal for a few days and at first occurred without chloride. Thus sodium entered cells. Within a few days the acidosis receded and the plasma CO_2 rose some 6 or 7 mEq. per litre above control values. This change was the same for the very different amounts of potassium lost in F1 and F2. The loss of nitrogen incurred with resin was not made good during the recovery period, though the intake of protein was adequate (74, 66, and 79 g. daily). The intracellular dehydration was corrected, and loss of phosphate was restored except for a fraction accompanying nitrogen. These changes were followed or accompanied by a gross increase in the volume of extracellular fluid: W, in whom we had had to stop collecting balance data, developed œdema of the legs and face. With the exception that F2 had tetanic carpal spasms for a few days, symptoms were not dramatic in the recovery period. The subjects were morose, apathetic, and tired easily. They still had no desire to eat.

On the day that experiment F2 ended, the subject of the experiment lacked some 600 mEq. of potassium. He did not know this and drove to North Wales. He went hill walking on the same day. He found the mental and physical effort no more than trying, but he was unaccustomedly breathless on going uphill. The only definite electrocardiographic changes in these experiments was the appearance of prominent U waves.

CONCLUSIONS

Depletion of potassium is not necessarily accompanied by an equivalent loss of other constituents of intracellular fluid.

The alkalosis of potassium deficiency may not occur without retention of sodium; even with retention of sodium the alkalosis may be slight, though depletion of potassium is great. Retained sodium enters cells but also causes an increase in extracellular fluid, and œdema may result.

If sodium is retained in place of potassium, symptoms may be neither severe nor urgent, but apathy and anorexia may be prominent. Lack of potassium may limit retention of nitrogen.

The body can lose large amounts of potassium; and, unless potassium salts are given, restoration may be very slow. We agree with Black and Milne[1] that, when possible, the oral route is to be preferred.

We are indebted to the Medical Research Council for a grant for expenses, and to Prof. L. J. Witts in whose department this work was done.

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"The theory of probability which was born out of problems that arise in connexion with gambling has become one of the most abstract departments of mathematics. The offspring of a practical need, to ascertain the rules governing the behaviour of collections with a view to manipulating them in ways conformable to our wishes (in short, to make money), the science of probability has transcended its origins and is now pursued for the intellectual satisfactions with which it delights its devotees. In this respect its development has been contrary to that of most of the sciences which, starting from the impulse to find out, are to-day carried on from the wish to modify and control, as the desire for knowledge increasingly gives way to the desire for power."—*Times Literary Supplement*, Aug. 8, 1952, p. 514.

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[2] Fourman, P. *Ibid*, p. 1042.

Reviews of Books

Solitude and Privacy

PAUL HALMOS, B.A., PH.D. London: Routledge & Kegan Paul. 1952. Pp. 181. 21*s.*

DOCTORS are enjoined nowadays to study not only the "whole man" but a good part of his environment as well. Those who are conscientious, especially if their interest is in social medicine or psychiatry, can be advised to try Dr. Halmos's book as a good example of the scope, method, and interest of this branch of knowledge. But they may find it rather hard going. There are words whose meaning they once knew but have probably forgotten; there is the vice (not unknown in their own field) of preferring the abstract word to the concrete; and there is an erudition which may give the ordinary medical reader an uncomfortable feeling of illiteracy. Nevertheless, he who persists will find the general conception original, the ideas stimulating, and the treatment of man's destiny essentially poetic.

Dr. Halmos holds that none of the scientific triumphs in the conquest of space has really changed the human sense of loneliness, or the longing for communion and "mystical participation" both with our fellows and with some suprahuman company of saints. His theme is that throughout history the growth of "culture" (the word is used to mean the standardising of social patterns and the mechanising of means of production) has resulted in a progressive "desocialisation" of the members of human communities. The more we are together, the less happy we seem to be. The pattern of the choral dance, evolved in prehistoric times, prevailed until the 18th century, and provided occasions for that merging of the one with the many, and for the experience of ecstatic states, which he believes to be not only a craving but a need. He contrasts with this the "taxi dance halls" of contemporary Chicago, where "there is little conversation, the patron may sit for hours besides others of his sex without conversing with them. The girls, likewise, stand for long periods without speaking. . . ." These halls epitomise the modern city, "in which the criteria of life are mobility, impersonality and anonymity." He makes the same sort of analysis of drinking habits. The consumption of alcoholic beverages cannot be traced over the same long period, but the evidence suggests (apart from a peak associated with the miseries of 19th-century urban life) a declining trend. Dr. Halmos holds with Belloc and Housman that "Beer does more than Milton can to justify God's ways to man," and that our modern tendency to substitute cola drinks, the cinema, and television is one more step towards imprisoning the human soul in its own ego. He also discusses ways in which modern psychiatric techniques break down some of the worst sorts of social isolation, and pleads for the use of "social psychotherapy" in group organisations of every sort. He is perhaps too optimistic in his hopes of what might be achieved by converting groups brought together for other purposes into therapeutic groups, but a note of optimism is not unwelcome in an otherwise gloomy picture.

This is an unusual book, something more than a careful well-documented scientific and statistical survey; indeed, it fulfils one of Mr. T. S. Eliot's requirements for literature, in that Dr. Halmos attends closely to the human heart as he knows it.

Practical Significance of Modern Cardiological Investigations

T. E. LOWE, F.R.C.P., divisional clinical research unit, Alfred Hospital, Melbourne; H. B. KAY, M.R.C.P.; H. A. LUKE, D.D.R. Melbourne: University Press. London: Cambridge University Press. 1951. Pp. 206. 45*s.*

THIS monograph suffers from the defects which might be expected of a prize essay put into book form. It is in three sections; one is devoted to the methods of cardiological diagnosis, and the other two to their practical application.

The first section gives a good description of the technique of modern diagnosis with a succinct account of the underlying principles and the possible errors in the use of the various instruments. It is not entirely confined to modern methods since palpation and auscultation find a place under the rather formidable disguise of vibrocardiography. The views are orthodox but the general reader will find the information useful and the explanation often illuminating. In the remaining sections the authors seem to have lost sight of their purpose or rather to have been overwhelmed by its magnitude.

The result is a miniature textbook of cardiology, which will not satisfy the specialist and will present others with a lot of tedious reading. The illustrations, though adequate in themselves, suffer from being compressed into consecutive pages without proper relation to the text.

Surgery and the Endocrine System

JAMES D. HARDY, M.D., F.A.C.S., assistant professor of surgery, University of Tennessee Medical College. Philadelphia and London: W. B. Saunders. 1952. Pp. 153. 25*s.*

THE title is ambiguous—and rightly so; for it embraces both the body's reaction to the stress of surgical trauma, and the surgery of the endocrine glands. In the first part Dr. Hardy shows himself to be a surgeon who is quite at home in endocrine physiology, and his account of the main features of the "alarm reaction" is an extremely good brief review of the subject. But his references to his own published and unpublished observations give the work a controversial flavour. Not all will accept his suggestion that the electrolyte depletion which commonly follows an operation may be more apparent than real (and is in any case part of a purposeful reaction to stress): though perhaps it will allay the alarm reaction of some of those over-conscientious house-surgeons who are for ever trying to restore the blood electrolytes to "normal." The second part describes the surgery of the endocrine glands on fairly conventional lines.

A Symposium on Essential Hypertension

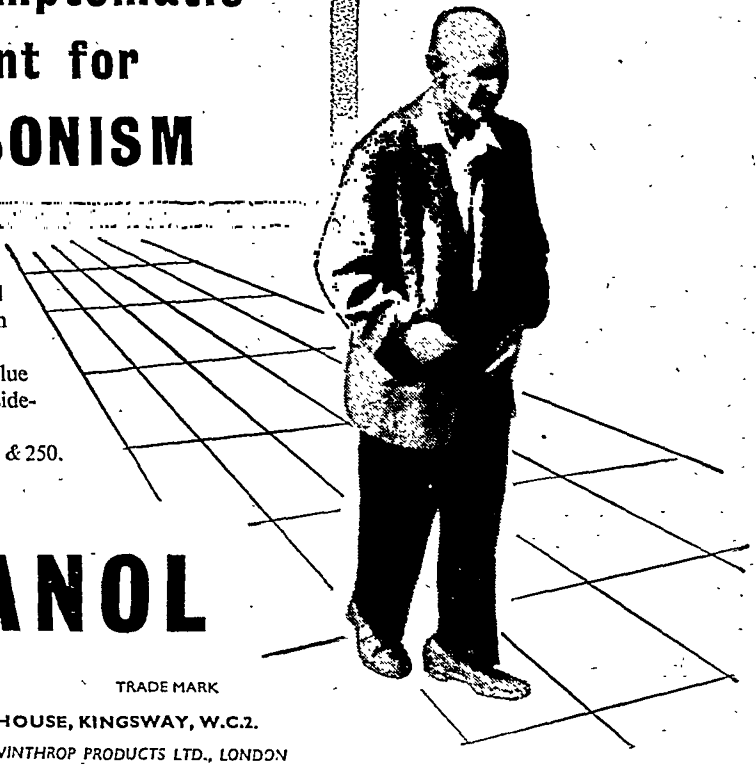
Sponsored by the Recess Commission on Hypertension. Secretary: VANCE L. ALDEN. Massachusetts: Commonwealth of Massachusetts. 1951. Pp. 373. $3.95.

IN 1950 the Court of Massachusetts decided they ought to determine what action, if any, should be taken by the State in the control and treatment of hypertension. To this end they appointed a commission, who convened a three-day discussion by experts not only in the clinical and laboratory fields, but in those of public health and social research. Symposia, followed by publication of the proceedings in full, have become a feature of American medical activity. There have been a number on hypertension, but this is the first with an epidemiological approach. Epidemiology is no longer confined to contagious disease, but covers the study of all factors and their interrelationships which influence the occurrence and distribution of any disease or disability. Accordingly the problem was defined—and difficulties were soon apparent.

A critical review of published work revealed the inadequacies of previous surveys, many of which have been based on life-insurance statistics. Apparently sampling of the population has rarely been statistically acceptable. There has been no agreement as to what constitutes hypertension and what allowance should be made for advancing age, nor even on how to take the blood-pressure. During the discussions hypertensive disease was defined and classified. Emphasis was laid on the importance of studying the prohypertensive state rather than patients who had developed symptoms, or in whom hypertension had been discovered on routine examination. It was suggested this might best be done by studying the children of hypertensive parents and following them through life. The case was stated for the neurogenic, psychogenic, renal, and endocrine hypotheses; and it was agreed that heredity was the only established ætiological factor. However, ætiology does not explain pathogenesis. Physiological investigations, pathological changes, and animal experiments were reviewed. The rôle of vaso-active substances, infection, injury, and pregnancy were discussed and attention then turned to social, economic, and physical environment and to constitutional and psychological factors. The adaptation syndrome was not forgotten.

If little new emerged, current knowledge was appraised and the problem classified. Gaps in knowledge were emphasised, and it was decided to make plans for a long-term community research. Not least in importance is the intention to publish a complete bibliography from 1920. No-one interested in hypertension could fail to derive pleasure and profit from reading this volume.

Effective symptomatic treatment for PARKINSONISM



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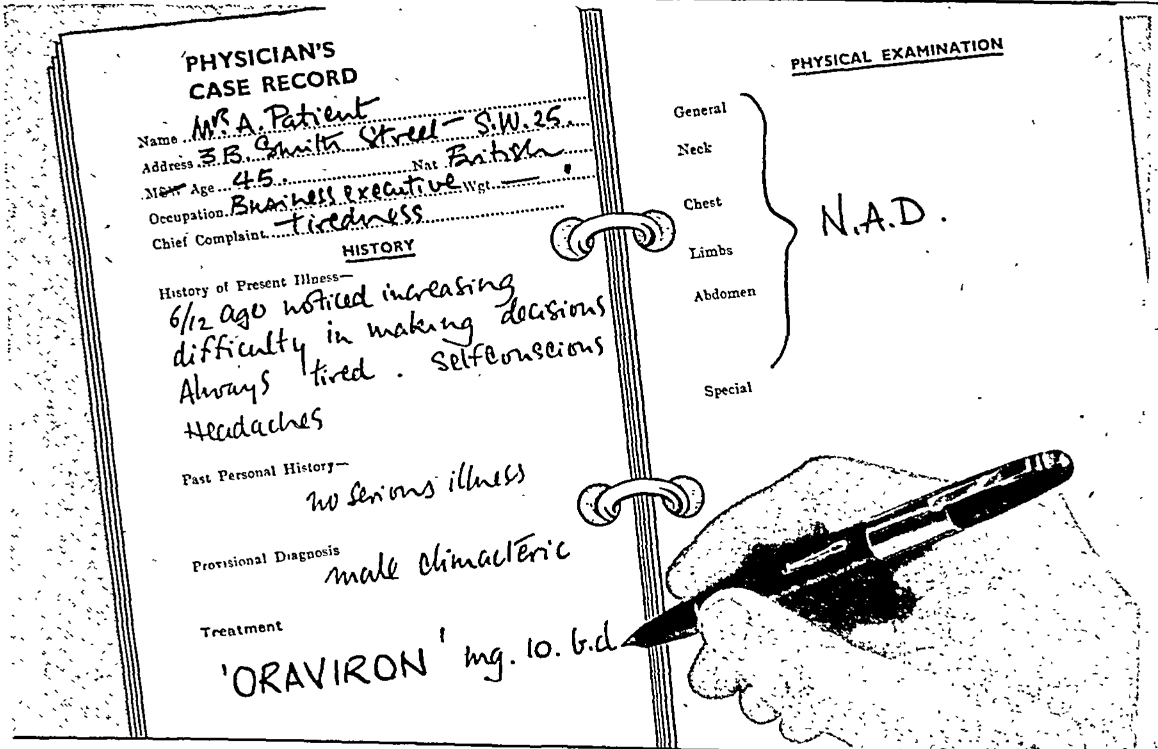

PHYSICIAN'S CASE RECORD

Name Mr. A. Patient
Address 3 B. Smith Street – S.W. 25.
~~M/F~~ Age 45. Nat British
Occupation Business executive Wgt. —
Chief Complaint tiredness

HISTORY

History of Present Illness—
6/12 ago noticed increasing difficulty in making decisions
Always tired. Selfconscious
Headaches

Past Personal History—
no serious illness

Provisional Diagnosis male climacteric

Treatment
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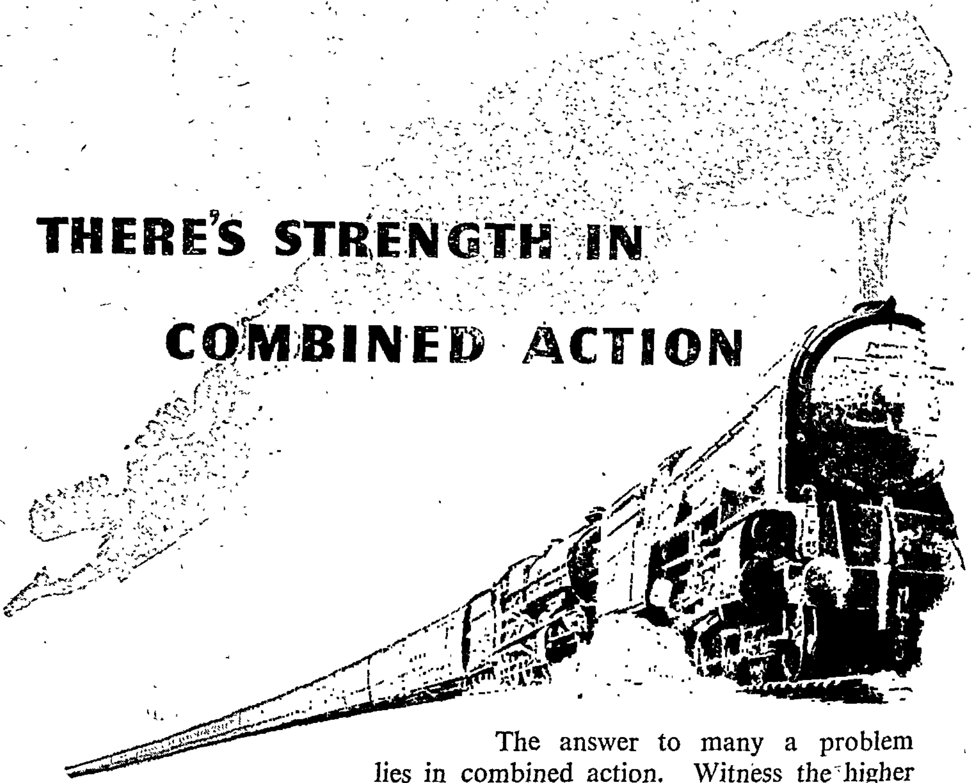

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THE LANCET

LONDON: SATURDAY, AUGUST 23, 1952

New Ways with Tuberculosis

The symposium from Clare Hall Hospital which we print on another page shows how much the treatment of pulmonary tuberculosis has been changing. Ten years ago, as Dr. Norman Macdonald points out, artificial pneumothorax and thoracoplasty were the standard methods, with extrapleural pneumothorax just coming for trial. Chemotherapy had not arrived, resection was hardly risked, and pneumoperitoneum had scarcely found a footing. Now, with chemotherapy in full swing at the chest clinics, and resection a commonplace in chest units and sanatoria, the indications for the various types of collapse therapy are changing, and it seems diminishing somewhat. Thus at Clare Hall, Mr. Robert Laird notes, thoracoplasty is still much used in selected cases—mainly those with cavitation and fibrosis in the upper lobe. The number of lung resections, however, is steadily rising, this operation being often performed for large solid foci, large or tension-type cavities, and lower-lobe cavitation, as well as in cases where one lung is destroyed while the other is healthy or relatively healthy, in cases of permanent bronchial stricture with tuberculosis beyond it, in cases of empyema associated with gross lung disease, and in cases where collapse therapy has failed. There is still some overlap in the indications for thoracoplasty and resection. In Laird's series resection gave a sputum-conversion rate of over 90%, as against 70–80% for thoracoplasty; and since resection often leaves little deformity, it is likely to be less unpopular with patients. On the other hand it is still somewhat more risky than thoracoplasty: in the six months after operation the mortality among Laird's 580 patients treated by thoracoplasty was only 2·1%, as against a rate of 4·5% among 132 patients treated by resection. The dislike patients feel for a deforming operation has also encouraged the development of plombage, in which the chest is packed extrapleurally with some neutral substance, such as 'Lucite' balls, strips of 'Polythene,' or the 'Polystan' sponge described by Laird. It remains to be seen how the body will tolerate such foreign materials over the years; but the immediate results are good, and here again a two-stage operation is avoided.

The development of these new measures, as Macdonald reports, has been associated with a decline in the use of artificial pneumothorax, anyhow at Clare Hall. It seems extraordinary that we should not yet be certain when a pneumothorax can best be terminated, but, as he says, it has been employed on a large scale only during the past ten or twelve years, and we are only just beginning to see late results in any quantity. When refills cease, various hazards develop which the pneumothorax had held in check: in fact the patient's common plea—"I feel much safer with it, doctor"—seems to be thoroughly justified. After years of relative good health he may, when his pneumothorax is given up, become an invalid again or a candidate for major surgery. The difficulty, as Macdonald remarks, is to decide on the positive criteria for inducing a pneumothorax. There are plenty of negative ones. Too much toxicity, too much disease, too little disease, disease that is either too new or too old, a large tension cavity, a segmental lesion, a thick-walled cavity, emphysema, and tuberculous endobronchitis—all these discourage the physician from considering artificial pneumothorax, and it is seldom nowadays that he finds himself certain that in any given case it is exactly what the patient needs. Pneumoperitoneum, however, is still holding its own, both as a useful accessory to chemotherapy and as a temporary procedure to prepare a patient for operation. At Clare Hall, except in special cases, it has lost its old ally phrenic crush. A paralysed diaphragm may be very convenient at the outset of treatment, but later, if it fails to recover, or recovers incompletely, respiratory function is permanently limited; moreover, if thoracoplasty has to be done, a partially paralysed diaphragm may add to the chances of massive collapse. Pneumoperitoneum without phrenic crush, but with chemotherapy, has particular value, Macdonald finds, in pulmonary tuberculosis of hæmatogenous origin. The disease is commonly apical and symmetrical, leading to much fibrosis which pulls up the hila. Pneumoperitoneum relieves the emphysema in the lower zones by raising the diaphragm, and encourages the apical lesions to go on contracting. The trouble is that there is a risk of relapse if the diaphragm is allowed to descend; so pneumoperitoneum must be continued indefinitely. Moreover, though Macdonald does not mention this, pneumoperitoneum is liked less by patients than by physicians; few people care to acquire a permanent pot-belly, and single young women can find it seriously embarrassing.

The changing methods at the sanatoria are, of course, largely the outcome of the swift advance of chemotherapy, for streptomycin and *p*-aminosalicylic acid have already changed radically the type of case reaching the sanatoria. Another factor, as Dr. F. A. H. Simmonds reminds us, has been the growth and development of the tuberculosis service. It is not merely that (as he happily puts it) more surgeons have closed more cavities, but also that more early cases are being effectively treated by the clinics. Thus a higher proportion of those admitted to sanatoria for active treatment are sputum-negative: the figure, in fact, has risen from 28·5% in 1950 to 44–45% in 1951. We do not yet know, however, what proportion of patients who become sputum-negative while having rest and chemotherapy at home will be able to consolidate their recovery without further measures. Dr. Simmonds warns us that such sputum conversion may well be transient unless backed by collapse or other active treatment; and indeed he finds that the disease may be just as extensive, and the need for active treatment almost as great, in sputum-negative as in sputum-positive patients. This encourages speculation once more on what constitutes "tuberculosis." Recent experience with isoniazid[1] has shown that patients can feel and look well, and have no tubercle bacilli in their sputum, and yet show very little change in a serious X-ray picture. We do not know yet what course their structural damage will follow, though there is some evidence coming in of a delayed healing process, first apparent only some months after the clinical improvement. Some would say that, in the interval between the clinical and the structural change, we must regard the patient as a sick man still in need of treatment, while others might look on him as a well man in whom a process of resolution and scarring is at work.

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[1] See *Lancet*, July 5, 1952, p. 19.

Whatever the ultimate picture may be, it is clear that chemotherapy has given us a big new advantage over the old adversary. Just as anæsthetics cleared the way for the surgeon by giving him time for careful and intricate work, so the new drugs have given chest physicians and surgeons time to consider the next move and develop new techniques—"room to manœuvre," as Macdonald puts it. Their influence on the rate of decline in mortality is already apparent in Simmonds's graph, though he warns us that the acceleration may not be maintained if the effect of the new drugs is merely to prolong life for a few years. But without undue optimism we may perhaps share his view that patients will in time separate into two groups: first, those with small lesions discovered early and for the most part treated successfully; and secondly, a diminishing group with incurable disease, who will need care for life.

Chlorophyll as Deodorant

One of the more bizarre items of recent news is the statement by Ritchie Calder [1] that the governor of a gaol in one of the Southern States of the U.S.A. does not allow his convicts to use chlorophyll preparations of any kind (even toothpaste) for fear that, if they escaped, the deodorant action of chlorophyll might prevent his bloodhounds from picking up the trail. Recommended to the public as a means of neutralising every form of unpleasant bodily odour, these preparations are sold in America on such a scale that the manufacturers are obliged to import substantial quantities of chlorophyll from this country, where it is prepared (largely from lucerne) as a by-product of the new grass-drying industry. In Britain, too, increasing sales show that the public is tentatively accepting the suggestion of certain advertisers that chlorophyll is a great help to social life in a small island.

Chlorophyll has the unique property of photosynthesis—building up sugars from water and the carbon dioxide of the air, and simultaneously releasing oxygen—and possibly this process is the key to its alleged deodorising action, which is more likely to be due to the oxidation than to the reduction of offensive gases and other substances. Though chlorophyll has not yet been completely synthesised, no doubt exists that its molecule is built up of a system of four pyrrol rings pivoted on a central magnesium atom. It is, in fact, closely similar to haem, in which the pyrrol rings similarly pivot on an iron atom. There is nothing to suggest that either of these molecules should possess any deodorant action; but this is merely another way of saying that the whole question of the connection between smell (positive or negative) and chemical structure is quite undeveloped. For the specific functions which chlorophyll and haem discharge with such incomparable efficiency in plant and animal life respectively, the *whole* molecule is indispensable. Any attempt to modify, by degradation or by synthesis, is immediately accompanied by a catastrophic reduction in catalytic efficiency. On the other hand, these molecules have, per se, a considerable stability not only to physical change but also to minor chemical modification, so that it is possible to effect substantial chemical reaction on them without the collapse of the pyrrol scaffolding. The central metallic atom may in either case be removed and replaced by another, or even by hydrogen. These modified structures retain many of the subsidiary characteristics of cholorophyll (or haem) and may be spoken of as chlorophylls, in much the same way as cholesterol and sex-hormone products are still "sterols." It will be seen that there is wide scope for marketing a variety of ill-defined mixtures of degradation products of chlorophyll; and if in fact the claims made on behalf of proprietary preparations of chlorophyll are justified there will be ample opportunity for the careful study of the potency and therapeutic indications of materials of known composition.

Westcott [2] claims to have shown that water-soluble chlorophyllin reduces the smell of benzyl mercaptan, thioglycollic acid, and trimethylamine. Dijkstra [3] has also reported in-vitro tests in which he incubated various foul-smelling materials—human pus, rotting cheese, and certain vitamin tablets—with a proprietary preparation of chlorophyll and found that the odours were abolished. On the assumption, then, that chlorophyll is a potent deodoriser, the most obvious way in which it might act is by inhibiting putrefactive bacteria. This possibility can readily be tested in the laboratory, and eight years ago L. W. Smith [4] and others worked on these lines. Smith concluded that "the ordinary pyogenic bacteria will neither grow nor survive for 24 hours in simple isotonic solutions of chlorophyll up to dilutions of 1 in 500," and he thought that an oxidation mechanism most easily explained the ability of chlorophyll to arrest anaerobic growth. Another relatively simple means of investigating the action of chlorophyll is to note the effects of applying it to infected wounds. Moss et al.[5] studied 36 patients and paid special attention to the rate of healing and to wound odour and appearance, and they concluded from their observations that chlorophyll is consistently an effective deodorant when used on foul-smelling wounds. They also said that the treatment improved the look of the wounds, giving them a healthy granulating appearance; but, though chlorophyll did not retard healing, there was no clear evidence that healing was accelerated. These results confirmed the earlier findings of Gruskin,[6] but not those of Bürgi [7] who claimed that water-soluble chlorophyllins stimulated epithelial growth and thus promoted healing of wounds and ulcers.

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[1] *News Chronicle*, July 25, 1952.

[2] Westcott, F. H. *N.Y. State J. Med.* 1950, 50, 698; cited in *Pharm. J.* 1952, 168, 145.

[3] Dijkstra, B. K. S. *Nederl. Tijdschr. Geneesk.* 1951, 95, 208; cited by Mitchell (footnote 8).

[4] Smith, L. W. *Amer. J. med. Sci.* 1944, 207, 647.

[5] Moss, N. H., Morrow, B. A., Long, R. C., Ravdin, I. S. *J. Amer. med. Ass.* 1949, 140, 1336.

[6] Gruskin, B. *Amer. J. Surg.* 1940, 49, 49; cited by Mitchell (footnote 8).

[7] Bürgi, E. Cited by Mitchell (footnote 8).

The reputed effect of chlorophyll as a general deodorant of body tissues and excretions is even more interesting and important, but it is also harder to understand. Many independent workers have now described investigations into the effects of chlorophyll on such odours as those often associated with sweating and with menstruation, and also the peculiar smells that sometimes emanate from the axillæ and the feet. Attempts have also been made to deodorise the breath or urine of people taking certain foodstuffs and beverages—garlic, asparagus, thiamine, and alcoholic drinks. There is an extraordinary measure of unanimity in claiming complete or almost complete success in these trials. Once again, however it must be emphasised that none of these workers has so far disclosed the exact nature of the chlorophyll preparation used: they mention merely the name of the proprietary brand. There seems to be an opportunity here for collaboration between an independent chemist and a clinical research-worker in an academic laboratory to provide a disinterested opinion on which of the chlorophyll products is responsible for these remarkable actions. If the action is simply that of an antibiotic, altering the bacterial flora of the intestinal tract, it is remarkable that the same effect does not seem to have been observed when streptomycin is given by mouth. Likewise, no remote deodorising action seems to have been noticed after administering succinylsulphathiazole as a preoperative measure to reduce the bacterial content of the colon. The alleged value of the chlorophyll preparations when given orally in cases of ozæna or of suppuration of bone adds to the evidence that the drug must be absorbed and exert its effects peripherally.

In a recent review on chlorophyll, Mitchell[8] refers to work by Calvin et al. which suggests that "pure chlorophyll *a* can act as an oxygen carrier, absorbing atmospheric oxygen and parting with it again when the absolute pressure is reduced to a low level." Mitchell also mentions observations made by his colleagues and himself which show that when the free acid chlorophyllin is exposed to air it is substantially altered—presumably by oxidation. He points out that when the sodium or potassium salt of chlorophyllin is given by mouth chlorophyllin is probably liberated by the gastric hydrochloric acid. It is suggested that after absorption and distribution to the various body tissues the chlorophyllin exerts its deodorising effect by acting as a mild reducing agent, itself being oxidised. Alternatively, Mitchell thinks, "it may catalyse oxidation of odorous material, perhaps by forming a loose combination with oxygen and parting with the latter at the sites of action." On the whole, he favours the hypothesis of mild oxidation rather than reduction and points out that this would be more likely to have a deodorising action on malodorous sulphur compounds. On the other hand, Kohler et al.[9] reported that chlorophyll is not absorbed from the gastro-intestinal tract. If this view is confirmed it will call for an entirely different approach to experiments on the fundamental pharmacology of chlorophyll in vivo. Meanwhile the statement provides some justification for the comment of the *Journal of the American Medical Association*[10]: "not only is the mechanism of action unexplained, but it is not at all certain that the action exists except in the mind of the observer." The *Journal* goes on to remark on the curious fact that not all herbivorous animals are entirely free from smell; and the same thought is expressed by R. W. Marsh in the following couplet which we take the liberty of reproducing from the *News Chronicle* of July 30:

> "The goat that reeks on yonder hill
> Has browsed all day on chlorophyll."

The biologist may point out that the characteristic smell of goats is confined to the male, but at least it proves that some smells are not abolished by chlorophyll in the diet. It would be interesting to know what other smells would appear if graminivorous animals were deprived of their chlorophyll.

Parahæmophilia

In 1947 Owren[11] reported the case of a woman with a hæmorrhagic diathesis who at first appeared to be suffering from lack of prothrombin in the blood, because Quick's one-stage prothrombin test gave a "prothrombin-time" considerably longer than normal. Owren, however, found that the prothrombin-time of this patient's plasma could be restored to normal by adding normal plasma from which all except traces of prothrombin had been removed. He therefore concluded that the patient was suffering from a deficiency of a hitherto unidentified factor, which he named "factor five"; and he called the condition "parahæmophilia" because of its clinical similarity to true hæmophilia. The deficiency seemed to be congenital in his case, but there was no family history.

Since 1947 it has become evident that Owren's factor V is probably identical with Quick's "labile factor" and with the "accelerator globulin" of Seegers and his co-workers. This factor acts by accelerating the conversion of prothrombin to thrombin in the presence of thromboplastin and calcium. This reaction, without the accelerator factor, proceeds only slowly, so that when the factor is absent the prothrombin-time—which measures the time prothrombin takes for conversion to thrombin in sufficient quantity to produce a clot—is considerably prolonged, even though adequate prothrombin is present. The accelerator factor is "labile" because it disappears gradually from stored citrated blood and after ten days none is detectable. Clinically these cases present with a hæmorrhagic syndrome that has been present for years. The usual investigations reveal a prolonged prothrombin-time (or apparently diminished prothrombin concentration), and this alone distinguishes them from true hæmophilia, in which the prothrombin-time is normal. Another, and convincing, distinguishing test is that the plasma from a case of parahæmophilia will restore to normal the clotting-time of the plasma of a known hæmophilic patient; conversely hæmophilic plasma, which does not lack the accelerator factor, will restore to normal the prothrombin-time of plasma from a parahæmophilic patient. The true nature of a case of parahæmophilia can be found by showing that the plasma prothrombin-time can be shortened by adding normal plasma from which prothrombin has been removed, and the finding can be confirmed by showing that plasma from blood stored for more than ten days will *not* have this effect. By tests like these, several more cases have now been detected and reported.

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[8] Mitchell, W. *Retail Chemist*, 1952, 23, 27, 65.

[9] Kohler, G. O., Elvehjem, C. A., Hart, E. B. *J. biol. Chem.* 1939, 128, 501; cited by *J. Amer. med. Ass.* (footnote 10).

[10] *J. Amer. med. Ass.* 1951, 147, 99.

[11] Owren, P. A. *Lancet*, 1947, i, 446.

In 1950 Frank et al.,[12] working in Turkey, reported the case of a man of 29 who came to their clinic with hæmaturia.

> This man presented the clinical picture of true hæmophilia; he had been known to be a "bleeder" since infancy and had, on that account, not been circumcised; he had had nose bleeding from the age of 2 and his first attack of hæmaturia when he was 3 years old; he had had no hæmarthroses and no purpura. A brother of the patient was said to have died in childhood from severe epistaxis. But further inquiry revealed that the patient's father had been affected; after circumcision the bleeding had been stopped only with difficulty and he had had severe epistaxes. Frank and his colleagues applied the usual blood tests to the patient and found that Quick's prothrombin-time was 47 sec. compared with the normal 11–13 sec.; and by further observation they found that when the prothrombin-time rose to 60–80 sec. the patient was liable to bleed. Transfusion of fresh blood or plasma reduced the prothrombin-time to 20–30 sec., and the effect lasted about 8 hours. They put this to practical use because, on this occasion, hæmaturia was found to be due to a stone in the kidney, and, by transfusing the patient with fresh blood 2 hours before, an operation for removal of the stone was successfully performed without undue hæmorrhage. Frank and his colleagues therefore considered that their patient had "parahæmophilia" and that in this case the defect was inherited.

Last year de Vries et al.,[13] in Israel, described a family that combined parahæmophilia with syndactilism. Of 7 siblings, 5 had syndactilism and a bleeding tendency, which de Vries et al. found was due to deficiency of prothrombin accelerator factor, and in 2 cases there was deficiency of prothrombin itself as well; both sexes were affected. The parents of this family were normal, and no other members were known to be affected. In the U.S.A., Stohlman et al.[14] recorded the case of a woman who had to receive a transfusion after severe postpartum hæmorrhage and who had a history of severe bleeding after tonsillectomy and a nasal operation. She also proved to have parahæmophilia, and they were able to show that the purified accelerator globulin provided by Seegers restored the clotting mechanism to normal. There was no family history in this case.

Lately Brink and Kingsley,[15] working in South Africa, have reported a hæmorrhagic syndrome among members of both sexes in more than one generation of a family; their investigations of 3 members showed that the condition was due to deficiency of the labile factor—i.e., parahæmophilia.

> Their first case was a woman of 27 who was in hospital for attacks of severe abdominal pain and menorrhagia. She had suffered all her life from hæmorrhages—epistaxes, bleeding after tooth extraction, and loss of blood from menorrhagia that had needed treatment with transfusions; nevertheless she had a daughter 8 years old, and the only complication of the labour had been a bloodstained vaginal discharge that persisted for 2 months. Her prothrombin-concentration, estimated by Quick's test, was 9–10% or even less. Brink and Kingsley showed that the deficiency was of prothrombin accelerator factor, and that transfusion of citrated plasma not more than 12 hours old restored the prothrombin-time to almost normal for about 8 hours. 1 sister and 1 brother had prolonged prothrombin-times, and the brother had serious spontaneous hæmorrhages from time to time. In this generation 3 other male siblings and 4 females were found to be normal; the parents were also normal. The family history showed that members of previous generations had had the same diathesis. The 8-year-old daughter of their patient had a slightly prolonged prothrombin-time, and so had the 2 daughters of the affected sister.

Deficiency of prothrombin accelerator factor can also, it seems, be acquired. Cosgriff and Leifer[16] have reported a hæmorrhagic syndrome apparently due to this deficiency in a man with cancer of the prostate and extensive bone metastases.

Parahæmophilia must therefore be regarded as a distinctive syndrome. It has justified its name. It resembles true hæmophilia in being a hæmorrhagic diathesis due to congenital or familial deficiency of one of the factors of the clotting mechanism, and it is liable therefore to be a life-long affliction. Unlike hæmophilia its inheritance is not sex-linked; Brink and Kingsley suggest that it is inherited through a recessive gene or a dominant gene with poor penetrance. It does not, like hæmophilia, appear to affect joints, but bleeding after tooth extraction or other operations and spontaneous bleeding from mucous membranes are typical features. In every case of hæmorrhagic diathesis the prothrombin-time should be estimated, usually by Quick's method or a modification. The discovery of a prolonged "prothrombin-time" in a patient with a congenital hæmorrhagic diathesis puts parahæmophilia into the differential diagnosis—and excludes true hæmophilia. Parahæmophilia can be distinguished from true hypoprothrombinæmia—which can also be congenital—by the tests mentioned above.

Treatment is simple. The bleeding can be controlled by a transfusion of fresh blood or plasma, preferably not more than 12 hours old. The resulting control, in the few cases reported, appears to be more successful than with true hæmophilia, and the case of Frank et al. suggests that major operations can be successfully performed. But, as with true hæmophilia, control lasts at best only a few hours, and it is not practicable to prevent hæmorrhagic episodes continuously.

Action of Antibiotics

Many years ago Ehrlich[17] recognised that the efficacy of a chemotherapeutic agent depends largely on the differences in its toxicity for parasite and host (Ehrlich's chemotherapeutic ratio). He showed that the affinity of a drug for an organism is closely related to its chemical structure and that its potency may sometimes be destroyed by changing a single atom—a specificity which he explained by his side-chain theory. At that time it was characteristic of all the compounds used in chemotherapy—the metals, phenols, and dyes, for instance—that though they had some selective action, mainly on the gram-positive bacteria, their power to kill micro-organisms varied with their concentration, and doses which were lethal to the invading organism were usually toxic to the patient. The notable fact about the first sulphonamide, 'Prontosil,'[18] was not so much that it inhibited bacterial growth as that it could be tolerated by the body in effective concentrations for a long time. Sulphonamides (like penicillin and streptomycin later) were used for several years before their action in interfering with the metabolic processes of micro-organisms was understood.

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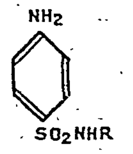
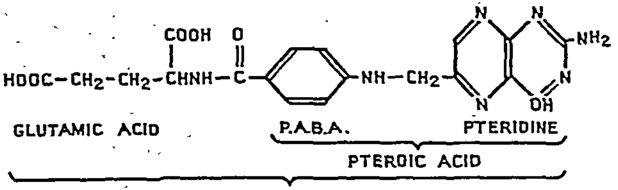
[12] Frank, E., Bilhan, N., Ekren, H. *Acta hæmat.* 1950, **3**, 70.
[13] de Vries, A., Matoth, Y., Shamir, Z. *Ibid*; 1951, **5**, 129.
[14] Stohlman, F. jun., Harrington, W. J., Moloney, W. C. *J. Lab. clin. Med.* 1951, **38**, 829.
[15] Brink, A. J., Kingsley, C. S. *Quart. J. Med.* 1952, **21**, 19.
[16] Cosgriff, S. W., Leifer, E. *J. Amer. med. Ass.* 1952, **148**, 462.
[17] Ehrlich, P. *Lancet*, 1913, ii, 445.

Sulphonamides were found to be inactive in the presence of pus and tissue extracts, and this observation led to Woods's[19] hypothesis that they inhibit bacterial growth by taking the place of *p*-aminobenzoic acid, which the organisms need for their metabolism and which the sulphonamides chemically resemble. This hypothesis led in turn to the remarkable work on biological antagonism between structurally related compounds.[20] The discovery of folic acid—a conjugated molecule of glutamic acid, *p*-aminobenzoic acid, and the base pteridine—which is essential for the growth of many bacteria, provided further confirmation.[21] It has been shown that micro-organisms which have no need of folic acid are resistant to sulphonamides, and so are those which must have ready-made folic acid as a growth factor.[22] On the other hand all those organisms which make their own folic acid from *p*-aminobenzoic acid are sulphonamide-sensitive. It is evident therefore that addition of *p*-aminobenzoic acid or folic acid should counteract the effect of sulphonamides on these bacteria. But as a matter of fact the exact rôle of folic acid in bacterial metabolism is not as simple as this picture indicates; for various compounds unrelated to folic acid—e.g., methionine, xanthine, and serine—have been found to oppose the action of sulphonamides, which suggests that several respiratory enzymes may be inhibited by sulphonamides. Further, folic acid seems to be concerned in the metabolism of nucleoproteins, especially with the reduction of desoxyribonucleic acid.[23]

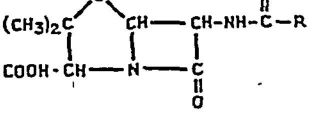


ULPHONAMIDES



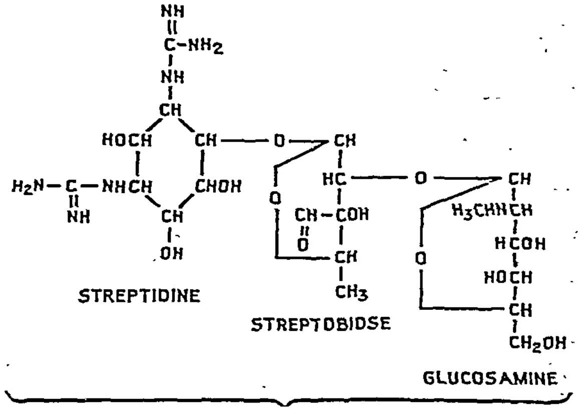
FOLIC ACID (PTEROYLGLUTAMIC ACID)

Penicillin excels in its lack of toxicity, even when given in massive doses and over a long period. It has been possible to synthesise the penicillin molecule,[24] which consists of a curious ring-condensation of two amino-acids, β-dimethyl-cysteine and alanine, but the mould has not yet been surpassed in efficiency by the laboratory. The various penicillins are distinguished by the different acids coupled to the alanine. Penicillin is bacteriostatic in threshold concentration, but bactericidal in higher concentration,[25] and it has a preferential affinity for gram-positive organisms. Brilliant research[26] has shown that in their normal metabolism gram-positive organisms—in contrast to gram-negative ones—actively take up free glutamic acid and lysine from their environment. This process is accelerated by the magnesium ribonucleic acid which is present in the cell wall, and which is incidentally responsible for the gram-positive staining. Glutamic acid and lysine are concentrated in the interior of the cell, whence they are mobilised for protein synthesis. If penicillin is added to a *growing* culture of gram-positive organisms, it acts on the cell wall and disrupts the metabolism of the ribonucleic acid, thus preventing the normal assimilation of glutamic acid. Penicillin is, however, without any effect on non-growing cells. The sensitivity of the gram-positive organism and the immunity of the gram-negative one is explained by the fact that in the latter glutamic acid is synthesised inside the cell and does not have to be taken in from outside. Organisms which suddenly become penicillin-resistant assume accordingly some of the properties of gram-negative bacteria; they acquire the ability to synthesise glutamic acid and need not then assimilate it from their environment, so attaining an independence against which penicillin is powerless. These differences in the amino-acid metabolism of bacterium and host are the nutritional basis on which penicillin works.



PENICILLIN

Streptomycin is a glycoside containing streptidine, a base which is related to inositol (one of the B group of vitamins), streptobiose (which is a methylpentose), and glucosamine (which is a derivative of dextrose). The gram-negative and acid-fast organisms are particularly sensitive to it. Unlike the sulphonamides and penicillin, it affects not only growing organisms but those in the resting phase as well. Its bactericidal effect increases with higher concentration.[27] The action of streptomycin seems to be more complex and is less well understood than the action of sulphonamides and penicillin. It is known, however, that it interferes with the oxidation of threonine and serine in gram-negative organisms, as well as with the oxidation of fumarates and pyruvates.[28] [29] There takes place in the living cell a process called the "oxalacetate-pyruvate reaction"[30] which consists in the condensation of oxalacetate and pyruvate molecules, with the probable oxidation of many unknown intermediate compounds. This reaction is apparently as important to the animal as it is to the bacterium and it is inhibited by streptomycin. But why is streptomycin so lethal to certain organisms and relatively innocuous to human cells?



STREPTOMYCIN

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18. Domagk, G. *Dtsch. med. Wschr.* 1935, 61, 250.
19. Woods, D. D. *Brit. J. exp. Path.* 1940, 21, 74.
20. Wolley, D. W. *J. biol. Chem.* 1946, 162, 383.
21. Angier, R. B., et al. *Science*, 1945, 102, 227.
22. Lampen, J. O., Jones, M. J. *J. biol. Chem.* 1946, 166, 435.
23. Prusoff, W. H., Teply, L. J., King, C. G. *Ibid*, 1948, 176, 1309.
24. du Vigneaud, V., Carpenter, F. H., Holley, R. W., Livermore, A. H., Rachele, J. R. *Science*, 1946, 104, 431.
25. Hobby, G. L., Meyer, K., Chaffee, E. *Proc. Soc. exp. Biol., N.Y.* 1942, 50, 281.
26. Gale, E. F. *Bull. Johns Hopk. Hosp.* 1948, 83, 119.
27. Garrod, L. P. *Brit. med. J.* 1948, i, 382.
28. Umbreit, W. W. *J. biol. Chem.* 1949, 177, 703.
29. Oginsky, E. L., Smith, P. H., Umbreit, W. W. *J. Bact.* 1949, 58, 747.
30. Umbreit, W. W., Tonhazy, N. E. *Ibid*, p. 769.

The enzymes involved in the oxalacetate-pyruvate reaction in animal tissues are mainly localised in the mitochondria, and streptomycin in relatively low concentration can only hold up the reaction if it is allowed to penetrate into the mitochondria. Streptomycin seems to concentrate largely in the extracellular fluids; little, if any, normally penetrates the cell itself. The explanation of its selective action seems to be that it is prevented from reaching the sensitive enzyme systems of the animal cell, presumably by permeability barriers at the cell wall and at the mitochondria,[31 32] whereas no such barriers exist in the bacterium. While penicillin and the sulphonamides upset anabolic reactions in the organism the strength of streptomycin is thought to lie in the blocking of a katabolic process—the oxidation of carbohydrates and amino-acids.

The effect of streptomycin on the acid-fast bacteria is even more complex. It has been impossible to demonstrate an oxalacetate-pyruvate reaction in the tubercle bacillus, but streptomycin has been shown to inhibit the oxidation of the higher fatty acids with twelve or more carbon atoms.[33] Very little is known about the metabolic pathways in acid-fast organisms, but everything discovered so far suggests a process comparable to the oxalacetate-pyruvate reaction.[31] In acid-fast organisms, therefore, the respiratory block seems to extend to the oxidation of fatty acids as well as carbohydrates and fats.

Organisms which have become resistant to streptomycin have apparently been able to dispense with the oxalacetate-pyruvate reaction or its equivalent in their metabolism. But there is another side to streptomycin resistance; Long[34] observes: "To begin with, although resistance to streptomycin may develop slowly, it can and frequently does occur precipitately by the production of mutants which are fast to streptomycin or, what is more astounding, by the emergence of mutants which need streptomycin as a growth factor!" Many pathogenic organisms, formerly susceptible to streptomycin, are now hardly affected by it, though fortunately *Mycobacterium tuberculosis* is seldom among the more resistant. As Long points out, it is this development which has led to the suggestion that streptomycin should be confined to the treatment of tuberculosis.

But not all the reported effects of streptomycin and the newer antibiotics can be attibuted directly to their action on bacteria and viruses. They can apparently produce remission in leukæmia, Hodgkin's disease, disseminated lupus erythematosus, and rheumatoid arthritis. Clearly our explanation is far from complete, and Dr. R. D. BARNARD discusses this perplexing aspect of the subject in a letter on p. 387 of this issue.

The interpretation of antibiotic action lagged many years behind its discovery and clinical application. It is interesting to look back upon the progress achieved and to see how much has sprung from a study of cell nutrition in man and bacterium. More potent drugs may be found as this work advances. Meanwhile we have yet to learn how the newer antibiotics such as chloramphenicol, aureomycin, terramycin, and isoniazid serve the purposes for which we thankfully use them.

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31. Umbreit, W. W. *Ann. N.Y. Acad. Sci.* 1950, **53**, 6.
32. Umbreit, W. W., Smith, P. H., Oginsky, E. L. *J. Bact.* 1951, **61**, 595.
33. Oginsky, E. L., Smith, P. H., Solotorovsky, M. *Ibid*, 1950, **59**, 29.
34. Long, P. H. *N.Y. St. J. Med.* 1952, **52**, 1637.

Annotations

TWO TYPES OF MENTAL DEFECT?

IN 1914 Pearson and Jaederholm[1] made an interesting suggestion based on their careful survey of the mentally defective children, other than imbeciles and idiots, in Stockholm. They thought that most of the defectives with an intelligence quotient above 50 formed the lower end of the normal intelligence range, but the rest of these children, together with the imbeciles and idiots, were defective because of definite pathological changes. In 1929 Lewis[2] came to much the same conclusion after his investigation of mental deficiency in this country in connection with the work of the Wood Committee. He divided defectives into those who were essentially normal but "subcultural," and those who were "pathological." He suggested that the pathological group all possessed some definite lesion or abnormality, either responsible for or associated with their mental defect. Penrose,[3] however, in his very thorough survey in Colchester showed that many idiots and imbeciles, who were certainly in the pathological group, had no obvious physical lesions, and he suggested that other means must be found of distinguishing between the two types.

In the last few years Roberts[4] and his colleagues have made a special study in Bristol and Colchester of the brothers and sisters and the social background of 271 children in the range of intelligence quotient from 35 to 60—i.e., where the two groups might be expected to overlap. Their preliminary results, reported in the Galton lecture for 1952,[4] give considerable support to the hypothesis that there are two types of mental defect. They found that no well-defined division was possible on the basis of the children's own intelligence quotients alone, but that the children fell readily into two groups when the intelligence quotients of their siblings were also taken into account. With one group the intelligence quotients of the siblings were evenly scattered about a mean figure of 80; this is what one would expect if the children's intelligence was conditioned by many genetic and environmental factors, each having little effect in itself, and if the siblings had on the average half these factors in common with the original subjects of the experiment. In the second group the majority of siblings had intelligence quotients distributed in the same way as those of any random sample of the population, with a mean of about 100; but a few of them were severely defective. It was as if most of them had entirely escaped some single influence which had severely limited intellectual development in their brother or sister, but which had on isolated occasions affected more than one member of the same family.

Roberts's division of the children into two groups was admittedly subjective, but a later analysis of their social background gave further support to his view that the distinction was, in fact, a biological reality. The two groups of children were found to differ more in the social class and fertility of their parents than did groups distinguished only by the intelligence quotient of the one defective child. *Parents of the "normal"* group, as would be expected, were on the whole appreciably lower in the social scale and more fertile than the parents of the "pathological" group.

This separation of mental defectives into two distinct categories will, if substantiated, prove a useful guide

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1. Pearson, K., Jaederholm, G. A. Mendelism and the Problem of Mental Defect. On the Continuity of Mental Defect. London, 1914.
2. Lewis, E. O. Report on an Investigation into the Incidence of Mental Defect in Six Areas, 1925–27. H.M. Stationery Office, 1929.
3. Penrose, L. S. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1938, no. 229.
4. Roberts, J. A. F. *Eugen. Rev.* 1952, **44**, 71.

to further research, and suggest possible ways of making mental deficiency less common. The chances of reducing the number of "normal" defectives will be good, for the theoretical basis is there; improved social conditions, with the lower fertility-rate that they bring, seem to offer the best immediate hope. A considerable reduction in the numbers of "pathological" defectives can be achieved only when ways are found of detecting the carriers of the recessive genes for such conditions as phenylpyruvic amentia, amaurotic idiocy, and gargoylism, and when the unknown forces of environment which must be responsible for the bulk of gross mental defect are accurately defined.

CHLORAMPHENICOL AND THE BLOOD

IN the U.S.A. the Food and Drug Administration has announced its decision on chloramphenicol. The administration undertook a national survey to assess the danger of aplastic anæmia during treatment with chloramphenicol, disturbing reports of which have been accumulating in the past few months.[1] The decision is to permit the continued distribution of the drug in the U.S.A., but a warning note about the occasional occurrence of blood dyscrasias will be added to labels and to advertising circulars. Both notes will point out the importance of regular examination of the blood during intermittent or long-continued treatment, and the one on the circulars will warn doctors against using the drug indiscriminately or for minor infections.

In weighing the evidence, the administration examined the case-records of 410 patients who developed serious blood disorders; but only 177 of the disorders were definitely known to have been associated with the use of chloramphenicol. In 61 cases chloramphenicol was the only drug given, and in the remaining 116 other drugs had also been used. In these two groups together the mortality from conditions attributable to depression of the bone-marrow was 50%. This figure alone is alarming, but, according to the best estimates, chloramphenicol has been given to about eight million people since its introduction in the U.S.A., so the actual risk is small. It would have been regrettable if a drug of undoubted value had been condemned outright on such a slender chance. The responsibility of measuring the danger has been properly left in the hands of the prescribing doctor.

YAWNING

To most minds yawning is an infectious habit of the bored; but it may also arise from hunger, overeating, drowsiness, or bad ventilation; and it may come on with gastro-intestinal disturbances, after severe hæmorrhage, in association with hysteria, as an aura of epilepsy, and in encephalitis, Huntington's chorea, and cerebellar abscess or tumour. The yawn may not be restricted to man: Crämer[2] suggested that the gaping of fishes, amphibians, and reptiles was closely analagous; and the gaping hen beating its wings on tiptoe is an everyday sight to the poultry-keeper.

Mayer[3] found that during the first part of the inspiratory phase there is expansion of the chest with descent of the diaphragm and larynx, elevation of the alæ nasi and soft palate, downward and backward displacement of the tongue, abduction of the vocal cords, and opening of the mouth. This is immediately followed by closing of the eyes and stretching, notably of the muscles of the neck and upper limbs. Mayer described yawning as an automatic expression of cerebral fatigue, in the sense that crying and laughing are expressions of sorrow and joy; while Hauptmann[4] suggested that it combated the loss of muscle-tone which results from enforced inactivity of the higher cerebral centres. Dumpert[5] suggested that it occurred when the cerebral circulation was unfavourably adjusted to maintain an alert state; he also held that it augmented the venous return to the heart, which in turn improved the arterial blood-supply to the tissues. Heusner[6] reviewed the evidence and showed that in the fingers and toes of normal adults yawning was followed by vasoconstriction, which was roughly proportional to the depth and duration of the inspiratory movement, and that it was attended by transient acceleration of the heart. These changes are similar to those recorded after deep inspiration.[7]

There is thus some reason for regarding the yawn as a mechanism for countering physiological aberration.

THE FORMATION OF ANEURYSMS

THE progress of peripheral arterial surgery during the last quarter of a century has led to the development of technical procedures which give ever-increasing scope to investigation and treatment. Arteriography and plethysmography now give accurate knowledge of the site, extent, and character of lesions, and of the functional state of the circulation. Antibiotics, anticoagulants, improved methods of arterial suture, and the successful preservation of homografts have strengthened the surgeon's hand. Disobliterative operations and the restoration of continuity by grafting have now been added to arterial surgery, which was formerly limited to operations on the sympathetic system, and amputation when these failed.

Mr. S. M. Cohen, in his Hunterian lecture,[8] has reviewed the surgery of peripheral aneurysm and arteriovenous fistula in the light of these recent technical advances. His observations are based on experience gathered at a special vascular centre during the late war, together with material collected from other sources. Close observation of his cases has suggested to him some physiopathological ideas which will attract the attention of all surgeons who are engaged in this difficult but challenging work.

Leriche[9] has written: "Dans tous les anévrysmes, ce qui domine, c'est l'affaiblissement de la média et la disparition de l'élastique. Il faut étudier *les conditions de vie et de souffrance de l'élastique*." Cohen has followed this precept, and he finds, as did Halsted before him, that the stimulus which prompts the elastic tissue to meet the demands of local stress, and so control the calibre of the vessels, is the "rhythmical tensile stretch of systole—i.e., pulsation; and this is as essential for the well-being of elastic tissue, as the nucleus is to the cell." In this way he explains the phenomenon of "arterialisation" of the vein in arteriovenous fistula; here the vein thickens and resists ballooning under the unaccustomed arterial pressure, whereas in veins subjected to far lower pressures—as in portal hypertension, superficial varicosities, and deep-vein incompetence—enormous dilatation may be found. Similarly, when a vein graft is inserted to bridge an arterial gap, the graft holds. Yet "of all the layers, the elastic tissue alone survives. As the pulsating stream strikes the vessel wall, the elastic tissue responds, gathers strength, and holds without aneurysmal dilatation."

In contrast the artery, proximal and distal to an arteriovenous fistula, dilates and may become tortuous and greatly enlarged. These changes, Cohen suggests, "arise from weakening of the systolic stretch stimulus." The force of the pulse wave is dissipated in the fistula, and a mere "bobbing and curtseying of the vessel wall" results. Other effects of this loss of the stretch stimulus are the fusiform aneurysm of the subclavian artery sometimes seen in cases of cervical rib, and the dilatation of the aorta beyond a coarctation and of the pulmonary artery beyond a stenosis.

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[1] See *Lancet*, July 19, 1952, p. 122.
[2] Crämer, F. *Arch. VerdauKr.* 1924, 33, 149.
[3] Mayer, C. *Z. Biol.* 1921, 73, 101.
[4] Hauptmann, A. *Neurol. Zbl.* 1920, 39, 781.
[5] Dumpert, V. *Z. Psychol.* 1921, 27, 82.
[6] Heusner, A. P. *Physiol. Rev.* 1946, 26, 156.
[7] Bolton, B., Carmichael, E. A., Stürup, G. *J. Physiol.* 1936, 86, 83.
[8] Cohen, S. M. *Ann. R. Coll. Surg.* 1952, 11, 1.
[9] Leriche, R. Anévrysmes arteriels et fistules arterio-veineuses. Paris, 1949; p. 180.

Cohen sees, in the varying hæmodynamic conditions resulting from arterial obstruction, changes in the pulsatile stretching of the collateral vessels, which is the appropriate stimulus to the elastic tissue in their walls, and which decides the development of their " tortuous and apparently ungodly jumble." This perhaps helps us to understand how it is that restoration of pulsatile blood-flow through the main artery, as occurs after disobliterative endarteriectomy, often results in lasting improvement in the circulation of the limb even though secondary thrombosis may lead to reobliteration of the main vessel.

Peripheral vascular surgery, having conquered most of the technical obstacles that delayed its early progress, now finds itself confronted by further difficult questions in physiology and pathology. These will only be answered by giving new thought, as Cohen has shrewdly done, to the whole subject of peripheral arterial injury and disease and the results of surgical intervention.

ANIMAL WELFARE LEGISLATION IN AMERICA

THE new Animal Welfare Institute (A.W.I.), lately founded in the United States, is experiencing the unpopularity usual among those who try to hold fairly to a middle course. In setting out its position,[1] however, it seems we have not adequately filled in the background. Dr. Herman E. Hilleboe, commissioner of health for the State of New York, writes :

> " The Hatch-Metcalf Act, which is now Section 5-a of the Public Health Law, does not ' make it a misdemeanour to harbor a stray animal without reporting it to a designated authority within twenty-four hours,', nor was such punitive action ever contemplated by the men who drafted the bill. The only penalties are those which are designed to discourage experiments upon animals without the approval of the State Commissioner of Health. The Act outlines the restrictions which are to be placed on the use of animals for experimental purposes and requires the Commissioner of Health to prescribe in detail and enforce the stipulated regulations.
>
> " I should like also to observe that this legislation which contains ' restrictions imposed from without ' was requested by research workers of the New York State Society for Medical Research who actively sponsored the law. The provisions of the law do indeed permit the requisitioning by the Commissioner of unlicensed, unwanted or unclaimed animals that are seized by municipalities or by legally designated private organizations. The bill also emphatically declares that no animal, licensed or unlicensed, may be requisitioned contrary to the wishes of the owner."

Certainly the Act makes no attempt to penalise those who harbour a stray animal without reporting it within 24 hours to the authorities ; and we regret having erroneously combined facts relating to New York legislation and that of Illinois, where a Bill as first proposed did contain this clause.

The animal protection clauses in the Hatch-Metcalf Act to which Dr. Hilleboe refers, are for the most part not new : they very largely restate an Act which has been on the statute-books of the State of New York for five years. But they contain the important new provision that violation of the law shall be a misdemeanour. The Commissioner of Health is authorised to approve laboratories and institutions where experiments on living animals may be conducted, and to prescribe the rules under which such approval will be granted. These rules will require that all such animals shall be kindly and humanely treated, properly fed and suitably housed, and that " commensurate with experimental needs and with the physiologic function under study " all experiments causing pain shall be done under adequate anæsthesia. The Act also provides that the State Commissioner or his duly authorised representative shall inspect the approved laboratories and institutions to ensure that the rules are being kept. Any failure to keep them may lead the Commissioner to revoke his approval ; and in any case approval will only be for a year at a time. A tentative " plan of operation," which Dr. Hilleboe has sent us suggests that laboratories and institutions will be inspected annually, but that those using cats and dogs will be inspected quarterly. It is clearly specified in the plan that animals should be given sufficient water and wholesome food, and kept in clean well-lighted and well-ventilated quarters maintained at a proper temperature ; and that quarters or cages should be large enough for the animal to sit, stand, lie, and turn round with ease.

The Act itself lays down that the rules shall be conspicuously posted in each laboratory and institution, so they may themselves serve an educational purpose ; but their influence, of course, will really turn on the character of the head of the laboratory. Approval is granted to the laboratory in his name and is not transferable ; and it is revoked if he ceases to be in charge. If he is humane, all should be well ; but it has to be borne in mind that some who have a genuine warmth for cats or dogs, or both, look on rats and mice much as they look on test-tubes. Responsibility ultimately lies with the State Commissioner of Health, but will be delegated by him to the division of laboratories and research, and to the district health officers, and sometimes to veterinarians, who will be the actual inspectors. In Great Britain, of course, the pattern is rather different, for responsibility lies with an authority entirely outside the health services—the Home Office—and the inspectors are highly qualified and carefully selected for their task.

The above provisions of the Hatch-Metcalf Act, if applied vigorously and sincerely, should serve their purpose well ; but there is still the question of the source of animals for experiment. Stray or unclaimed animals brought not only to municipal pounds, but to the pounds of private organisations, may be requisitioned for laboratory use—though, only, it seems from those private organisations which receive subsidies from municipal or State funds. This is the aspect of the Act which the A.W.I. found it impossible to support, since private animal welfare societies are formed to serve clearly defined purposes, and voluntary subscriptions are given to them on the understanding that they will be spent on those purposes. Some of the subscribers may disapprove entirely of animal experiment ; many others feel an objection—possibly sentimental, but easy enough to understand—to handing over an animal to those who may cause it pain, in however good a cause. True, the Act provides that licensed dogs surrendered to either private organisations or municipalities may not be requisitioned without the written consent of the owner ; and that other animals shall not be requisitioned if the owner so requests in writing. Moreover if a lost animal is requisitioned an extra three days' grace is allowed to give the owner a chance to claim it. Nevertheless the hard fact remains that private societies are compelled by the law to hand over animals whether or not they object in principle. It may be argued, of course, that they are at liberty to forgo their municipal subsidies and maintain their right of choice ; and it is true that most of our own humane societies would regard it as a bad principle to become dependent in any way on an agency, such as a State department, which had a vested interest in their affairs. But a private organisation which is financially committed—which, before this crisis arose, had accepted a municipal subsidy for building a pound, for instance—may not be free to choose independence. We still think the Hatch-Metcalf Act, good in so much, is marred by this arrangement.

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[1] *Lancet*, 1952, i, 1104.

Special Articles

THE GENERAL PRACTITIONER AND THE LABORATORY SERVICE [*]

M. N. S. DUNCAN
M.R.C.S.

GENERAL PRACTITIONER, PORTSMOUTH, HANTS

ALTHOUGH it has always been felt that in the National Health Service the general practitioner should have access to the laboratory, many hospital authorities remain reluctant to open their laboratories to him, fearing that to do so may lead to an overwhelming amount of largely unnecessary work. My object in this article is to show that access by general practitioners to a laboratory service would in fact save time and trouble alike for patient, general practitioner, and specialist. John Hunt,[1] describing the pathological investigations carried out in his practice during five years, makes the point that general practices differ enormously, and nowhere more than in the centre of a large city. He has found it satisfactory to employ a technician who is supervised by a consultant pathologist from time to time. In the area where I work, which is largely industrial, I have been able to refer my cases to a central laboratory where the advice of a consultant pathologist is available.

The practice to which I belong is carried on from a central surgery with three partners and part-time help from an assistant. Each of us gives all-round service. The practice is situated in the centre of a city of approximately 220,000 inhabitants, most of whom are N.H.S. patients.

THE PATIENTS

I have classified, from the point of view of pathological investigations, the patients I treated during nineteen months into the following seven groups. In the first group no laboratory investigations were required. In the remaining six groups was a total of 241 patients—about 8% of all patients who were attended over the period of nineteen months.

Group 1, in which diagnosis and treatment do not require help from the laboratory, contained over three-quarters of all patients. This may seem an abnormally high proportion, but it included the comparatively trivial, such as people with a common cold or a boil, and those who needed a certificate. In an epidemic there were many cases of, for example, influenza or the acute specific fevers of childhood, when only a minority of patients have severe complications presenting difficulties in diagnosis or treatment. Simple side-room tests or the use of some other simple therapeutic test often served to clinch the diagnosis. This group will tend to increase as doctors gain more experience in working with the laboratory, and my pathological colleagues have found that demands for many investigations tend to fall for this reason. For example, a general practitioner can easily carry out one of the simpler calculations for the estimation of hæmoglobin and need only refer for further investigation those which are found to be below an arbitrarily decided standard.

Group 2, in which the clinical diagnosis is fairly certain, but confirmation is desirable, contained a fair number of cases which, with increased experience, might easily be transferred to group 1. The investigations of urinary infections, renal function, or a possible pregnancy in an unmarried girl are all problems with which general practitioners are familiar. Though it is very desirable to establish the causal organism in say, a recurrent cystitis or pyelitis, I do not think it always necessary to do this in a patient infected for the first time who responds satisfactorily to expectant treatment. Renal function and pregnancy tests are difficult and specialised work, demanding the help of a skilled laboratory worker.

Group 3, where the clinical diagnosis is fairly adequate but confirmation is essential, contained cases where, without the aid of the laboratory, I could arrive at only a general diagnosis—e.g., "anæmia" or "glycosuria"—and more accuracy was needed for rational treatment. Many patients with diabetes mellitus, for example, can be adequately and safely treated by their own doctor (apart from pre-coma or coma), but before undertaking such treatment I regard a glucose-tolerance test as essential. Similarly, a patient with anæmia can easily be treated on scientific lines if skilled help is available for blood examinations. With this help, there will be no empirical use of liver, and no patient requiring liver will be treated only with iron. A pathologist who sees many thousands of blood films yearly may also, on occasion, suggest a test-meal, and a carcinoma of the stomach may thus perhaps be diagnosed before dyspeptic symptoms occur.

Group 4 contains the cases in which clinical diagnosis is quite insufficient. Pyrexias of undetermined origin are probably the commonest conditions of this kind that we general practitioners see, but there are many others which often turn out to be very interesting and instructive—the patient who may be an early Addison's disease, the case of hepatic or renal failure, the differential diagnosis between an anxiety state and a masked thyrotoxicosis, the case of fever with intense headache and no respiratory symptoms which turns out to be a virus pneumonia. In this group the general practitioner and the consultant pathologist, working together, may save the hospital beds and the hospital staff many hours of work. I have gained the most instructive experience when I was able to remain in direct charge of these patients, and when a consultant clinician was called in he was presented with a case in which a serious effort had been made to arrive at a diagnosis and there was every need for his special skill and experience.

Group 5, where the presence of active disease is in doubt, comprised the patients whose treatment I found it difficult to decide. Was it justifiable to treat this patient on expectant lines; or should I refer him to an outpatient department, which might waste a great deal of everybody's time? By asking for a simple erythrocyte-sedimentation rate (E.S.R.) or plasma-viscosity measurement, I could often solve the problem. A not uncommon example of this group is subacute rheumatism in children where in the absence of such help, the vagueness of the symptoms and the slightness of the signs might well have led me to postpone any action until the disease had become well established. Another example is possible early pulmonary tuberculosis. Despite the excellent work of the chest clinics, mass-radiography units, and school doctors, we are still often the first doctors to see such cases, and our task will be made easier if we have access to the laboratory for sputum and other tests.

Group 6, the therapeutic control group, contained patients who were receiving, for example, thiouracil, 'Tridione' (troxidone), or liver. All those under my care who are receiving the two former have a total white and granular cell count weekly. As a result, in one of my patients with thyrotoxicosis a steady diminution in the granular-cell count was noticed in good time, and the dose of thiouracil was adjusted with a consequent rise in the granular-cell count. This treatment still causes agranulocytosis, which is occasionally fatal,[2,3] and the precaution of a weekly white-cell count is essential on both clinical and medicolegal grounds. The same is true when troxidone is given for petit mal, while the necessity for periodical blood examinations of patients under treatment for pernicious anæmia is generally accepted.

Group 7 are the maternity cases. If the general practitioner is to undertake antenatal care and conduct domiciliary or nursing-home confinements, he should be able to offer as good a service as an antenatal clinic. He cannot do this unless he can obtain the routine blood-tests regarded as essential by all who practise obstetrics. The general-practitioner obstetrician has the great advantage of knowing his patients and their background well, but unless he can also offer up-to-date scientific safeguards to any pregnant woman who places herself under his care he cannot do his job properly.

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[*] Based on a paper read before the 48th general meeting of the Association of Clinical Pathologists, at Southsea, on April 3, 1952.

[1] Hunt, J. *Brit. med. J.* 1951, ii, 1575.

[2] Beaumont, G. E., Dodds, E. C. Recent Advances in Medicine. London, 1952; p. 324.

[3] Holliday, T. D. S. *Lancet*, 1951, i, 265.

THE INVESTIGATIONS

I also kept records of the investigations I requested from the central laboratory for these patients during the same nineteen months. Below is an analysis of my requests.

Investigations	798
Patients	241 (approx. 8% of all patients seen)
Domiciliary visits by the pathologist..	45
Patients attended the laboratory ..	226
Investigations per patient	3·3

Hæmatological (*496*)

Red cells	31	Mean cell diameter ..	10
Hæmoglobin	122	Mean cell hæmoglobin content	8
White cells	121	Packed-cell volume ..	40
E.S.R. and plasma viscosity	71	Platelet-count	5
Blood-group	42	Bleeding-time	2
Rhesus factor	42	Clotting-time	2

Bacteriological (*99*)

Sputum	15	[illegible] ..	2
Throat swabs	16	[illegible] ..	2
Vaginal swabs	4	[illegible] ..	2
Wassermann reaction ..	41	Blood-culture	6
Gonococcal flocculation..	3	Fæcal culture	5
Paul-Bunnell	3		

Biochemical (*102*)

Basal metabolic rate ..	16	Fæcal fats..	1
Blood-cholesterol ..	17	Blood-urea	17
Fractional test-meal ..	8	Urea-clearance	3
Glucose tolerance ..	5	Microscopical examination of centrifuged deposits in urine ..	15
Plasma-protein	18		
Serum-iron	2		

Other investigations (*101*)

Hogben pregnancy test ..	54
Others	47

DISCUSSION

The high number of hæmatological tests is due to investigation of anæmias, pyrexias of undetermined origin, routine antenatal examinations, and therapeutic controls. As I gained experience, I asked for more packed-cell-volume estimations and fewer red-cell counts and colour indices. One of the advantages of liaison with the laboratory is that they are able to advise on the way in which the desired information can be obtained with most economy of time. Likewise, plasma-viscosity measurements were increased at the expense of the E.S.R., for I found them more accurate. The high number of Hogben tests was due in part to a particular problem in this city, which is a naval port. Many Service wives (for reasons connected with postponing the overseas postings of their husbands) wish to have unequivocal evidence of their pregnancy as early as possible. At one time also those seeking admission to hospital for their confinement had to apply at the second month, and they were unwilling to do so unless sure of their pregnancy. A few are accounted for by my custom of always asking for this test on unmarried girls who suspect they may be pregnant. Under the heading "other" tests I have included those which have been carried out by the laboratory staff in amplification of those I have requested.

CONCLUSIONS

The result of having access to the laboratory service has been that, with the help of the consultant pathologists, with whom I discussed any difficult case, I have been able to deal with many patients whom I would otherwise have had to send into hospital or, at least, refer to an outpatient department. Before seeking a consultant clinician's advice I have been sure that every effort has been made to solve the problem.

Many, if not all, of these patients would have had the same investigations, and perhaps more, requested for them in the wards and outpatient departments, for newly qualified house-officers sometimes ask for more investigations than are really necessary. I have myself found that increased experience of general practice, in close liaison with the laboratory, tends to prevent a continual rise in the number of investigations, and in some instances it has led to a fall.[4] Any increase in the investigations carried out by the laboratory due to general practitioners having access to their services is probably only apparent.

I am convinced that everyone will benefit from opening the laboratory to the general practitioner. Specialists will not have their outpatient departments crowded with comparatively simple cases who need no more than a few routine investigations, nor their time wasted in domiciliary visits to similar cases. Pathologists will be drawn more into the stream of medical practice in the town, seeing the patients themselves, and discussing them with their clinical colleagues. Patients will be safely treated at home far more often, and will avoid the domestic upset caused when the housewife and mother is admitted to hospital, and the emotional upset to a small child separated from his mother when he is ill.[5] The family doctor will be given an opportunity for closer coöperation with other doctors and a greater incentive to keep up to date. Access to the laboratory may also help him to regain, where he has lost it, his position as the trusted adviser to his patients on scientific medicine, as he is on so many of the other problems which they bring to him.

SUMMARY

1. The pathological investigations requested by one partner in a large general practice over nineteen months are analysed.

2. The effect of giving the general practitioner access to a laboratory service is a reduction in the demand on hospital bed space and outpatient sessions.

3. Such access does not necessarily mean an increase in the total demand on the laboratory. If the patient had been sent to the hospital outpatients or ward, the same investigations would probably be requested.

I should like to thank the pathology staff in this area, for their unfailing help in the problems of general practice, and also for their help in the preparation of this paper.

BOOKS ON HOSPITALS

FROM A CORRESPONDENT

COMPARATIVELY few books dealing solely with hospitals have been published in this country. More have appeared on the other side of the Atlantic, but not many of them are really useful to the newcomer to hospital work. The professional administrator will now have his treasured copy of the fourth edition of Captain J. E. Stone's encyclopædic *Hospital Organisation and Management.* He may too sometimes refer to MacEachern's similar volume from Chicago, which bears the same title. There are, of course, useful technical books like Mr. S. R. Speller's *Hospital Law* and several concerned with building and construction, but of those I shall not speak here.

THE LAST HUNDRED YEARS

Florence Nightingale's *Notes on Hospitals* came out in 1859, and there were later editions; copies are still easily obtainable through the second-hand booksellers. Anyone who takes hospital work seriously should not fail sometime or other to handle this old classic. It starts with notes on the sanitary conditions of hospitals, and goes on to deal with defects of hospital plans, principles of hospital construction, and Indian military hospitals. It has an appendix on five different systems of hospital nursing—Miss Nightingale's first analysis, which shows how she approached the subject. Much of the book is obsolete: times have changed—"don't bring the sick out of fresh air into foul, as in a town hospital." It should be read now, not for guidance as to what we should do today, but to see *why* our hospitals are what they are.

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[4] Peterson, O. L. Study of the National Health Service of Great Britain. London, 1952; see *Lancet*, 1952, i, 910.

[5] Bowlby, J. W.H.O. Monograph Series, no. 2. Geneva, 1951; p. 146.

What for example do we think about the size of wards? "Taking sanitary and administrative reasons together thirty two patients is a good ward unit." Or we discuss curtaining in wards: "In most French hospitals, and in some in this country, the beds have curtains. They are not necessary. They interrupt the ventilation and entail additional cost in washing: a low movable screen is preferable." *Notes on Nursing* is another classic; and so is E. T. Cook's two-volume *Life of Florence Nightingale*. Mrs. Woodham Smith's recent biography has had the benefit of access to much personal material denied to Cook, and some will prefer it to the older book. Both are excellent, but Cook has had too long an innings among the discerning to be easily displaced.

Florence Nightingale was followed by Sir Henry Burdett, editor of the *Hospital* and of his formerly popular *Hospital Annual*. In 1893 he brought out four volumes entitled *Hospitals and Asylums of the World*. The first of these volumes made an attempt to survey hospital history; but this was somewhat patchy and failed to take account of a good deal of information one would have supposed readily accessible to him. He ranged about the world and published plans from all quarters of a world which for more than a generation had been busy building hospitals with great enthusiasm. Copies of Burdett's four volumes are not easy to come by, but as a substitute any old volume of his *Annual* will help the reader to recapture the atmosphere of hospital work of that time. But perhaps only those with a liking for his rather bombastic Victorian style will find Burdett worth while.

Sir John Simon's *English Sanitary Institutions* was produced in 1890. Describing as it does at first hand the spate of public-health legislation of the late 19th century, its vigorous language helps to remind us of the astounding story. But it hardly mentions the hospitals.

Apart from the works I began by mentioning, almost nothing has appeared in Great Britain in the last half-century strictly on hospitals as such. There are one or two popular or semi-popular books: Redmond-Howard and Evans wrote in half-historical, half-descriptive vein in 1928 on the *Romance of the Voluntary Hospitals* in the latter heyday of voluntary sentiment, and recently Mr. A. J. Wise has edited a volume entitled *Your Hospital* which offers a sketch of the kind indicated by its title. But of serious stuff for interested laymen there is nothing but P.E.P. reports and white-papers. A very brief sketch from the historical angle by A. G. L. Ives entitled *British Hospitals* was included in Collins's Britain in Pictures series in 1948. An outline account of the history of the last fifty years by Mr. J. F. Milne, which may serve as a peg on which to hang the various reports, appeared in the *Hospital* for January, 1951. The student will look out the Cave Committee report of 1921, and, more to the point, the Dawson report of 1920 which has recently been reprinted by King Edward's Hospital Fund for London as a text indispensable to a course of thinking on hospital topics: we have not yet seen the last of the ideas which this farsighted report first put into words. There are sections too of a report by the Liverpool Hospitals Commission of 1935 which gave an unrivalled description of the working of the voluntary hospital system between the wars.

HOSPITAL HISTORIES

The gap in the picture must therefore be filled in from other sources, among which the histories of individual hospitals are important. In the forefront in point of interest is Sir Ernest Morris's *London Hospital*, first put together in 1910. It has an appendix on Modern Administration, which offers many quaint contrasts with hospital affairs today. Florence Nightingale was nearly out of date about wounds: "wounds heal in towns just as well as anywhere else, in the majority of cases," thought Morris. In the outpatient department "men are always seen first in order that they may get back to work. Women afterwards." Despite archaic touches like this, as well as an almost unbounded and uncritical enthusiasm for the voluntary system, and despite too a certain Edwardian sentimentality, the book is full of good sense and ought to be widely read again today. "I never go round the hospital at night but I picture the shades of the great dead walking the long corridors and down the great wards." Morris was probably the best hospital administrator of his generation. He died in 1937.

St. Thomas's and the Middlesex have brought out excellent short illustrated histories recently, and Guy's a commemorative volume on a similar scale. There are longer histories of the two ancient foundations, *St. Bartholomew's* by Sir Norman Moore (1918) and *St. Thomas's* by Prof. F. G. Parsons (1932–36) in two and three volumes respectively: both quote extensively from old documents and minute-books and make one wonder whether nursing was so uniformly incompetent in the immediate pre-Nightingale era as one is often led to suppose. There are a good many other histories. That of Worcester by Dr. W. H. McMenemey, published in 1947, is one of the most generally interesting. The latest of all is *Portrait of a Hospital* by Dr. William Brockbank published this summer on the occasion of the bicentenary of the Manchester Royal Infirmary.

PAST TO PRESENT

Cushing's *Life of Sir William Osler* helps too to bridge the period of hospital affairs from the Nightingale epoch to the 1920s, and conveniently brings America into the picture. It is now reissued in one volume, much too heavy for comfortable handling. It is a book which should be read casually by the fireside; if the author's commentary is sometimes tedious, the many quotations from Osler himself are never dull and often throw light on aspects of hospital affairs which otherwise escape the lay administrator. His *Evolution of Modern Medicine*, though not very modern, provides the layman with an easy introduction to medical history. More solid general histories of medicine are of course Prof. Charles Singer's *Short History of Medicine* and Dr. Thomas Guthrie's more recent illustrated volume. There is too the *British Medical Journal*'s stimulating compilation *The Last Fifty Years*. For a very brief but excellent sketch made vivid with portraits in colour there is McNair Wilson's volume in the Britain in Pictures series. Reverting to Osler, one must not forget to glance at, if not to seek out, a copy of *Æquanimitas*, a book of talks and addresses on hospital topics, sometimes found on the shelves of wise hospital matrons and others who need ideas for talks to nurses.

Dr. S. S. Goldwater's book *On Hospitals* is one of the relatively few books from the other side of the Atlantic which is sufficiently general to be useful to the hospital world here. It is a reprint of essays and articles which reflect the mentality of the man who was probably America's foremost hospital administrator of the last generation. He was a great advocate of training for the hospital administrator, and he pitched his standards high: "to carry out the policy of the average board of trustees is not enough." Another of the recent books from the other side which is well worth attention has the unpromising title of *The Hospital in Contemporary Society*; it hails from Harvard medical men at the Massachusetts General, in Boston, and contains what is all too rare in hospital literature, a few thoughts on the philosophy behind hospital provision. The first historical essay of some 70 pages by Dr. Edward Churchill is one of the best short accounts of the history of hospitals. There is a searching, questioning note running through it that is a refreshing contrast to the complacency which marks too much of the American hospital literature. Simon Flexner's reports to the Rockefeller Foundation on Medical Schools may seem remote from British hospital affairs in 1951, but to open one of his books is to observe a strong mind at work, and it is salutary to be reminded of fundamentals.

NURSING

There is very little about hospital nursing that the layman will find worth while. Miss McManus's book, *Hospital Administration for Women*, was first published in 1934, and despite revision it does not quite reflect the thought of today on hospital affairs as seen from the matron's office. Mrs. L. R. Seymer's history of nursing is the best of its kind and includes a useful section summarising the characteristics of the four main systems of nursing—the Nightingale, the American, the Motherhouse, and the Continental. But it is open to the criticism that it does not discuss difficulties: no reader would imagine, for example, that the legislation of 1919 could be regarded as seriously mistaken. Both these books are, in parts, liable to harden the attitude of the nurses of tomorrow on matters where an open mind would offer better hope of happy hospitals. Another history is the *Story of the Growth of Nursing* by Miss Agnes E. Pavey.

BACKGROUND READING

Ranging further afield, one may ask how else should the general reader try to fill in his background? If he only wants to appear knowledgeable at the house committee he may have secret recourse to the King's Fund Visitors' Manual (1950) which will suggest questions that can fairly be asked without delving too deeply into financial or other complications. But if he really wants to understand the principles of hospital administration as understood in 1952 in the light of all that has gone before, he will have to pick out something here and something there from a not very extensive literature such as I have tried to indicate above. He may try to leaven it with a reading of one of the modern guides to management in business, such as Urwick's *Elements of Administration*; but this, though useful, will not take him very far, and it is hard to find a really satisfactory peg which will keep in their proper place the different hints which may be drawn from the field of industrial management. If he wants to understand how nearly the hospitals were transferred to the county and county-borough councils in 1946, and just why in the end that solution was rejected, he will have to know something of the history of the county councils, from their creation in 1888 through their heyday during the first third or so of the century. For this he might look at the *Life of Sir Robert Morant* by Bernard M. Allen; and Beatrice Webb's short and readable autobiography will help too to throw light on the period. He will need to understand the complications of the white-paper of 1944, which Mr. Bevan so promptly rejected when the Labour Government came into power. Whilst reading all this he will have to try to carry in his mind the strength and the sentiment behind the old voluntary tradition, with which the county councils had found themselves in uneasy partnership since 1930, and the revealing light thrown upon the scene by the war-time experience and the Ministry's hospital surveys of 1942–45. Prof. Richard Titmuss in his *Problems of Social Policy* touches on this period, but his approach will seem somewhat cold and unsympathetic to the difficulties of many of those who were actively engaged in keeping the hospital system going. It does, however, help to explain the position as seen from Whitehall and the difficulties of reconciling the old independence of the voluntary hospitals with the central control inseparable from war-time, and in any case needed to meet changing social conditions.

There is a conspicuous lack of material dealing in non-technical terms with the medical staffing of the hospitals. Few people outside the medical profession—and not all within it—appreciate the importance of the medical committee in the evolution of the hospitals. It is not merely important, it is an integral part of the structure of all hospitals where consultant work is taken seriously. Now, in the last few years, a revolutionary change has occurred in the staffing of the hospitals. Instead of having groups of consultants here and there to whom general practitioners can refer their cases, we have decided officially to have consultant staffs in *all* hospitals. Nowhere is this epoch-making change described or discussed, except incidentally in the surveys—before the recent changes had really been thought out—and, to some extent, in the Ministry's illuminating guide entitled The Development of Specialist Services (R.H.B.[48]1). But there the emphasis is on the various specialties rather than on the administrative implications. Yet every regional board and every hospital management committee has had to discuss these matters and worry its way through towards a working solution.

Hospital administration raises many interesting and really important questions, and the principles involved are only now beginning to be discussed with the attention that they deserve. I have previously attempted a brief sketch of some of the more fundamental principles under the title of Preface to Hospital Administration.[1]

CONTROL OF MEDICAL MAN-POWER

The Ministry of Health and the Department of Health for Scotland announce the appointment of a National Medical Manpower Committee to replace the Medical Priority Committee. The members of the new committee are:

Lord Haden Guest (chairman), Sir Russell Brain, Dr. E. A. Carmichael, Dr. H. R. Frederick, Dr. J. M. Gibson, Dr. D. F. Hutchinson, Dr. W. M. Knox, Dame Hilda Lloyd, Sir Sydney Smith, and Sir Cecil Wakeley.

The acting secretary is Mr. F. Bliss, Ministry of Health, Savile Row, London, W.1.

The committee has been appointed, in consultation with the medical profession, "to keep under constant review the best methods of utilising the available medical manpower and to make recommendations to the Government from time to time." It will carry on the task, hitherto performed by the Medical Priority Committee, of allocating doctors to the three fighting Services. It will be helped by advisers appointed by the Health, Labour, and Service departments.

Two central medical recruitment committees, one for England and Wales and one for Scotland, and a number of area recruitment committees dealing with the different branches of the service (general practitioner, hospital, and public health) in the different regions of the country, have been set up. The central committees, assisted by the area committees, will deal with the recruitment of young doctors to the Armed Forces for their national service. The committees, with the help of the Service and other departments concerned, will also screen doctors with reserve liabilities to determine their availability for service in the event of war.

The central medical recruitment committees are as follows:

England and Wales

Dr. E. R. Boland, Dr. J. B. Harman, and Dr. T. C. Hunt (appointed by the Royal College of Physicians); Mr. P. H. Mitchiner, Mr. J. B. Oldham, and Mr. Julian Taylor

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[1] *Lancet*, 1950, ii, 450.

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Occasional Survey

BONE REGENERATION

Problems of bone growth and regeneration have interested surgeons and other experimenters for over 200 years. Their systematic study can be said to have been under way by 1739, when Duhamel[1] published his paper on the red staining of the bones of animals fed on madder. With the development of aseptic surgery the use of bone grafts became general, and a voluminous literature on the subject has accumulated during the past 70 years or so. Much of this, though forming a valuable record of advances in surgical technique, throws little light on the fundamental problems of bone growth and regeneration.

The Fate of the Bone Graft

The observation that a successful bone graft becomes incorporated in the skeleton, is fixed to and merges with the surrounding bone, and is found to be vascularised, naturally led to the conclusion that it had retained its vitality and produced the new bone which welded it to the surrounding bone of the graft bed.

REPAIR BY VASCULAR INVASION

The first person to produce good evidence against this interpretation of the naked-eye appearances was Barth,[2] [3] who in 1892–3 made careful histological studies of the sequence of events in the healing of bone grafts in animals. He used trephine discs from the skull and cortical grafts of long bones, and he worked mainly with dogs, replacing the graft immediately or within a few minutes in the site from which it had been removed. He concluded that in all bone grafts detached from their blood-supply the bone cells died and the tissue was incapable of growth. Repair was carried out by an active invasion of blood-vessels and connective-tissue cells from the surrounding tissue. This new tissue became attached to the surface of the graft and also rapidly invaded the available spaces and cavities in the graft, depositing new living bone on the surfaces of the dead bone, not only as layers on the outside but also as a lining to the cavities and spaces in the graft. Thus the graft became revascularised and welded to its surroundings.

Although there has been much controversy on the matter since Barth's time, and although some of his interpretations of the histological appearances cannot now be accepted, there can be no doubt as to the accuracy of his main conclusion that the bone cells of the graft die and disappear, and that the bone is therefore dead and can take no active part in the healing process. Dead bone, however, unlike necrotic soft tissue, is, if aseptic, accepted by the body, and can serve as a scaffolding on which new living bone is deposited. Although the bone cells are dead, the calcified bone matrix is very resistant to the action of enzymes, and it does not undergo autolysis. It may be absorbed—removed piecemeal by osteoclastic cells—by the same process which remodels living bone. If it is not absorbed, it often has new bone deposited on it, and is thus built into the skeleton where it can remain structurally intact for a long time. For example, detached bone fragments at the site of a fracture are found to be dead; some of them, however, often escape absorption and become incorporated in the bony callus where they can be identified, sometimes years later, as islands of dead bone, structurally intact but lacking osteocytes in the cell spaces.

From what is known of the transplantation of soft tissues, both normal and neoplastic, it is only to be expected that the cells of a bone graft will die. Tissues separated from their blood-supply can only survive if transplanted as small fragments in which the cells are in close contact with the host's tissues, where they can get sufficient oxygen and nutrients to keep them alive until they have been revascularised by the ingrowing capillaries of the host.

SOME EXPERIMENTS

Hancox[4] transplanted fragments (measuring about $2 \times 2 \times 0{\cdot}5$ mm.) of an embryo chick's skull into the chorio-allantois of developing chicks; they survived and became revascularised within 18 hours—apparently by junction of the host's capillaries with the cut ends of those in the graft.

Conditions are very different even in the smallest bone graft, and it is obvious histologically, both with larger grafts and with bone chips, that the bulk of the cells die. It has been argued that a few of the surface cells can survive and are responsible for, or at least play an important part in, the production of the new repair bone. It is, of course, impossible to exclude the survival of a few surface cells, and this is not unlikely with a fresh autogenous graft. But the number of surviving cells must be very small, and it seems improbable that they can make any significant contribution to the repair process. This question has been examined by Reynolds and Oliver.[5] Using a standardised technique with inlay grafts in the tibial cortex of dogs, they compared the results obtained with fresh autogenous grafts taken from the opposite tibia and with homogenous (dog bone) grafts. Some grafts were preserved in a 'Merthiolate'* bone bank; others were frozen at −20°C; and others boiled for ten minutes and then stored under sterile conditions. They confirmed Barth's observation that there is no evidence of cell survival in fresh autogenous grafts, all the osteogenic tissue being furnished from the surrounding bone. In the fresh grafts, however, the healing process was more rapid in its early stages; this was the result of a more rapid penetration of the graft by capillaries and osteogenic connective tissue from the surrounding bone. With the homogenous merthiolated or frozen grafts the penetration, though slower, was finally just as complete, and after ten weeks no difference between these and the fresh autogenous grafts could be detected. The boiled bone grafts were considerably more resistant to penetration by blood-vessels, and union proceeded much more slowly. This resistance of boiled bone to vascular penetration was also noted by Hancox.[4] It is clear, however, that in Reynolds and Oliver's experiments the reason for the resistance of boiled bone to vascular penetration was not the fact that it was dead, for the stored merthiolated bone which vascularised quite well was certainly dead when implanted. Some other factor must be responsible—possibly the coagulated and denatured state of the tissues in the Haversian canals and marrow spaces.

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* 'Merthiolate' is sodium ethyl-mercurithiosalicylate. It was introduced about 20 years ago as an antiseptic and preservative for biological products. It has a relatively low cytotoxic action.

[1] Duhamel, H. L. *Mem. Acad. roy. des Sci.* 1739, 52, 1.
[2] Barth, A. *Arch. klin. Chir.* 1893, 46, 409.
[3] Barth, A. *Beitr. path. Anat.* 1895, 17, 65.
[4] Hancox, N. M. *J. Physiol.* 1947, 106, 279.
[5] Reynolds, F. C., Oliver, D. K. *J. Bone Jt Surg.* 1950, 32A, 283.
[6] Buchsbaum, R., Bloom, W. *Proc. Soc. exp. Biol., N.Y.* 1931, 28, 1060.

It appears therefore that under standard conditions the rate of healing of a bone graft depends not on its content of viable cells but upon the ease with which the osteogenic tissues of the host can penetrate it and gain attachment to it. Drastic treatment such as boiling, which coagulates and denatures its organic constituents, makes it less susceptible to penetration and reconstruction by the host's cells.

The Origin of the Osteoblast

Another aspect of bone regeneration concerns the origin and specificity of osteoblastic cells. From what sources can the osteoblasts responsible for the bony union of a graft or fracture be derived? This problem has stimulated much experimental work and much controversy in the past. Some have thought that osteoblasts are specific cells which can only be produced by the periosteal or endosteal cells, others that any connective-tissue cells in the neighbourhood of bone may become osteoblastic under the stimulus of trauma and its sequelæ.

The study of cells of the connective-tissue group by tissue-culture methods was started by Maximow about 30 years ago. He and his successors have stressed the mutability of these cells, and the ease with which they can undergo structural and functional modifications.[7] It is now generally accepted that the reticulum cells of the bone-marrow have most of the potentialities of the embryonic mesenchyme, and can give rise, as occasion demands, to either the hæmopoietic group of cells or the collagen-forming types—fibroblasts and osteoblasts. Fibroblasts and osteoblasts are closely related structurally and functionally; they both produce a tissue composed of abundant collagen together with mucoid substances—mucopolysaccharides.

In bone repair, such as healing of a fracture or a bone graft, bone formation is always preceded by a proliferation of fibroblasts. The first sign of bone appears as an area of more closely packed collagen fibres, which gradually become partly obscured by the development of an amorphous refractile cement substance around them, giving rise to an island of coarse-fibred (non-lamellar) bone which rapidly calcifies. Before the development of cement substance all the cells have the appearance of fibroblasts, and there can be little doubt that here osteoblasts arise as a modification of fibroblasts. The conversion of fibroblasts to osteoblasts seems to take place easily enough in tissues close to bone, but much less often in connective tissues further away. However, small deposits of heterotopic bone are not uncommon on the edge of calcified foci—e.g., calcified tuberculous lesions in the lung, calcified arteries, and sometimes in laparotomy scars. Damage to muscle may also lead to bone formation (the so-called traumatic myositis ossificans).

Bone Formation by Induction

The exact nature of the stimulus which encourages fibroblasts to become osteoblastic is not known. It has been suggested that, in the region of a damaged bone, chemical agents diffusing out from injured bone or cartilage may "induce" fibroblasts to become osteogenic. (The term "induction" is used by experimental embryologists to describe the process by which one group of cells determines the direction of development of a neighbouring group. In some instances this effect has been shown to depend on the production of diffusible substances.)

INDUCTION BY TRANSPLANTS

Some of the most striking experiments demonstrating the production of bone by induction are those of Huggins,[8] who showed that, in the dog, bone was almost invariably formed in the fibrous tissue which surrounded an autogenic transplant of epithelium from the bladder, ureter, or renal pelvis. Such a transplant produces new epithelium which spreads out from its edge, and grows round to form an epithelial cyst. Huggins showed that the bone forms in the connective tissue near that part of the cyst wall formed by the newly proliferated epithelium, and not in the tissue near the surviving, but non-proliferating, epithelium of the transplant. Similar transplants of epithelium from gall bladder, stomach, jejunum, and prostate did not induce bone formation. The effect was produced on connective tissues of various fasciæ, on the capsule of the knee-joint, and on the connective tissue in muscle; it was not produced on the connective tissues of the kidney, liver, spleen, or wall of the bladder. Huggins found that the fluid in cysts developed from urinary-tract epithelium contained a higher proportion of calcium and phosphorus than the blood plasma—usually about 50% higher. He thought that the permeation of calcium and phosphorus through the cyst wall, particularly through the areas covered by thin newly formed epithelium, might be the stimulus which induced bone formation. Whatever may have been the nature of the stimulus, it is of interest that the tissues in which it acted—fasciæ, joint capsules, and the interstitial connective tissue of muscles—are also liable to undergo ossification in man.

INJECTION OF EXTRACTS

Levander,[9] following an observation on the development of new bone round transplants in the subcutaneous tissue and muscles of the rabbit, considered that substances inducing bone formation must diffuse from the transplant. He then made extracts of bone and fracture callus from the rabbit, and injected these into the thigh muscles of rabbits. Bone developed at 60 out of 70 sites of injection with alcoholic extracts; but 10 injections of watery extracts and 20 injections of alcoholic extracts of plain and striated muscle were negative.

Annersten [10] repeated this work on a larger scale, and obtained about 20% of positive results at over 200 sites of injection of various types of alcoholic extract of bone and cartilage. With alcoholic extracts of various tissues other than bone he obtained 2 positives in 43 experiments—one with tendon and the other with muscle extract. Another paper [11] from Levander's department reported positive results with alcoholic extracts of calf marrow, and twelve papers by other workers give results of similar experiments with alcoholic extracts of bone.[12 13] Six of these are confirmatory and six either negative or positive in control series with alcohol alone.

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[7] Bloom, W. *Physiol. Rev.* 1937, 17, 589.

[8] Huggins, C. B. *Arch. Surg.* 1943, 22, 377.

[9] Levander, G. *Surg. Gynec. Obstet.* 1938, 67, 705.

[10] Annersten, S. *Acta chir. scand.* 1940, 84, suppl. 60, 1.

[11] Willstaedt, H., Levander, G., Hult, L. *Acta orthop. scand.* 1950, 19, 419.

Heinen et al.[13] obtained a higher percentage of positive results with alcohol alone than with alcoholic extracts of homogenous bone. They injected the material into triceps and quadriceps of rabbits, using Annersten's technique for preparing and injecting the bone extracts. They obtained 45% of positives with alcohol alone in a total of 77 injections, 29% with 24 injections of alcoholic extracts of bone, and 50% with 10 injections of alcoholic extracts of muscle. Their proportion of positive results with bone extract was about the same as that obtained by Annersten. It is difficult to understand the negative or very rare positive results which Levander, Annersten, and others obtained in their control series injected with alcohol alone or alcoholic extracts of tissues other than bone.

Certain types of muscle damage thus produce a connective-tissue reaction which is apt to result in bone formation. All those who have observed cartilage and bone formation in muscle after the injection of alcoholic extracts of bone, alcohol alone, or other types of irritant—e.g., calcium chloride—describe much the same sequence of histological changes. There is a central area of necrosis outside which lies a zone of vascular granulation tissue, showing a great proliferation of fibroblasts between muscle-fibres, some of which are necrotic and some calcified. Cartilage forms among the cells in the fibroblastic tissue, as isolated cells or as conglomerations of cartilage cells forming small nodules. A little coarse-fibred bone may form at this stage, but most of the bone is produced by secondary endochondral ossification in the cartilage nodules. (There is no evidence that the cartilage or bone formation is particularly related to the calcified muscle-fibres.[13])

NEW EVIDENCE

Although the existence of a specific osteogenic substance in extracts of skeletal tissue has not been proved, there is little doubt that pieces of dead bone or cartilage can in some way induce bone formation in adjacent connective tissues, even when these are remote from the skeleton. Urist and McLean[14] have brought forward further evidence on this question. They transplanted osseous and non-osseous tissues into the anterior chamber of the eye in rats. All the tissue used, with the exception of some epiphyseal cartilage, was autogenous. The fragments, introduced through a needle, were small enough to permit of cell survival. They found that the periosteum of normal mature rats did not produce bone, but the periosteum of young rats (aged three weeks) and that taken from the region of a three to four days old fracture in mature rats produced bone in about 50% of implants. Bone-marrow of mature rats also produced bone. Cancellous bone nearly always produced bone, but cortical bone, free of periosteum and marrow, rarely did so. It is of interest that the bone cells of even such small implants died and disappeared. Where new bone was formed, there was surface erosion by a vascular "mesenchyme" adjacent to the fragment; bone was then deposited on the eroded surface of the transplant, apparently by the vascular fibroblastic tissue ("mesenchyme") of the host, but bone formation by surviving surface cells of the implant could not be excluded.

Interesting results were obtained with cartilage, implants of which were made from epiphyseal and articular cartilage and from fibrocartilaginous callus. There was a high proportion of "takes" with all these cartilage implants, which were examined at intervals from six to thirty-six days after implantation, and the sequence of events was essentially the same with all of them. During the first week the implant became surrounded by an inflammatory granulation tissue forming a capsule round the graft. During the second week the capsule was divided into two layers by the formation of an inner layer of vascular mesenchyme; this produced absorption of the cartilage followed by a deposition of new bone on the remains of the cartilage matrix. This is exactly the same process as occurs in normal endochondral ossification, in the ossification of cartilaginous fracture callus, and in the ossification of cartilaginous nodules in muscle. The point of interest here is that the invading tissue which produces the cartilage absorption and deposits the new bone is, or appears to be, furnished by the tissues of the host.

Urist and McLean then showed that the same result can be produced by induction. They implanted fragments of fibrocartilaginous fracture callus, killed by boiling in saline for three minutes (and also by freezing, but boiling is the more certain guarantee of death), and they found that the dead implant was absorbed by a similar vascular tissue (here unquestionably derived from the host) which also deposits bone on the surfaces of the partly absorbed cartilage. This process differed from what happened with the living implant only in the production of a much thicker fibrous capsule, and in the slower development of the cellular reaction leading to cartilage absorption and bone deposition.

It has usually been assumed that the production of bone by induction is dependent on soluble substances diffusing from the inducing tissue; experimental embryologists have, however, shown that in some tissues direct contact between the cells of the inducing and the induced tissue is necessary.[15] This may be the case when implants of bone or cartilage are the inducing agents. On the other hand, since erosion of the surface of the implant by the action of osteoclasts or similar cells commonly precedes bone formation, soluble products, both organic and inorganic, must be liberated from the transplant. So far, however, no specific inducing substances have been identified.

Medicine and the Law

Defamation Proceedings

THE Ministry of Health has assured the British Medical Association that, in the event of proceedings for defamation against a doctor arising out of his entries on a hospital patient's case-papers by reason of their loan to, and use by, the Ministry of Pensions or the Ministry of National Insurance, the Minister will indemnify the doctor against any damages that may be recovered and against all reasonable costs that he may incur in defending the proceedings. The indemnification of medical practitioners called on to disclose confidential information before tribunals is also covered by this assurance.

If legal proceedings seem likely to arise it is advisable for the doctor to consult his defence society in the first instance, since some cases are more appropriately handled by such a society. The Ministry's assurance will not apply if the defence of the doctor is undertaken by the defence society, and will be subject to the Minister being informed at once of any threatened proceedings and having complete control over the conduct of the defence.

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12. Lacroix, P. The Organisation of Bones. London, 1951.
13. Heinen, J. H. jun., Dabbs, G. H., Mason, H. A. *J. Bone Jt Surg.* 1949, 31A, 765.
14. Urist, M. R., McLean, F. C. *Ibid*, 1952, 34A, 443.
15. Weiss, P. *Quart. Rev. Biol.* 1950, 25, 177.

In England Now

A Running Commentary by Peripatetic Correspondents

MY daughter-in-law is expecting a baby, and I said wasn't she lucky to be having it in such a famous London hospital where she could be sure everything would be all right. My daughter-in-law said yes she supposed so, but doctors didn't know everything. In fact there were some things she wished they knew a little more about. She would tell me.

She goes every week to the hospital and a month ago the doctor said she would have the baby in a week. Then she went back in a week and another doctor said you can't possibly tell for certain and she might easily be another fortnight. So my daughter-in-law went home again.

The next time she went a third doctor said she ought not to be alone and was there anybody with her when her husband was away at work? My daughter-in-law said she would get her mother to stay with her in the day-time, though it was not very convenient.

The next week the mother of my daughter-in-law said she was not coming any more. She weighed fifteen stone and lived thirty miles away and in this heat she couldn't stand the tubes and the buses. And anyway my daughter-in-law had the telephone, hadn't she?

At the hospital a fourth doctor said they had better induce her and would she please come in tomorrow. My daughter-in-law went and they did all sorts of queer things to her, and while they were at it one of the other doctors popped his head round the door and said hullo, it's you is it, and he'd better take her over. So he took my daughter-in-law over and said nothing seemed to be happening so she could go home now.

There is a board up in the hospital saying if you notice anything unusual you should tell the doctor at once. My daughter-in-law said the baby made queer clicking noises inside her at night just as if it was pulling its fingers and making them crack. So she told the doctor and asked him what caused it, and the doctor said it was caused by the baby pulling its fingers and making them crack. My daughter-in-law did not think this was funny.

My daughter-in-law says doctors shouldn't argue over your tummy about whether the baby is lying right, because it rather frightens you if you are having a baby for the first time, doesn't it? And anyway she knows she is a left occipito-posterior because she read it on the folder before sister came and snatched it away and said goodness what would doctor say if he saw her. And that's another thing, my daughter-in-law said. If they don't want you to read your folder they shouldn't give it to you and then leave you lying on a couch for half an hour with nothing to do. Because what do they think a girl is going to do all that time.

My daughter-in-law said of course they knew all about having babies there, but she did think if these young doctors studied psychology a little as well so that they knew what their patients were thinking, it would be a good thing, if I saw what she meant.

I thought I did.

* * *

"I am not addressed as Fellow, my lord. I am a Master Executioner . . ."

You may remember these words as the end almost of the skilful cascade of falling anticlimaxes by which Shaw lets us down from the tension of the trial scene in *Saint Joan*. But I am more concerned with it as authority for the relative grading of the letters after our names. A Fellow, it appears, is less than a Master. Now a Master as everyone knows is something between a Bachelor and a Doctor, and a Member is less than a Fellow. Yet there are people, knowing one to be an M.D., who dare to suggest one would be better with an M.R.C.P. as well.

* * *

He was a shunter, in hospital for treatment of a peptic ulcer. The history-taking was thorough, and he was asked whether he had been subject to any stress at the time of onset of his symptoms. "Yes, there was something," he said, "I 'ad a bit of bad luck. Drove into the side of another train where the lines converged—pushed 'im clean off the road and telescoped three carriages. Week later, I went into the back of a train; saw the signal but didn't stop; why I don't know to this day. And five days after that, bless me if I didn't leave me train too near a crossing and the other bloke 'it me—my fault of course. Didn't do much damage that time, I didn't. Just smashed up the driving cabin. No, can't say I did get dyspepsia just then. Takes a lot to put me off me food. Besides, these things 'appen every day. How much was the damage? About £27,000 worth."

I thought of the sleepless nights caused by the £8 bill for beating out the door of my Morris Minor . . .

* * *

At some time in the 1860s the youngest daughter of a Truro physician contracted scarlet fever. She recovered, but one of her brothers died of the disease. After this experience she became a diffident and apprehensive child; and when she was dying, sixty years later, she said to her firstborn son, "You don't know what a comfort it is to think that I am never going to be shy again." Although a dutiful wife and a good mother, she had withheld from her family all outward appearance of affection.

When her son, at the age of nine, was sent to boarding-school, he was a sensitive and timid child eagerly seeking the love denied him by his mother; instead he encountered, nightly and for six terms, the remorseless cruelty of other boys. The life of imagination became his real existence, and he fed it daily with innumerable novels and romances. This day-dreaming disturbed his studies and prevented the acquisition of the common skills and the ordinary practicalities of modern life. Throughout his life his imagination continued to be preoccupied by terror and obsessed by cruelty. He described his undergraduate career at Cambridge as shabby and furtive with "no honour and much timidity." There, however, he first practised that extraordinary impetuosity in search of friendship which brought him some distress but greater happiness. "Er liebte jeden Hund, und wünschte von jedem Hund geliebt zu sein." All men were his fathers and brothers; but no woman was to be his lover, for maternal rejection destroys the sexual impulse.

He liked his food and when "out to tea, he would gleefully eat half-a-dozen macaroons like a guilty schoolboy"; and at forty-one, developing diabetes after the death of his mother, he was neglectful of diet and erratic with insulin. He was sympathetic, generous, industrious, intelligent, and eloquent. He was ambitious, acquisitive, vain, obtuse, and disposed to tantrums of great violence. He died, as my readers will have forecast, of coronary thrombosis. His name was Hugh Walpole, and I have just been reading his biography which Rupert Hart-Davis has written in friendship, wisdom, and restraint.

* * *

Doctors' children are commonly, if erroneously, supposed to be less healthy than the offspring of non-medical parents, and I sometimes think I detect among my friends a malicious pleasure in discovering that the children of an embryo psychiatrist are at any rate not better behaved or conspicuously better adjusted than their contemporaries. The other day, a neighbour of mine described to me the small schoolfellow of one of her own children as being the worst mannered and most horrible child she had ever met. "But" she added, "then I found out that the father is a psychiatrist, so of course the child is allowed to do exactly what it likes and has never been taught any manners."

Naturally I don't accept this as final, or even fair, but certainly the psychiatrists haven't yet given us all the answers. Meanwhile enlightenment sometimes comes from unexpected sources. Last week, over the dinner table, an unusually intelligent old lady of 80 quoted the wisdom of her father's coachman, who had helped to bring the whole family up. "Children" he said, "must be with other children. Only children can be sufficiently unkind to each other." I find this a consoling thought when our daughters beat each other up, steal each other's possessions, insult each other with the worst words at their command, and, in fact, give every evidence of having a psychiatrist for a father.

Letters to the Editor

THE SITUATION OF THE MENTAL HOSPITALS

SIR,—The scarcity of beds in mental hospitals is due to lack of nurses, but, as you remarked last week, "the remedy is not yet in sight" and "the problem of recruiting mental nurses needs special study." This study is bound to take time, and any decisions will take still longer to implement. During all this time the beds that are needed now will not be available.

There is, however, one way in which many more beds could be made available without recruiting a single extra nurse, and that is by discharging many of the harmless chronics who now make up a big proportion of the permanent residents in every mental hospital. If local authorities, together with the Ministry of Health, would organise "day hospitals" more or less on the pattern of the one in Blackfriars Road,[1] these chronics could be effectively supervised, occupied, and treated by day, and at night could be sent to their homes or to relatives or friends accepting responsibility for them. As an immediate temporary solution, this would enable acute cases to obtain the urgent treatment they need, thus perhaps preventing chronicity. In many cases the chronics and their relatives would welcome the release from hospital. Not only would this effect a general all-round economy, but also it could help to dispel the mental-hospital stigma, proving how many mental patients need not remain incarcerated for life.

Manchester. J. F. WILDE.

"A.P.F. EFFECT" AND ISONIAZID

SIR,—Dr. Mosonyi and his colleagues[2] say that streptomycin sometimes improves the health of children to an extent which is apparently unrelated to the type of disease for which it is given or to the eventual outcome. They do not enumerate these streptomycin-responsive diseases; but if they are the same as those I have listed as responsive to "mycin" or adrenocortical hormones[3] the statement will have my full support.

At hospital conferences, when I have presented patients with leukæmia, Hodgkin's lymphoma, disseminated lupus erythematosus, or rheumatoid arthritis, which has apparently been brought into the remissive phase by mycin administration, I have been assured that, if correct, my observations would mean that all these diseases are due to "infection" by "mycin-susceptible" viruses or bacteria. Even admitting that all the mycins —even streptomycin—are "broad spectrum" antibiotics, it is of course impossible to take this explanation seriously. In the United States a large proportion of our domestic poultry, swine, and fur-bearing animals have had their growth-rates increased by the addition of a mycin supplement, under the name of animal protein factor (A.P.F.), but one can hardly suppose that all this improvement is due to the cure of active infections from which they previously suffered.[4]

A closer though not complete approximation to the true rôle of what (in animal husbandry practice) has been termed the A.P.F.-mycin effect may have been given by Selye[5] in citing evidence that streptomycin,[6] penicillin (which is an A.P.F. in chickens), and terramycin[7] are non-specific "stressors" in his adaptation mechanism scheme. To make the adaptation theorem explain the facts fully, we need to redefine the term stressor.

Obviously the major rôle of an antibiotic is not that of a *non-specific* stressor, for then its administration would in itself constitute the stress, and all antibiotic administration—even to normal individuals—would elicit an adrenocorticomimetic response. We know, however, that in the perfectly intact (i.e., the non-stressed) individual mycin administration does not have much effect; nor does the administration of dehydroascorbic acid, a corticomimetic agent under certain circumstances,[8] have much effect in the "unsensitised" (i.e., non-stressed) animal, according to Dr. Kelemen and his co-workers who seem to have recognised the necessity of designating the subject's state in the interpretation of general adaptative responses.[9]

The failure of a patient with adaptative disease to react properly to his stress situation is remedied by ingestion of A.P.F. which seems to work by curtailing absorption of proteose from the lower bowel. There is now strong indirect evidence that certain types of hyperproteosæmias, derived intestinally or otherwise, may competitively block the unique polypeptide synthesis by which the anterior pituitary elaborates its corticotropin.[10] Any A.P.F., by substitution of a predominantly saccharolytic intestinal flora, may mitigate hyperproteosæmia from this source and thus permit an adrenocorticomimetic response in a stress situation.

The above explanation of the operation of mycin, or other A.P.F., in adaptative disease is now put forward for a very practical reason. It appears that isoniazid, the recently exploited "anti-tuberculosis" drug, is a potent A.P.F. in vivo. Though presumably devoid of any capacity to inhibit, in vitro, the development of clostridial or coli-aerogenes organisms, it nevertheless may promote implantation of a predominantly saccharolytic intestinal flora. Hence the same remissive tendencies previously produced by mycin ingestion in patients with lymphoma and collagen-vascular diseases are being duplicated by isoniazid administration. It is to be hoped that this last fact will not be seized upon to "prove" the universally tuberculous nature of adaptative disease. After all, the days are not long past when everything except childhood exanthems was explained away as a manifestation of tertiary syphilis.

Laurelton,
Long Island, N.Y. ROBERT D. BARNARD.

HALLUX VALGUS

SIR,—We are grateful to Mr. Turvey (Aug. 2) for his criticism of our radiographic method.[11] We are ourselves acutely conscious of its limitations, which have been dealt with more fully in papers referred to at the end of our text.

Two observations may go part of the way to meet his criticism:

1. There is no association between high longitudinal arch and increase of hallux valgus. In fact the opposite holds.
2. It is not, we think, possible to get any reliable information whatever about the size of the first intermetatarsal angle by any external measurement of any kind.

This leaves his objection that a high longitudinal arch is associated with an apparent diminution of intermetatarsal angle. In any future survey statistical analysis of this point by means of the partial-correlation coefficient might be advisable. We doubt whether, in fact, this factor will be of much significance, and would only add that, however much radiography may be a *pis aller*, it is at present the only available method of making any measurement at all.

Department of Anatomy,
University College, London. R. H. HARDY
J. C. R. CLAPHAM.

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1. Bierer, J. The Day Hospital. London, 1951.
2. Mosonyi, L., Juthasz, J., Pollak, L., Zulik, R. *Lancet*, 1951, ii, 81.
3. Barnard, R. D. *Ibid*, 1952, i, 612.
4. Barnard, R. D., Orens, L. R. *Med. Times*, 1951, 79, 94.
5. Selye, H. Annual Review of Stress. Montreal, 1951.
6. Patrono, V., Valletta, G. *Ormonologia*, 1949, 11, 219.
7. Barnard, R. D. *N.Y. State J. Med.* 1950, 50, 1852.
8. Kelemen, E., Olah, F., Majoros, M. *Lancet*, 1951, ii, 886.
9. Kelemen, E., Majoros, M., Ivanyi, J., Kovacs, K. *Experientia*, 1950, 6, 435.
10. Barnard, R. D. Unpublished observations.
11. *Lancet*, 1952, i, 1180.

PANCREATICOGASTROSTOMY

SIR,—In their paper (Aug. 9), Professor Ingebrigtsen and Professor Langfeldt say that they "resected the antrum of the stomach so that it contained no free acid postoperatively." They make the same point in their summary. Their use of the phrase "extensive resection" of the antrum in the second place suggests that the word does not refer to the pyloric antrum in Norwegian nomenclature as it would in British, but in any case it is difficult to see how any partial resection of the stomach, however extensive, could get rid of the gastric hydrochloric acid unless the vagi were resected at the same time.

London, W.1. HENEAGE OGILVIE.

MEPHENESIN IN INTRA-OCULAR OPERATIONS

SIR,—As is well known, in intra-ocular operations it is essential that the extra-ocular muscles should be relaxed, thus keeping the vitreous back and preventing the patient from "squeezing" the eye.

I have, in the past, hesitated to use curare for this purpose. Some two years ago, however, I started to use mephenesin ('Myanesin Elixir'), which I have found produces relaxation with no danger to the patient. I have used this preparation in 26 cataract operations, 22 glaucoma operations, about 70 iridectomy operations, and 4 cases of nystagmus.

One tablespoonful of the preparation was administered two hours before the operation, followed by a further tablespoonful one and a half hours later. This dosage was used whether or not tension was present. Half an hour after the second dose, the eye muscles became relaxed and the patients experienced a slight "numb sensation" throughout the body. During operation the vitreous remained in place and did not present forward, and the operation could proceed with ease and safety. In the cases of nystagmus, mephenesin either stopped oscillations or minimised them in 2 children, lessened them in a girl of 15, and appeared to abolish them (after repeated administration) in a man of 45.

I should be interested to know whether anyone else has tried mephenesin in these conditions.

Coptic Hospital,
Cairo, Egypt. ABDEL MESSIH GIRGIS.

THE PROSPECT OF GENERAL PRACTICE

SIR,—Your anonymous and egotistic correspondent (Aug. 16) has decided that his "intellectual thirst" cannot be satisfied in general practice as it is, and goes on to give about the most distorted account of a G.P.'s life and work I have ever read. To answer his 4 points in order:

1. After enlarging on his skill and intellect, he states: "I shall be too busy to examine or follow any case adequately." I would say that any G.P. who fails to examine or follow any case adequately will very soon be in trouble. If we organise our work properly by making special appointments, &c., we can always ensure that a patient requiring a detailed examination is given it at leisure. Now that X-ray and laboratory facilities are generally available we can fully investigate the majority of our cases without troubling the consultant.

2. If this is his idea of a G.P.'s family life even before "Danckwerts," then I am truly sorry for him. Has he never heard of arrangements with his colleagues?—but, of course, he does not trust them (see point 4). Has he never heard of a rota for night work, group practice, or partnership?

3. "Whatever insult, stupidity, thoughtlessness, or unnecessary demands he [the State patient] may submit me to, I must smile and comply." Does he really think G.P.s are as spineless as this? Anyone with this outlook would soon collect a practice of malingerers and be treated by his patients and colleagues with the contempt he deserved. Every practice must have some discipline, and the patients respect their doctor for applying it.

4. "...if an influential competitor gets a seat on the Regional Board not only are my hopes of advancement killed, but my very livelihood endangered." This is an amazing statement, and I confess I cannot conceive how a G.P. could possibly be affected in any way by a "competitor" being appointed to a regional board. Sir, may I ask your anonymous correspondent to give chapter and verse for his statement and explain what he means? For his information a G.P.'s authority in the N.H.S. is the executive council, and we are only too grateful for the work and time spent on this council by those of our colleagues who are appointed to it. If this statement is indicative of your anonymous correspondent's ideas of how G.P.s treat each other, then it is no wonder that he has not considered working an off-duty or holiday rota with his neighbours.

With his suggestion that there should be more research in general practice I have no quarrel, but I strongly object to his picture of general practice, and his condescending attitude as exemplified by his suggestion that a G.P. would be ridiculous in a professorial chair. I can think of many G.P.s who would bring dignity, knowledge, common sense, and much-needed liaison as professors in our universities.

Research in general practice will, in my opinion, best be stimulated by increasing liaison between hospital and G.P.s, and by making G.P. beds available in hospitals. It will not be helped by articles such as your anonymous correspondent's, which can only have the effect of discouraging this desirable and necessary liaison.

Wingerworth, near Chesterfield. J. F. HANRATTY.

PRESERVATION OF ARTERIAL GRAFTS BY FREEZING

SIR,—The article by Professor Hufnagel and myself[1] included a reference to the work of Smith and Parkes[2] at Mill Hill on recovery of frozen stored ovarian tissue and red blood-cells. Our comment that "survival is quite unpredictable, even with constant technique," though it certainly applied to previous methods of frozen storage, does less than justice to the work of the Mill Hill group.

A recent visit to that centre confirmed that the glycerol-saline technique provides consistently viable tissues after storage. Ovary, sperm, and testis, and some endocrine tissues seem to be perfectly preserved. It is to be hoped that this method may soon be applied to problems of stored functioning transplants in man; such tissue preparations are now being banked along with the arterial grafts in this department.

Surgical Unit,
St. Mary's Hospital, London, W.2. H. H. G. EASTCOTT.

FLYING AND LIFE ASSURANCE

SIR,—A peripatetic correspondent writes in your issue of July 26:

> "I wonder how many of my peripatetic colleagues . . . realise that if they fly more than 15,000 miles in the course of one year they are automatically depriving their dependants of all benefits under their F.S.S.U. scheme should they be involved in a fatal accident? Apparently all the leading life-assurance societies have a clause in their policies which imposes this limit on flying unless an extra premium is paid."

This conveys an entirely wrong impression, since British life offices issue, whenever possible, policies unrestricted as regards airline travel. So far as I am aware, no life-assurance policy issued in this country, whether under the F.S.S.U. scheme or otherwise, would contain any clause by which cover would cease after the policy-holder had flown in one year 15,000 miles, or indeed any other distance.

The future flying prospects of a proposer for life assurance are elicited at the time of his proposal. In the great majority of cases the expected yearly amount of passenger flying is less than 15,000 miles, and the issue

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1. Hufnagel, C., Eastcott, H. H. G. *Lancet*, 1952, i, 531.
2. Smith, A. U. *Ibid*, 1950, ii, 910. Smith, A. U., Parkes, A. S. Ibid, 1951, ii, 570.

in such cases of policies unrestricted in respect of airline travel is normally automatic. If the expected amount of passenger flying exceeds 15,000 miles per annum, the usual course is for a quite small additional premium to be paid in order that a policy without restriction on airline travel can be issued.

Under an unrestricted policy a life office would expect to meet in full any claim arising out of airline passenger flying, no matter how much such flying the policyholder had done, provided of course the office was satisfied that his answers at the time of his proposal were given in good faith.

7, Chancery Lane,
London, W.C.2.

J. H. KITTON.

OXYGEN TENTS

SIR,—May I be allowed to correct several misleading impressions given to users of oxygen tents by your special article, Ingenuity in Whitechapel (Aug. 2, p. 237).

While such costly tents as those referred to (£180–237) may be available for sale, the majority of hospitals and institutions have long known that a range of the most modern completely equipped oxygen tents can be bought at a fraction of such prices through my own organisation. Oxygenaire Ltd.—probably the largest manufacturers of oxygen tents in the British Empire—i.e., from £30 to £135 according to size. As with most other manufactured goods, cheaper qualities of oxygen tents might possibly be introduced at lower cost, but not if all the modern refinements of construction and performance—now almost universally demanded—are to be included.

From our twenty years' specialisation in the manufacture and supply of oxygen tents, it is not our experience that hospitals in this country find the hire of tents as expensive as your article implies, when all the factors behind a day-and-night rental service are taken into account. Our own service, for instance, includes the immediate delivery of a tent to any part of the country with qualified operators; free instruction and demonstration in the ward; free inspection and maintenance of equipment; the free provision of medical films and filmstrip lectures for training purposes; the benefits of continuous research and the development of improved methods and apparatus; and frequent non-profit-making coöperation in experimental work in hospitals.

I am somewhat dismayed that the results obtained with the tents described in the article should be regarded as "almost identical with those from a standard oxygen tent," since they fall very far short of the results to be obtained with tents of our manufacture—and which are indeed expected of our tents by the majority of hospitals.

If authorities using our tents would avail themselves of the free inspection and maintenance service we provide with our equipment, they would readily appreciate the higher efficiency that can be attained when a tent is overhauled and restored to our own critical standards of operation.

8, Duke Street, London, W.1.

G. W. HIGGS
Managing Director
Oxygenaire (London) Ltd.

***We have shown Mr. Higgs's letter to the surgeon at the London Hospital who was responsible for the tests made on the oxygen tents. An extract from his reply is given below.—ED. L.

"The dismay expressed by Mr. Higgs is surprising, since the results we obtained correspond completely with the aims expressed in the useful little booklet 'Oxygen Therapy,' published by Oxygenaire Ltd. It must be explained that we did not set out to obtain maximum oxygen concentration levels, and have not subjected our tent to such purely theoretical trials, as we see no practical advantage in so doing. We took one of our tents and an Oxygenaire tent, and ran a series of identical tests on both, supplying the oxygen at the rate recommended by Oxygenaire Ltd. The detailed figures were:

Tent	*Oxygen concentration after*		
	20 min.	*60 min.*	*120 min.*
L.H.	39·9%	48%	48·1%
Oxygenaire ..	40·2%	47·6%	48·1%
	Carbon dioxide concentration (max.)		
L.H.		1·7%	
Oxygenaire ..		1·72%	

Temperature and humidity tests both showed a steady line with each tent. As we did not perform the tests simultaneously, but first tested our own and then the standard pattern, the figures do not correspond, but in neither case did the temperature or humidity rise significantly.

We did these tests purely to satisfy ourselves that our tent was as efficient *in our hands* as the standard model, as sold; and for no other reason. Better figures are no doubt obtainable with both models. We were only concerned to be sure that the results were good enough for use on patients requiring oxygen therapy, when the tent was erected and run by our normal nursing staff, with due regard to economy in oxygen. We satisfied ourselves on these grounds; and only after a year of hard, steady use did we feel that other hospitals might care to benefit by our experience."

PLEA FOR PSYCHOTHERAPY

SIR,—May I take up one or two points in Dr. Mullner's letter of Aug. 16?

I had no intention either of decrying the value of modern physical treatment in psychiatric cases, or of denying the need for research to give greater knowledge and certainty. I maintain merely that, in our enthusiasm for the physical approach, we should not forget that psychotherapeutic methods have their proved value and are, to say the least, no more empirical than many physical methods. I hold no brief for psycho-analysis on Freudian lines, but on the contrary, believe in the utmost flexibility of technique. Until we know more, we are not justified in withholding any form of treatment which promises benefit, even though we cannot argue its value as scientifically as we should like.

I would query the implication by Dr. Mullner that confession is equivalent to Freudian psycho-analysis (the word psycho-analysis of course denotes the Freudian procedure). Surely the first deals with the conscious, and the second with the unconscious, content of the psyche.

London, W.1.

MARION GREAVES.

FEEDING DISORDERS IN INFANTS

SIR,—While I feel sure that Miss Morrison and I would find some points we could agree upon in the care and treatment of infants suffering from feeding disorders, yet when we come to the interpretation of these disorders it is obvious that we think quite differently.

Most of Miss Morrison's letter (Aug. 9) is little more than a direct negative to the points I tried to make in the article of July 19. Briefly, the points Miss Morrison endeavours to establish are that the feeding disorders are mainly due to a wrongly balanced mixture, that each infant requires a varying type of modification of the food to meet its own special needs, and that overfeeding is something that has to be carefully avoided. On the other hand, I put forward a plea for more generous feeding with food of good concentration, and I tried to make out a strong case for the belief that most feeding disorders were due to wrong feeding technique and to under-feeding. In this I find myself strongly supported by Dr. Wood in his letter last week; and I should like —very belatedly—to take this opportunity of saying how much I agree with his article,[1] which dealt in a practical way with some of the causes of vomiting in infancy.

Leeds.

C. W. VINING.

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[1] Wood, B. S. B. *Lancet*, 1952, i, 28.

Obituary

ALFRED SCHWEITZER

M.D. Cologne, Ph.D., D.Sc. Lond.

Dr. Alfred Schweitzer, reader in experimental physiology at University College, London, was killed in a mountain accident in the Dauphiné on Aug. 9. He was 43 years of age.

Schweitzer was educated in Germany and took his M.D. at Cologne in 1932. In 1934 he worked under Koch in the Kerckhoff Institute at Nauheim where he acquired an interest in the physiology of the carotid sinus. At this time he also wrote his book, *Die Irradiation Autonomer Reflexe*, which was published in 1937.

He came to England in 1935 and immediately settled down to a most fruitful research partnership with Prof. Samson Wright at the Middlesex Hospital Medical School. Their studies on the actions of acetylcholine and anticholinesterases on the reflex activity of the spinal cord marked the first experimental attack on the problem of chemical transmission within the central nervous system. These investigations continued up to the war when Schweitzer turned his attention to more immediately pressing problems and worked with Prof. G. A. H. Buttle and Prof. Alan Kekwick on the value of plasma and serum in the treatment of experimental hæmorrhage.

In 1940 he went to the department of physiology in Leeds, where he remained as lecturer until 1947. He there worked with Prof. Albert Hemingway on the isolated kidney and they studied the cardiac output in exercise. During the latter part of his sojourn in Leeds he worked with Dr. Eric Neil on many aspects of the physiology of the sino-aortic nerves. Schweitzer continued and expanded these studies when he was appointed as reader in experimental physiology under Sir Charles Lovatt Evans at University College. In conjunction with Dr. Michael de Burgh Daly he had recently demonstrated reflex effects from the carotid sinus and carotid body on bronchomotor tone, and his development of a technique for measuring blood-flow through the minute carotid body was a technical *tour de force*. Schweitzer and Neil were writing a book on the baroreceptor and chemoreceptor activities of the sino-aortic nerves.

Besides his versatile research activities Schweitzer was a wonderful teacher whose enthusiasm and powers of expression were reinforced by a real anxiety to make his point clear to everyone, so that no trouble was too great to achieve this purpose.

From the day of his arrival in this country he wanted to attune himself to the British way of life. It seemed perfectly natural for him to accept our ideals and aspirations, and he was never in any sense of the word a foreigner.

Schweitzer loved people and was the most delightful companion imaginable. He wanted everyone to be his friend, and it was not his fault if they were not. His kindness and generosity were proverbial, and if he did occasionally become indignant about something it was always on behalf of someone else. It is indeed most tragic for his wife and family and for his innumerable friends that a man of such inspiring character should be lost to us at the very height of his powers.

He was gifted in many ways. He was a first-rate violinist and had a profound knowledge and understanding of music, which was one of his great passions in life. He was a most experienced and able mountaineer, and in recent times he went annually to tackle the formidable peaks of the Dauphiné. These arduous holidays meant much to him, and they seemed to give him inspiration for the rest of the year. It is fitting that he should be buried in a village among the mountains which he loved. C. A. K.

LIONEL NATHAN GRUNBAUM

M.A., M.B. Camb., M.R.C.P.

Dr. L. N. Grunbaum, an assistant chest physician at Edmonton, died on Aug. 2, after an attack of poliomyelitis.

He studied medicine at the University of Cambridge and at St. Bartholomew's Hospital. After qualifying in 1939 he spent a year doing house-jobs in the Barts sector before he turned to pathology at the Radcliffe Infirmary, Oxford. While there he produced one of the first of a series of Christmas pantomimes of great merit performed during the war by the Oxford clinical students. From 1942 to 1946 he served in the R.A.M.C. with the rank of major as a specialist in pathology, but after the war he felt the need for the direct personal contacts between patient and doctor which clinical medicine affords. He took his M.R.C.P. in 1949 and he chose chest medicine as his specialty. Later he held registrarships at the Westminster Hospital and at Fulham chest clinic. He was working as a chest physician at Edmonton and was preparing a thesis on Mantoux conversion of tuberculous contacts at the time of his death.

C. M. F. writes: "Lionel Grunbaum brought to medicine an understanding of many things. Profoundly musical, he was an accomplished pianist. A most shrewd judge of character, he showed a humorous tolerance of human foibles. It was his great interest in people that led him to forsake the humanities, in which he had taken his degree at Cambridge, and start upon his medical course at Barts later than his contemporaries; and his deep concern for the material well-being of those less privileged than himself led him to argue and work for Socialism. His fellow-students at Barts will recall many loud-voiced arguments on politics with him, which often verged on the acrimonious until his sense of humour came to the rescue, and agreement, or agreement to differ, was reached with an increase of understanding on both sides. He will be remembered by many friends among his colleagues, his patients, and in many other walks of life, orthodox and bizarre. We shall miss his shrewdness, his sympathy, and his loyal friendship; but the liveliness of his memory will go with us, and he will not have lived and worked, played and talked, in vain."

MR. H. E. MOORE

H. O.-C. writes: "One of H. E. Moore's outstanding traits was his modesty. No doubt this is the reason why his remarkable contribution in the field of rehabilitation received such mediocre recognition in his lifetime. The value of curative workshops in military orthopædic centres had been well recognised by Sir Robert Jones in the first World War, and after the war quickly forgotten by most surgeons. Moore was the real pioneer of the rehabilitation of injured workmen in this country. He, almost alone, appreciated that a half-hour spent receiving passive treatment three times a week in the massage department of a hospital was neither the best way to mobilise joints and restore muscle-power, nor the way to instil into patients the confidence without which they could not recover. Indeed apathy and despair were often induced—and still are—by passive methods of treatment. It has taken nearly thirty years, the investigations of many committees, and another world war to impress this obvious lesson on our profession and its auxiliaries.

"Moore was appalled by the conditions of railway workers coming to his hospital at Crewe; after long periods of 'treatment' elsewhere most of them were dispirited and seemingly incapable of improvement. In the early days of his work at this hospital, of 165 patients of this type 115 were returned to their former employment after an average period of seventeen days' rehabilitation. In those days this was a startling achievement accomplished entirely by active exercises with simple gymnastic apparatus, and above all by Moore's dynamic driving force which inspired confidence where hope of recovery had long been lost. This same technique and the instigation of this same spirit—the will to recover—he brought to the rehabilitation centres of the Royal Air Force during the second World War. Before then it had been confidently predicted that all injured air-crew personnel would be useless for further military duties, so seriously complicated and multiple were their injuries. True enough their injuries were complicated and multiple, but 77% of injured airmen were returned to full duty. It is therefore hardly surprising that the Royal Air Force has with great benefit continued its rehabilitation centres to this day embodying everything taught by Moore. Throughout Britain and the British Commonwealth there are old R.A.F. pupils of his, all too few, carrying on his principles and emulating his practice.

It is sad, however, to see how slow the development rehabilitation facilities has been in civilian practice. a letter written a few weeks before he died Moore plored this tardiness 'as a brake on the economic overy of the country by an unnecessary wastage of n-power, and a diminution of the span of human ppiness and the enjoyment of living'; and he exhorted to spare no effort to advance the importance of a re comprehensive remedial service for the injured.

"Moore was an inspiring companion and a most lightful and coöperative colleague. His life work, rformed so efficiently and effectively, is a lasting bute to his philosophy as a staunch believer in the wer of mind over matter. We often deplore the opagandist in medicine, but it is a thousand pities at Moore's modesty prevented him from being a more tspoken evangelist of what he knew so well to be ue—that men and women could be restored to working pacity by simple, practical, but essentially personal ethods, methods which he lived to see abundantly oven in the hard schools of industry and war."

Public Health

Poliomyelitis

POLIOMYELITIS notifications (uncorrected) in the week ded Aug. 9 (the 32nd week of the year) were (previous eek in parentheses): paralytic, 167 (139); non-aralytic, 83 (91): total, 250 (230).

The following table compares this year (up to and cluding the 32nd week) with the preceding five years.

Year	*Total cases up to and including 32nd week*	*Cases in 32nd week*
1947	2252	624
1948	912	39
1949	1457	254
1950	2986	393
1951	1511	112
1952	1910	250

Slaughter of Horses

The Public Health (Meat) (Amendment) Regulations, 952, which come into force on Aug. 31, give effect to n announcement by the Minister of Food that horse laughterers would be required to notify authorities of heir intention to slaughter.

The purpose of the amending regulations is to put the laughter of horses, asses, and mules for sale for human onsumption on a similar basis to that of cattle, sheep, oats, and pigs. The chief requirement is that anyone ntending to slaughter horses, asses, or mules must give t least three hours' notice to the local authority. Where, owever, slaughter takes place at a particular place at xed times, no individual notices are required; and where immediate slaughter becomes necessary because of ccidental injury, illness, or exposure to infection, notice must be given as soon as possible before or after slaughter.

Responsibility for enforcing the Public Health (Meat) Regulations remains with the local authorities. The present amendments will help local authorities in their task of arranging for the inspection of horse-meat intended for sale for human consumption. Local authorities will also be placed in a better position to execute and enforce the provisions of the Slaughter of Animals Acts, which are designed to ensure that animals are slaughtered in a humane manner.

Revised Regulations for Sea and Air Travel

The Minister of Health has made certain changes in the regulations governing travel by sea and air.[1] The revision became necessary when the Fourth World Health Assembly adopted the International Sanitary Regulations,[2] which will replace the present International Sanitary Conventions on Oct. 1 next. Though the British regulations have not been under general review since 1933, no substantial alterations affecting the traveller have been made. The personal declaration of origin and health, at present required from all persons arriving by air, is to be abolished. The revised regulations will also come into force on Oct. 1.

Notes and News

DISTRIBUTION OF DANCKWERTS AWARD

THE additional remuneration for general practitioners for the period ended March 31, 1949, and for each of the years ended March 31, 1950, March 31, 1951, and March 31, 1952, and the provisional addition for the quarter ended June 30, 1952, is to be divided among executive councils in proportion to the amounts already allocated to them from the practitioners' fund for each of those periods—including the allocation for temporary residents. The distribution of each council's share of the additional remuneration among the doctors who were included on its medical list at any time between July 5, 1948, and June 30, 1952, will similarly be made in proportion to the amounts allocated to the doctors out of the council's practitioners' fund—i.e., excluding mileage payments. The amount due to each doctor for each period can conveniently be represented as a percentage of the amount already allocated to him. Further particulars of the procedure to be followed will be found in E.C.L. 65/52.

DOMESTIC SUPERVISION

THE hospital service probably employs more domestic workers than any other organisation in the country. As domestic labour today costs a good deal—though probably not more than it should—"wages" are a heavy item in the National Health Service budget. The Ministry of Health is rightly anxious that those who earn these wages should be efficiently and economically organised. In a memorandum on hospital domestic management (R.H.B.[52]91) the Ministry affirms that any hospital with a domestic staff of over 75 would probably save money by employing a domestic superintendent who would give all her time and attention to organising this large and important part of the hospital service.

Outlining the duties of a domestic superintendent, the Ministry suggests that she should be directly responsible to the matron, but should keep in close touch with the heads of all departments. Besides organising the work of the domestic staff she would be responsible for their engagement, training, and welfare. Supervision of the work and allocation of duties within the wards and departments would probably continue to be undertaken by the sisters and officers in charge. The Ministry do not however propose any hard and fast range of duties for the post. In a smaller hospital, for instance, the duties might well be combined with catering, and an appointment of housekeeper-caterer made. On the other hand in a large hospital the domestic superintendent might well require an assistant.

People with suitable qualifications for these jobs, the Ministry admits, are scarce and anyone with experience of large-scale domestic management should be considered; but ideally a domestic superintendent should have completed a two-year course in institutional management, should hold a degree or a recognised certificate or diploma in household and social science, and should have had one or two years' practical experience.

University of Cambridge

On Aug. 2 the following degrees were conferred:

M.D.—G. S. Crockett, M. A. Floyer, E. L. McDonald, K. N. V. Palmer, * J. S. Pegum, D. R. Smith.

M.B., B.Chir.—* D. M. E. Allan, J. D. C. Anderson, N. W. Ashworth, * P. A. J. Ball, Robert Baxter, A. W. Beard, Kathleen M. Bennison, M. H. H. Bishop, C. J. Booth, * M. J. Boyle, June E. Brett, * H. G. Britton, B. W. Broadhurst, David Bryant, * G. M. B. Bulman, T. F. Bushby, A. R. Butterfield, * G. R. C. Campion, * S. McC. Cannicott, * Harold Caplan, * J. B. Chapman, * Betty Chester, * W. J. Colbeck, * R. R. A. Coles, * C. E. T. Cones, A. S. Cooper, Betty R. Corbin, * P. F. A. Crawshaw, * R. G. Daniels, * J. G. Davies, * J. I. W. Davies, * R. J. L. Davis, * R. H. Davison, * P. J. Dawson, E. M. Douglas, * I. C. Dow, * Michael Dulake, * A. V. Dunlop, * Warren Eade, J. H. Edwards, * J. R. Edwards, * J. N. T. Evans, R. T. D. FitzGerald, * J. R. Flury, * H. W. S. Francis, * O. H. French, * Nathan Gee, I. M. Glynn, * Rainer Goldsmith, Peter Griffiths, Eric Hainsworth, Thomas Hall, * Douglas Harrett, * Rex Harrison, * D. S. Harry, * E. P. Hilary-Jones, * A. L. Hilton, * John Innes, * D. S. Jeffery, * J. M. A. Jepps, * J. H. Jones, * D. H. Kay, * E. I. Kohorn, J. S. Lewis, * James Liddell, * J. S. H. Lodge, * A. B. Lowther, * P. J. Lyne, * J. M. S. McCoy, * J. A. McHardy, * P. J. McQuade, * Roger Mangnall, * R. J. Mather, * M. K. Mead, * G. C. Metcalfe, * J. F. Newcombe, * R. C. Norton, J. O. Ojukwu, W. N. B. Parker, J. E. Phillips, * Cyril Rashbass, * T. W. Rayner, P. S. Reay-Young, J. M. Rigg, J. H. Robson, R. W. Ross Russell, Vishnu Sarma, * J. H. Sewart, * C. A. Sharples, G. M. Shaw, Hilary J. Shimmin, * M. P. Siddons, J. M. Simister, * F. V. Simpson, G. W. Smallcombe, * R. L. Smith, R. J. Spray, * R. M. Standish-White, C. M. Stafford, * J. W. M. Stone, * J. H. Swallow, D. G. Thomas, * M. L. Thomas, D. H. Trapnell, * B. G. S. F. Vergano, G. I. Verney, D. G. D. Vint,

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[1] Public Health (Ships) Regulations, 1952. Pp. 21. 9d. Public Health (Aircraft) Regulations, 1952. Pp. 15. 6d. H.M. Stationery Office.

[2] See *Lancet*, 1952, i, 1216.

* R. F. Warnock, * M. F. R. Waters, * O. H. Watkins, * John Watson-Farrar, * J. S. H. Whitehead, * Eric Wilkes, * E. A. Wilson, * David Wise, * R. E. Wolfendale.

* By proxy.

Renal Association

At a meeting of this society to be held at 4.30 P.M. on Friday, Sept. 19, at the Ciba Foundation, 41, Portland Place, London, W.1, Prof. J. G. G. Borst (Amsterdam) will speak on *Electrolyte and Water Balance with Relation to the Kidney.* Invitations may be had from Mr. John Sophian, 66, Harley Street, W.1.

Ability of the Disabled to Work

This topic has been chosen as the theme of the residential course which the British Council for Rehabilitation is to hold, with the University of Bristol, at Manor Hall, Lower Clifton Hill, Bristol, 8, from Sept. 9 to 11. Further particulars may be had from the secretary of the council, Tavistock House (South), Tavistock Square, London, W.C.1.

Central Midwives Board for Scotland

The board is to be reconstituted on March 1, 1953, in accordance with the recommendations in the report of the Midwives Working Party in 1949. The new board, like the old, will consist of 16 members, but 7 instead of 4 will be practising midwives. The Secretary of State for Scotland will appoint 3, and midwives practising in Scotland will elect the remaining 4. This will be the first time that midwives have elected members to their governing body. The other 9 members will be representative of medical bodies, local authorities, the universities, and the hospital services.

Singapore Pædiatric Society

This society has been formed to advance the knowledge and practice of pædiatrics and to promote child health in Malaya. It is open to all doctors registered in the Colony of Singapore or in the Federation of Malaya. The following office-bearers have been elected: president, Dr. G. Haridas; vice-president, Prof. E. S. Monterio; hon. treasurer, Dr. William Heng; hon. secretary, Dr. G. Keys Smith (St. Andrew's Mission Hospital for Children, Singapore); members of the executive committee, Prof. J. A. P. Cameron; Dr. Tan Jiak Hoon, Dr. W. B. Young, and Dr. Wong Kin-Yip.

Ministry of Health Circulars

Consultant in Administrative Charge (R.H.B.[52]93).—Where there is more than one consultant on the staff of a special hospital department the Ministry considers it advisable that one should be given administrative responsibility for the organisation of the auxiliary professional and technical staff and for the care and custody of apparatus and equipment. The appointment would not confer any authority over the clinical freedom of other consultants, nor carry any additional remuneration.

"Private" Work in Hospital Pathological Laboratories (R.H.B.[52]92).—This memorandum sets out the types of work which come under this designation.

W.H.O. Regional Committee for Africa

The first meeting of this committee to be held in Africa opened on July 31 in Monrovia, Liberia, under the chairmanship of Prof. Francisco Cambournac, of the Institute of Tropical Medicine, Lisbon. Presenting his report to the delegates of eight member States, Dr. François Daubenton, director of the regional office, said that it was hoped to move the regional administration from Geneva to Brazzaville in September. He added: "This is not a land in which to introduce preconceived ideas. Here the people have developed along their own lines and will further develop, perhaps for historical reasons, in another direction from the rest of the world—and they have the right to do so. The international specialist agencies must give them all the facilities possible and applicable, but the people of this sympathetic, vast country have the right to develop their own philosophy. Only in this way will they be happy. Physical well-being may, perhaps, be prescribed or even introduced, but mental and social well-being can only be achieved with the understanding and coöperation of the people themselves, not by imposing foreign ideas. To assist in the attainment of the well-being of Africans remains the aim and duty of the W.H.O. Regional Office for Africa."

At the close of the meeting Professor Cambournac was appointed regional director in succession to Dr. Daubenton who will reach retiring age next year. Professor Cambournac will take up his appointment in January, 1954.

State University of Iowa

Dr. R. S. Duff has been appointed research assistant professor of internal medicine in the university college of medicine and university hospital, Iowa City, U.S.A.

Dr. Duff graduated M.B. with commendation in the University of Glasgow in 1943. He was elected F.R.F.P.S. in 1947 and he took the M.R.C.P. the following year. He has held a research fellowship in applied physiology at St. Thomas's Hospital, London.

University of Otago

Mr. M. F. A. Woodruff, assistant surgeon to Aberdeen Royal Infirmary and the Royal Aberdeen Hospital for Sick Children, and senior lecturer in surgery in the University of Aberdeen, has been appointed to the chair of surgery in succession to Prof. F. Gordon Bell, who is retiring at the end of this year.

Mr. Woodruff, who is 41, studied at the University of Melbourne, where his father held the chair of bacteriology. He graduated first in electrical engineering and then in medicine in 1937. After appointments at the Royal Melbourne Hospital, Queen's College, and the university, he graduated M.D. in 1940 and M.S. in 1941. With the rank of captain in the A.R.A.M.C. he served in Malaya and he was taken prisoner in 1942. During his imprisonment he studied deficiency diseases and his investigations have recently been published as a Medical Research Council report. In 1946 he joined the surgical professorial unit in Sheffield, and with a World Health Organisation travelling fellowship he later visited the U.S.A. and Canada. In 1948 he took up his present appointments in Aberdeen. He is also an associate examiner in surgery to the University of London, and in 1951 he gave a Hunterian lecture to the Royal College of Surgeons of England.

CORRIGENDUM: *Pancreaticogastrostomy.*—In the article by Prof. R. Ingebrigtsen and Prof. E. Langfeldt (Aug. 9, p. 270) the last two sentences in section (1) under the heading "Methods" should read: "Trypsin gives no turbidity with either of the two solutions. Erepsin gives turbidity with serum-protein, but none with peptone."

On Aug. 18 the staff of Broadmoor Institution presented a silver statuette to Dr. J. S. Hopwood, the retiring superintendent.

Appointments

FARQUHAR, J. V. L., M.R.C.S., D.P.H.: asst. senior M.O., Liverpool Regional Hospital Board's headquarters staff.

HOUSTON, J. C., M.D. Lond., M.R.C.P.: honorary asst. physician, Hospital of St. John and St. Elizabeth, London.

HUDSON, J. R., M.B. Lond., F.R.C.S., D.O.M.S.: honorary ophthalmic surgeon, Hospital of St. John and St. Elizabeth, London.

MCARTHUR, J. B. H., M.B. Lond., M.R.C.P.: consultant physician, St. Helens area, Liverpool [illegible] Hospital Board.

O'GRADY, T. P., M.B. N.U.I., D.P. [illegible] lth division no. 13 (Heywood), Lancash[illegible]

STRANG, C., M.D. Durh., M.R. [illegible] physician, Newcastle upon Tyne and [illegible] oups.

WILSON, R. N., M.B. Durh., D. [illegible] nworks Co. Ltd., near Nottingham.

Sheffield Regional Hospital Board:

BARCLAY, R. C., M.A. Camb., F.R.C.S.: consultant thoracic surgeon, Nottingham City Hospital and associated sanatoria.

FRASER, W. D., M.B. Glasg., F.F.R.: senior radiotherapist, the Hogarth radiotherapeutic centre, Nottingham General Hospital.

WALLS, H. E. C., M.B. N.U.I., D.M.R.T.: senior asst. radiotherapist, radiotherapy centre, Leicester Royal Infirmary.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

CAMPBELL.—On Aug. 8, at the Norfolk and Norwich Hospital, Norwich, to Elizabeth (née Morris), wife of Dr. J. A. Campbell—a daughter.

GRIFFITHS.—On July 23, to Vivienne, wife of Dr. F. E. D. Griffiths, of Kenilworth—a son.

LONGMORE.—On Aug. 17, at Shrewsbury, to Virginia (née Centlivres), wife of Dr. John B. Longmore—a daughter.

MARRIAGES

PEARCE—WOOD.—On July 26, at Oxford, John Kingsley Pearce, B.M., to Gwendolen Wood.

DEATHS

BROOKS.—On Aug. 15, at the Royal Sussex County Hospital, Gertrude Brooks, M.B. Lond., of Paygate, Woodmancote, near Henfield, aged 77.

HORTON.—On Aug. 13, at South Elmsall, Horatio Nelson Horton, M.D. Lond.

MARSH.—On Aug. 9, at Saltash, Cornwall, Ernest Louis Marsh, M.B. Glasg., of Shanghai.

WALKER.—On July 1, Herbert Walker, O.B.E., M.C., M.R.C.S., lieut.-colonel, R.A.M.C. retd.

THE DANGERS OF CHRONIC INACTIVITY IN THE AGED *

MARGARET HILL

BETWEEN 1871 and 1950 the number of old men and women has increased from $1^{1}/_{4}$ million to $5^{1}/_{2}$ million. It is estimated that in another 20 years there will be nearly 10 million people of pensionable age. Although in 1931 there were about four times as many young women as old, there are now only a little over twice as many. The burden on the social services and on the wage-earners will then be proportionately even heavier than it is now.

It is easy to think of old people as infirm old people, as these are so much more in evidence than the rest. Actually the number in hospitals and institutions is only between 3% and 5% of the total number of the old, although many others are desperately in need of care of some sort though not necessarily in institutions. There is a great deal of untreated disease in old people, and it must always be remembered that the process of growing old, apart from disease, produces biological changes, none of which are to the good. The problem which must be faced, unless an intolerable burden is to be borne by the younger members of the community, is how to prevent unnecessary illness in the middle-aged and elderly.

IMPORTANCE OF EARLY TREATMENT

Modern medicine is lengthening life in all countries, yet the best methods of dealing with chronic ill health in the old have not received sufficient attention. Much could be done at earlier stages and this is the all-important matter at the present time. The first preventive is to provide suitable living conditions so that old people may live independently and manage their own affairs for a longer period. From the point of view of activity which is essential to well-being there is nothing to excel the work involved in doing their own household chores, and the necessity for getting out regularly in all weathers to do their shopping. No contrived activities are so valuable or so health-giving as the necessary acts involved in living alone and independently. The emphasis must be on keeping the middle-aged young as it is difficult to rejuvenate the old; but even for these latter fresh air and exercise, no lying in bed unless absolutely necessary, good food, the absence of apprehension for the future, and the companionship of others of their own generation can do much to alleviate their disabilities.

I have had considerable opportunity of observing all this from a housing trust which has now been in existence for over twenty years. During this period some 320 people, most of them old, have been accommodated, and of the 48 who have died only 2 did so in hospital. All the rest stayed in their homes to the end. They were provided with visiting nurses and home helps where necessary. How much more economical for the community, and how much happier for the old people, if simple comfort and security of tenure in suitable surroundings enables them to live at home until the end.

HOUSING FOR THE OLD

While the more vigorous old undoubtedly like a little extra space and the privacy of a small flat, a single room with every convenience is better later on. I regret that in planning for the future, authorities and organisations are still preparing to provide perfection for the few and nothing for the rest. They could comparatively easily provide single rooms, with common bathroom and water closet for tenants on the same floor, either by building or by the conversion of larger dwelling houses, for a fraction of the cost of erecting blocks of self-contained flats. It is not even certain that the perfect flat is always appreciated or preferred. As a general rule it is far better for people of not more than two generations to live together, and undoubtedly it is happier for the older folk to live independently, and so remain active in the course of looking after themselves, rather than to try to adapt their lives to those of younger people or to become entirely dependent upon them for their care. Although there are happy family groups, especially in the country, on the whole old people prefer their own little home wherever possible. When the security of their own home is absent it may make them unwilling to go to hospital for essential treatment, fearing that they may lose both home and independence while away. Fear that old people may be left on their hands may prevent hospitals from taking them for treatment in the early stages when chronic illness might be prevented. Despite the shortage of beds many old people have to be taken to hospital or institution for purely domestic reasons rather than because of ill health. To keep sick old people from deteriorating into chronic invalids because of the lack of mental and physical stimulation of any kind is of the greatest importance. It is even more weakening for the elderly to remain in bed than for younger patients, owing to their lack of resilience.

SUITABLE FORMS OF ACTIVITY

From birth onwards exercise is necessary to health, and this still holds good in old age. It is far too easy, often with the encouragement of relatives, for an old person to get into the habit of spending much time in bed and the rest of the day sitting by the fire instead of making the effort to put on outdoor clothes and get going. I have rarely seen harm come from the daily walk, even for those in frail health, if they can manage it, and it is undoubtedly stimulating both to mind and body. Going up and down stairs in moderation is good exercise and is especially beneficial in keeping joints flexible. With children it is often easier to do the work than to allow them to help, as they would like to do, and the same thing applies to the old whether in their relatives' homes or in residential establishments: but it is undesirable.

Over-anxiety for the old may be as harmful as neglect. This is often so with old people living with their families. In the name of kindness they are gradually prevented from any activity or independence and this finally wears them down. I have several times met interesting examples of this.

Mrs. J was married to a man considerably younger than herself who waited on her hand and foot. She allowed him to do more and more—the cooking, the shopping, and the housework—while she became less and less active and simply sat about or lay in bed smoking cigarettes; she even reached the stage of incontinence through laziness. Then one day her husband had a seizure and was removed to hospital. Mrs. J was cared for by a middle-aged son for a time, but this situation became impossible and she was removed to a voluntary home. Re-education started at once and, at first, much against her wishes. She was encouraged to get up and walk about and even to help with minor household jobs. If she had an accident she was made to clear it up herself, and this quickly cured her of incontinence. She became in fact quite a normal old person. Her greatest pleasure was to go to hospital to see her husband and on one occasion I took her myself. When she reached the hospital and she got out of the car, she suddenly found she could hardly walk at all, and had to be more or less dragged in. It was clear that the old attitude was returning with the prospect of seeing her husband, and if he had come back to live with her, she would quickly have relapsed into her old habits.

This is an extreme case, but many old people can be reduced to invalidism if nothing whatever is expected of them.

NURSING OF THE AGED

One of the skills necessary in nursing old people is that of knowing when to leave them in bed, and when

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* F. E. Williams' lecture for 1952, delivered before the Royal College of Physicians of London on July 15.

to encourage them to get up and then to move about and go out. The difference in will-power for recovery is always unpredictable. Desire for the adventure of living is easily lost, but can recover to a surprising extent in skilful hands. It depends largely on whether interests have been developed earlier in life. As one woman said, "I have never read a book because I have never had time, but I am told I have missed a rare treat!"

I remember one old woman of ninety who was sent to me by the milkman. He had found her sitting on the pavement tired out with searching for a room. No one would accept her as a tenant for she looked poor, dirty, and ill. She had been offered a place in an institution, but she had said that this was out of the question as she must be able to have access to a library and be able to read. She was found a single furnished room and here she lived for some years completely happy reading Milton, Byron, and Shakespeare, first with both eyes, then with one, and finally, when she became almost blind, she gave up her reading and died.

It is impossible to overemphasise the fact that the function of the hospitals is to cure illness and their equipment is not suited to any other purpose. When no further treatment is possible different conditions than those of the hospital ward are required. There must be some place for chronic patients where there is every incentive for the activities of which they are capable, and for encouragement to be up and about. There is no more dreary sight than rows of chronic sick beds. Prof. A. P. Thomson, of Birmingham, in his report on the *Care of the Chronic Sick*, writes:

> "My most vivid impression of the chronic ward of this hospital is an atmosphere of profound apathy. . . . The hospital treatment was surprisingly good . . . the words 'medical treatment' are used in the narrowest sense to signify therapeutic use of rest and drugs."

Most of the inmates of the chronic wards must be regarded as a sad inheritance of a long period of neglect. There are, of course, notable exceptions, but these words describe the lot of thousands of old people in all parts of the country.

It is essential that the most helpless of the chronic sick should be cared for permanently in some kind of hospital, but there is no reason why conditions in some hospital wards should be so deplorable. Years of lying in a ward sometimes amounts to actual cruelty; where, for instance, it is rarely possible to get out of doors, and where there are no decisions to be made, no responsibilities to be accepted. Life is regularised, movement limited to sitting on a chair beside a bed, attired in a dressing-gown, and possessions are almost non-existent. Unfortunately many hospitals have no provision for patients' clothes, even when they remain in hospital for many years. The effect is psychologically bad and not conducive to a return to ordinary living; also from the point of view of geriatric treatment there is little better gentle exercise than that of slowly dressing.

An old woman of my acquaintance suffering from rheumatoid arthritis lived alone upstairs. She managed two small flights of stairs and with a home help succeeded in keeping her home very well. Recently she went to hospital on account of digestive trouble. This quickly cleared up, but she was kept in bed and when sent home at the end of a few weeks she could do nothing for herself and became completely bedridden. Again, an elderly woman came to one of our homes suffering from rheumatoid arthritis. She had been in hospital for 3½ years and, although mentally alert, she had never been dressed, as she had no clothes in hospital, and had therefore never been out. She had most successfully learned to do absolutely nothing, and unfortunately had lost all power or incentive to help herself; she was greedy of one thing only, and that was attention by the nurses to her physical wants, and she assumed a garrulous, demanding attitude to anyone who would attend her.

POSSIBILITY OF BETTER CONDITIONS

There are residential homes where it has been shown that old people who have been rendered immobile by crippling diseases can still find much enjoyment of life. In one such home they are taken for bus-rides, even the very crippled, which resuscitates them more than any physic. They spend much of their time in the garden in summer and have their possessions round them at the cost of tidiness. They go to bed and get up when it suits them, and they are encouraged to occupy themselves in any way possible. All this, incidentally, costs only a third or less of a hospital bed. Although few of these patients can walk out in the road, they have a spirit of gaiety and happiness due to activity of mind even if not of body. A series of very small activities makes all the difference between complete lethargy and liveliness, but all such activities take time on the part of the attendants. Through the overemphasis of safety-first methods, old people are kept in bed for long periods for fear of falls or other accidents. This may be done to save possible censure of the hospital staffs, but it is at the expense of liberty and happiness.

The will to live is the strongest of all instincts and persists in old age. Old people rarely want to die even when life seems to have little to offer. Sometimes fear of death inclines an aged invalid to accept a life involving no sort of effort as the safest means of preserving it. Furthermore, when old persons with an income are cared for by the regional hospital board they contribute nothing for maintenance. Their income can be given to their relatives and this can continue for an unlimited period of time. A return to activity and the resulting transfer from a hospital bed to other accommodation may mean payment of the cost of maintenance. The improvement in health resulting from this change is consciously or unconsciously resisted both by the old people and their relatives. A heavy reward is paid for a continuance of infirmity.

Old people sleep much less at night than younger people and it is acute misery for many of them to lie in bed perhaps up to fifteen hours nightly, sleeping little, listening to the coughing and snoring of their fellows, and waiting for the coming day. Old people are extremely individualistic, and to have any rule by which they must all go to bed and get up at one set time cannot possibly be right. Incontinence alone should rarely be a reason for bedfastness. It may be easier for the nurses to keep them in bed, but it is wonderful how this disability can be managed by experienced and patient attendants. The treatment of incontinence is, indeed, a special science and it is a sign of failure on the part of the nurses when an active-minded patient is restricted to a chronic bed for this reason alone.

Extreme cleanliness and tidiness is of course essential in a surgical ward, but in the wards for the chronic sick the constant struggle for tidiness often results in unintentional but nevertheless cruel discipline. Probably the basis of the whole trouble is that old age and sickness have been for too long confused. Actual skilled nursing, though important, should not be the predominant feature in caring for the aged. Kindliness and resourcefulness should come first, the skilled nursing being reserved for those in real need of it.

The chief difficulty in employing untrained attendants for the chronic sick is their difficulty in lifting the more helpless patients. If they could be taught the best methods, the situation would be greatly eased, since in other respects they can give much of the care required.

Lack of possessions is a sore trial, and the care of even a small assortment of personal treasures gives occupation. Indeed in some cases of mental instability, the arranging and rearranging of possessions is the one steadying influence. I remember one old lady who was getting extremely vague about everything. She tidied her chest of drawers for many hours a day. When it was suggested that so much standing was bad for her and she was prevented from doing it, she became quite violent.

One of the causes of the liability to become bedfast fter arrival in hospital or home is the shock which old eople suffer from any sort of transference from one lace to another. We have observed that on arriving t a strange place this tendency to shock makes them eem much more incapable than they really are. Great atience is needed at this stage to make the change-over asy for them, and where this help is not given they may apidly break up altogether. This is not always due to a ack of desire for the change, for even when they have hosen this themselves they still seem to undergo mental isturbance for a time after arrival. In bringing people o our homes, we often advise them not to give up their previous dwelling until they have settled in. This gives hem the feeling that they have not completely cut away nd could, if necessary, still return to their old way of life. Even so we can rarely form any correct estimate of their condition for the first week or two.

With the old there is a special danger of paying too much attention to their physical ills and too little to their mental troubles. Actually disabled old people are still capable of considerable happiness where they are not in bondage to an exaggerated and soul-destroying emphasis on the need for cleanliness of the body and tidiness of surroundings. Mental deterioration is inevitable with unlimited and unoccupied leisure. Chronic inactivity of the mind is even more harmful than that of the body. It is as important to take early steps to prevent disease in the elderly as in any other section of the community although it may require more realisation of the close connection between ills of the mind and body. People are still expected to know by instinct how to look after their ageing relatives as they were once expected to know by instinct how to care for young children.

IMPORTANCE OF COÖPERATION

Since at present accommodation and service are insufficient, it is important for each district to take stock of its resources and use them to the best advantage. Many organisations are not fully used from lack of concerted effort, and because of the difficulties of getting the right people into the right places. Those who are not in need of hospital treatment help to fill the beds; old people die neglected at home because the hospitals and homes for the old have too many people in them who could live in their own homes if flatlets were available for them.

In one area which I know well a great deal of coöperation between all these forces has been achieved. Let us follow the fortunes of an imaginary old lady.

> She lives alone and is well known to the Old People's Welfare Committee who have helped her by arranging for meals to be brought to her, and giving useful advice and occasional help in cleaning. She has fallen ill and the doctor cannot get her a bed in hospital and she cannot afford help at night. However, the wheels get moving. In order to admit her to hospital, a convalescent old lady is moved out into a half-way house or convalescent home that has been set up by the King Edward's Hospital Fund; to vacate a bed there, an old lady is moved to a permanent voluntary home; and again in order to find room for her, the local voluntary housing association finds a furnished room or flatlet for an elderly woman who has improved in health and would like to live independently again.

This combined effort is much more effective than isolated action on the part of the hospital, home, or housing trust. The hospital will cease to be wary about taking a temporary patient nor will a home be afraid of taking a frail old lady with whom they might be left when she became bedridden. Not only do these particular organisations work together but they assist and are assisted by the welfare authorities, regional hospital board, and Assistance Board. Mutual goodwill and coöperation can save much effort.

Coöperation is greatly facilitated if, instead of setting up one large institution, several homes are grouped in such a way that residents of various mental and physical grades can be classified and placed together in most congenial surroundings. When there is a change in a patient's condition a shift from one home to another can be made without shock, since the management and atmosphere are so similar throughout and the residents are accustomed to sharing entertainments and excursions.

CONCLUSION

As much understanding and careful management is required for old people as is now afforded for infants and young children. Immense strides may be possible in the next few decades in the reduction of chronic sickness in old age, and these may be as dramatic as the recent drop in infant mortality. There are few more miserable sights than a ward of chronic sick invalids, and few more depressing occupations than their care. Robert Burton once said: "There is no greater cause of melancholy than idleness"; and we might add—no greater cause of ill health than melancholy.

CONVERSION OF TISSUE POLYSACCHARIDES TO AUTO-ANTIGENS BY GROUP-A BETA-HÆMOLYTIC STREPTOCOCCI

L. E. Glynn
M.D. Lond., M.R.C.P.
DIRECTOR OF PATHOLOGY

E. J. Holborow
M.A., M.B. Camb.
RESEARCH BACTERIOLOGIST, SPECIAL UNIT FOR JUVENILE RHEUMATISM

CANADIAN RED CROSS MEMORIAL HOSPITAL, TAPLOW, BUCKS

The ætiology of nephritis and the rheumatic diseases is still unknown, but many workers have suggested an antigen-antibody reaction as a possible mechanism (e.g., Klinge 1933, Rich and Gregory 1943, Hawn and Janeway 1947). Although lesions resembling in various degrees those of the corresponding human disease have been produced in laboratory animals by the injection of massive doses of foreign protein, this artificial procedure can only serve as a remote analogy to the sequence of events in the naturally occurring disease. It has seemed possible, however, to many investigators that specific antibody production in response to the individual's own tissues (acting as antigen) may be involved, rather than a non-specific antigen-antibody reaction induced by foreign material (Smadel 1936, Cavelti and Cavelti 1945). Unfortunately for this hypothesis, the experimental production of auto-antibodies has proved extremely difficult, although a-priori evidence of the possibility exists in the acquired hæmolytic diseases (Loutit and Mollison 1946).

In rheumatic fever (and to a lesser extent in nephritis) recent infections with hæmolytic streptococci are accepted as an essential ætiological factor. It has been suggested that the effect of these is to render the tissues auto-antigenic. The claim of Cavelti and Cavelti (1945) to have utilised this mechanism in the experimental production of nephritis and carditis has not, however, been confirmed (Humphrey 1948).

The classical work of Landsteiner (1945) has shown that the antigenicity of a protein may be profoundly altered by chemical combination with various non-protein substances (haptenes). Among the latter the polysaccharides are of outstanding importance in conferring specificity on bacterial antigens (Heidelberger and Avery 1923, 1924, Avery and Heidelberger 1923, 1925). A possible mechanism, therefore, for auto-antibody stimulation would be the combination between bacterial protein and tissue polysaccharide, acting as haptene. The work of Morgan and Partridge (1940) on the structure of the somatic antigen of *Shigella shigæ* has well shown that the protein moiety of this antigen can readily combine with polysaccharides such as agar and cherry gum to produce antigens capable of eliciting antibodies reacting specifically with the corresponding polysaccharide. It has been shown by Sordelli and Mayer (1931) that this property is by no means confined to dysentery organisms, and we have recently reported that hæmolytic streptococci are particularly active in endowing with antigenicity various polysaccharides of plant origin (Glynn and Holborow 1952). If it can be shown that these organisms can similarly react with polysaccharides of animal connective tissue, it is conceivable that the production of auto-antibodies to these tissue polysaccharides might occur in natural infections. Such a reaction could well underlie the pathogenesis of the group of diseases under discussion.

We report here results of such experiments, in which a preparation of chondroitin sulphate was used as tissue polysaccharide; a limited quantity only was available for this experiment, which was therefore restricted in scope. A note is also included on the production of nephritis in rats, using a tryptic digest of rat kidney as a source of kidney polysaccharide.

METHODS

Chondroitin sulphate * was prepared from stored wet human costal cartilage by the method of Einbinder and Schubert (1950) as a dry powder, readily soluble in saline solution.

Preparation of vaccines.—18-hour cultures in Todd Hewitt broth of a group-A type-4 strain of β-hæmolytic streptococcus were centrifuged, and vaccines prepared from the organisms washed twice in saline solution. The live cocci were suspended in a small volume of 1% chondroitin-sulphate solution in saline solution and kept at 37°C for an hour. They were next centrifuged, washed twice, and resuspended in saline solution to give an opacity equivalent to about 1000 million cocci per ml., and killed by heating at 56°C for thirty minutes. Control vaccines were prepared identically but without the chondroitin sulphate.

Immunising procedure.—Young cross-bred Dutch or Copenhagen rabbits, weighing 1·4–1·8 kg. and kept in individual cages on a mixed diet, were given intravenous injections of vaccine three times a week. On a dosage beginning with 0·5 ml. and increasing to 1·0 ml., and given a vaccine prepared in bulk at the outset of the experiment (schedule A), a high proportion of rabbits died or sickened after two or three doses. On a reduced dosage (starting with 0·1 ml. and gradually increasing to 1·0 ml.) and given freshly prepared vaccine for each injection (schedule B), the rabbits remained well during the initial stages of the immunising course.

Two Copenhagen rabbits received intracutaneous inoculations of chondroitin-treated vaccine in six daily doses of 0·1 ml. Three control rabbits received chondroitin-free vaccine, or chondroitin-sulphate solution only, intracutaneously.

Tests for precipitating antibody to chondroitin sulphate.—Sera were obtained from the rabbits at intervals and tested for precipitin reaction with 0·1% chondroitin-sulphate solution in saline solution. Ring tests, chondroitin solution being layered on serum, were unsatisfactory owing to the slow rate of appearance of precipitate, and precipitation was best observed in capillary tubes, as in the technique described by Swift et al. (1943) for streptococcal precipitin typing. Equal quantities of serum and chondroitin solution were drawn up into a capillary tube and incubated at 37°C for two hours. With positive sera maximal flocculation was observed after refrigeration at 4°C for up to forty-eight hours. Normal rabbit sera gave no trace of precipitation with the polysaccharide solution under these conditions.

Streptococcus-kidney-digest vaccine.—A tryptic digest of perfused rat kidney was prepared by the method of Cole et al. (1951) and a streptococcus-kidney-digest vaccine made in the same way as the vaccines described above.

RESULTS

Antigenicity of Chondroitin-sulphate Preparation Alone

A solution of chondroitin sulphate alone gave rise to no precipitins when injected intravenously—e.g., 60 mg. given over twelve days. Repeated intracutaneous injection over eight days (6 × 0·1 ml. of a 1% solution) did not cause skin sensitivity in two rabbits.

Antigenicity of Streptococcus Alone

Plain streptococcal vaccine gave rise to no chondroitin-precipitating antibody in the three rabbits immunised.

Antigenicity of Streptococcus-chondroitin Vaccine

Intravenous immunisation.—Six rabbits received intravenous streptococcus-chondroitin vaccine; four according to schedule A, and two according to schedule B. The sera obtained from these rabbits after immunisation all gave precipitation with chondroitin solution, varying from a trace to a ++ reaction (see table). One of these rabbits developed a limp in the left hind leg after fourteen days and was killed on the sixteenth day. Its serum gave a relatively strong precipitin reaction with chondroitin-sulphate solution. Post mortem the left knee-joint showed acute inflammation but was sterile on culture. The synovial membrane was œdematous and injected, and there was much hyperæmia round the articular margins. Another rabbit showed no clinical symptoms but died on the twenty-third day of schedule B. Serum obtained at this time precipitated strongly with chondroitin-sulphate solution, and post mortem both knee-joints showed much œdema and inflammation of the synovial membrane. As shown in the table, histological evidence of arthritis was obtained in five of the six rabbits receiving the streptococcal-chondroitin vaccine. In one this consisted of a slight infiltration with poly-

PRECIPITIN REACTIONS WITH CHONDROITIN-SULPHATE SOLUTION OF RABBIT ANTISERA TO STREPTOCOCCUS-CHONDROITIN VACCINE

Immunising agent	Rabbit no.	Total dosage (ml.)	Period of experiment (days)	Fate of rabbit	Precipitation of rabbit sera with Ch.SO$_4$	Joint lesions
Streptococcus-chondroitin: Schedule A	21/2	4	7	Died	Trace	..
,,	21/2A	5	16	Killed	+ +	Acute synovitis
,,	21/2B	3·5	9	Died	+	Slight polymorph infiltration
,,	23/4	2	7	Killed	Trace	Acute synovitis
Schedule B	23/3	4	18	Died	+	Severe acute synovitis
,,	23/4A	6·5	23	Died	+ +	Subacute synovitis
Chondroitin solution only (1%)	21/4	6	14	Survived	0	..
,,	21/5	6	14	Survived	0	..
Streptococcus only: Schedule A	23/1	3·5	30	Died	0	Normal
,,	23/2	2·0	7	Died	0	An occasional polymorph
Schedule B	23/2A	7	26	Killed	0	Normal

Precipitin reaction after 48 hr. at 4°C: trace, fine deposit; +, small aggregates in deposit; + +, large aggregates in deposit.

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* Kindly supplied by Dr. Gerald Loewi.

morphs; in two others there was considerable hyperæmia, with polymorph infiltration; in the fourth the inflammation was intense and acute; and in the fifth it was severe, but polymorphs were few, the predominant cells being lymphocytes and plasma cells forming well-marked perivascular aggregations. Cultures taken from all the joints examined were invariably sterile. No comparable degree of inflammation was found in any of the controls; in one rabbit only a slight polymorph infiltration was present.

Intracutaneous inoculations.—Of the two pairs of rabbits inoculated intracutaneously one member of each pair received streptococcus-chondroitin vaccine and the other received the streptococcus alone. Six daily injections were given in the skin of the flank, and skin tests with 0·1 ml. of 1/1000 chondroitin sulphate were made after an interval of five days. Considerable skin sensitivity to chondroitin was elicited in the rabbits receiving streptococcus-chondroitin vaccine; negative results were obtained with the rabbits receiving streptococcus only. The positive skin reaction obtained was of the delayed type, appearing at about six hours, and maximal at twenty-four to thirty-six hours, taking two days to fade.

Experiments with Rat-kidney Digest

A rabbit antiserum to the streptococcus-kidney-digest vaccine was obtained, which when given intravenously to rats gave rise in twenty-four hours to gross albuminuria and to glomerular lesions in the kidney comparable to those induced in a parallel experiment by nephrotoxic serum (Smadel 1936). Normal rabbit serum or plain antistreptococcal rabbit serum produced no lesions or albuminuria.

DISCUSSION

It is evident from these results that the production of antibodies to polysaccharides of animal origin can be induced in the same way as those previously obtained against polysaccharides of plant origin. We cannot regard the haptene in these experiments as strictly autogenous, since the chondroitin was obtained from human cartilage; but there is little evidence that the composition of this material varies from species to species. It will, of course, be necessary in repeating these experiments to use chondroitin prepared from cartilage of the homologous species. A point of great interest relates to the extremely minute quantity of polysaccharide necessary to impart its own immunological specificity to the streptococcus. For example, with electrophoretic methods capable of detecting a few microgrammes of galactose, it has been impossible to detect even a trace in 2 mg. of dried cocci, previously treated with agar, although vaccines prepared from these readily elicited antibody to agar. Figures for the purity of the chondroitin sulphate are unfortunately not available; its N content, however, was only 2·2–2·4%. Since chondroitin sulphate has an N content of less than 3%, other protein could not have been present in more than traces. This is confirmed by the absence of antigenicity of the polysaccharide solution alone.

Of the six rabbits injected with the streptococcus-chondroitin the two showing strongest serum precipitation showed also the most conspicuous joint lesions. Less severe lesions were also present in two of the rabbits showing less precipitation. This does not necessarily imply that the lesions are due to the antibodies responsible for the precipitation reaction; it is quite conceivable that, if antibodies are responsible for the lesions, they belong to the non-precipitating type. It does, however, suggest that lesions are most likely to occur in those animals with the most responsive antibody mechanisms.

As already mentioned, the scope of these experiments has been limited by the small quantity of animal polysaccharides available in a relatively pure and undegraded state, and we hope to confirm and extend these observations with more polysaccharide material.

SUMMARY

A vaccine prepared from group-A β-hæmolytic streptococci in the presence of chondroitin sulphate gave rise to rabbit antisera precipitating with this polysaccharide.

Of six rabbits immunised with such a vaccine five showed macroscopical and/or microscopical evidence of joint lesions. Control rabbits receiving either streptococci or polysaccharide alone showed no joint lesions apart from an occasional polymorph in the synovial membrane.

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DEFORMING FACTORS IN THE EARLY STAGE OF POLIOMYELITIS

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THE term "muscle spasm" has often been used to describe various types of muscle dysfunction in poliomyelitis, but there does not seem to be any general agreement on its definition and cause.

Pohl and Kenny (1943) consider muscle spasm to be a decisive factor in the course of poliomyelitis. Pollock et al. (1949), on the other hand, deny the existence of muscular spasm, which they define as a state of sustained involuntary tetanic contraction of muscle—a definition with which I agree. Excluding the types of muscular spasm attributed to the meningeal reaction, they found no evidence of true spasm in patients studied during the first ten days of poliomyelitis.

Because of the existing controversy I have tried here to describe more accurately the various clinical findings which are sometimes collectively described as spasm, and to discuss their ætiology.

DEFORMING FACTORS

In patients who have had little or no treatment in the early months of poliomyelitis, deformities are occasionally found which seem to be due to abnormal overaction of unaffected or mildly paralysed muscle groups. It is therefore essential to study the factors concerned in the limitation of passive mobility in the first few weeks of the disease. Deformities appearing later, which are due to neglect of a paralysed limb or to the influence of simple muscle imbalance on growth, will not be discussed.

For the present purpose the term "deforming factors" is used to describe any conditions which interfere with the passive mobility of the limbs in the early stage of poliomyelitis. The observations are based on the study of over 100 cases examined during the isolation-hospital stage and subsequently in the orthopædic hospital.

Deforming factors appear to be manifested in three ways: (1) limitation of straight leg raising; (2) limitation of shoulder abduction beyond 80°; and (3) muscle resistance to stretch. These conditions do not all necessarily proceed to established deformities if untreated.

Limitation of Straight Leg Raising

The limitation of straight leg raising referred to here is that persisting after the initial acute meningeal reaction has subsided. When present to any great extent it persisted for many weeks and could not be completely abolished by treatment in the early stage, but improved in the later stages on mobilisation of the patient, particularly by walking and sitting.

In severe cases pain was produced when the leg was raised to an angle of 30°, accompanied by painful resistance to stretch of the hamstrings when these muscles were not paralysed. Where the muscle on one leg was considerably weaker than that on the other, there was only a minor difference in the angle obtained. Even when complete paralysis affected the hip and leg, straight leg raising was limited by pain often to 30° unaccompanied by muscle resistance.

The limitation of straight leg raising was always bilateral and not necessarily proportional to the degree of paresis, but was not present unless there was some paralysis of the leg.

In these patients the hip-joints were mobile and could be flexed to over 90°. All the patients had lumbar pain in the early stages, and several had neck stiffness, but severe degrees of neck stiffness were often unaccompanied by any limitation of straight leg raising.

Limitation of Shoulder Abduction

This was an outstanding feature in the few patients presenting severe degrees of resistance to muscle stretch in the biceps and shoulder adductor muscles. It was also present in patients with respiratory weakness, when the pectorals were used as accessory muscles of respiration.

Limitation of shoulder abduction persisting after the initial meningeal phase was found in many patients with paralysis affecting the arms. Pain was produced on abduction beyond 80°, accompanied by strong resistance in the shoulder adductor muscles when these were active. It was only seen where the arm or the trunk was affected, and was bilateral in severe cases. Neck stiffness was a feature of the febrile stage in these patients. When the shoulder was abducted to a few degrees below the pain-producing angle, pain could be produced by lateral flexion of the neck to the opposite side.

This limitation of shoulder abduction was more easily overcome than the limitation of straight leg raising.

Muscle Resistance to Stretch

A state of sustained tone or "spasm" in the muscles of the neck and back was often observed during the meningeal reaction of the first few days in both paralytic and non-paralytic cases. This sustained tone disappeared as the fever subsided, but was sometimes followed by muscle resistance to stretch, which developed on attempted flexion of the spine. This muscle resistance gradually subsided over a longer period.

As has been mentioned, muscle resistance to stretch developed in the hamstrings during the straight-leg-raising test and in the shoulder adductor muscles during the shoulder-abduction test. This resistance was only present when the muscle was able to contract, and it was therefore considered to be a secondary phenomenon.

In a few patients considerable muscle resistance to stretch was noticed in certain muscles, particularly the biceps, when the elbow was held in a flexed position and any attempt at extension initiated contraction at about 90°. This was considered to have a more complex ætiology than the muscle resistance mentioned in the preceding paragraphs, and was considered to be a significant deforming factor if untreated. For this reason it will be discussed under a separate heading.

This type of increase in muscle tone in the extremities was an infrequent finding. In 100 patients treated from the onset by the methods in use at Oxford and previously described by me (Mitchell 1952), 4 patients showed significant muscle resistance to stretch of a degree likely to persist if untreated. The biceps muscle was affected in 3 cases, and the calf muscles in 1 case; 2 other patients developed biceps resistance during the respiratory stage of the illness. No example of true spasticity was found; clonus and increased tendon-reflexes were not obtained. Observation at the onset did not reveal any muscle contraction in the limbs when at rest; this state was brought on by any attempt to stretch the muscle and was accompanied by pain. The term "muscle resistance to stretch" is preferred to the more common term "spasm" in describing the muscle dysfunction.

The muscles usually affected were the elbow flexors, adductors of the shoulder, and calf muscles. If such a muscle is allowed to remain in a position of advantage, the temporary state of resistance by contraction is gradually superseded by shortening, the muscle being felt as a tight cord under general anæsthesia in contrast to the relaxation obtained in the early stage.

CLINICAL OBSERVATIONS

In an attempt to explain these changes in the cases we have examined, the clinical features only will be discussed, no necropsy material being available.

Limitation of Straight Leg Raising

As has been mentioned, in these cases the hip-joints were mobile and could be exonerated. The degree of muscle power present did not materially affect the angle of straight leg raising obtained, which was severely limited even when muscle power was minimal or absent. The limitation was caused by muscle resistance to stretch plus pain where muscle power was good, and by pain alone when muscle power was absent. Intravenous thiopentone was given in 1 case with persistent limitation of straight leg raising six weeks after the onset. Under anæsthesia the straight-leg-raising angle was increased from 30° to 90°, showing that permanent shortening of the muscle had not taken place. It was not thought justifiable to paralyse the muscle, since Schlesinger (1951) found that limitation and pain persisted even with muscles rendered atonic with intravenous mephenesin. It is unlikely that brain-stem lesions were responsible for the limitation where muscle power was unequal or absent. Muscle resistance to stretch, when present, did not correspond to the spasticity seen in proved traumatic brain-stem lesions. Lasègue's sign was positive in all cases where limitation was severe.

The most likely site of lesions causing pain and limitation on attempted straight leg raising was considered to be in the region of the meninges and dorsal roots. The backache and limb pains of the early stage were considered attributable to inflammatory lesions at this site. The clinical picture in the early stage closely resembles certain cases of intervertebral-disc protrusion.

Limitation of Shoulder Abduction

Limitation of shoulder abduction over 80° was seen less often than the leg limitation, but certain features were similar. It was always accompanied by some degree of upper-limb paralysis—the abduction limit was caused by pain where muscles were paralysed, and by pain plus muscle resistance to stretch where power was present. Possibly the limitation and neck stiffness could also be due to changes in the region of the dorsal roots and meninges.

uscle Resistance to Stretch

This was only a transient complication when cases ere treated from the onset by rest, sedation, gentle assive movements, selective positioning, and splintage. dvanced cases were seen where inadequate early treatent had been given. The muscle resistance was usually lateral and occurred in slightly affected or apparently ormal muscles. The flexor adductor groups of the arm ere more commonly affected, particularly the biceps, ny attempt to extend the elbow being opposed by rong contractions. Patients with much biceps resistance ossessed highly emotional temperaments. Pain was a oticeable feature in all the cases.

Several factors were considered to contribute to the ate of muscle resistance to stretch as seen in these atients: (1) incoördination of muscle action caused by nternuncial lesions; (2) overaction of muscle, either eliberate or from emotional tension; and (3) limb pain.

(1) *Incoördination of muscle action* in the early stage as found in many patients. Kabat and Knapp (1944) ttribute this to the internuncial lesions.

(2) *Overaction of muscle.*—Continued overaction of a tronger over a weaker muscle could cause fatigue and ggravate pain; if untreated, this might progress to hortening and resistance to stretch of the stronger muscle.

An example of deliberate overaction of partially affected muscles progressing to actual muscle shortening was found in . female patient with paralysis of all limbs and trunk. While n the respirator she developed considerable limitation of houlder abduction owing to the continued use of the pectoral nd latissimus dorsi muscles as accessory muscles of respiraion. During her periods out of the respirator adjustable wooden wedges were inserted between arm and thorax and adjusted to the greatest comfortable abduction. By this neans abduction was gradually improved and eventually a useful range obtained without interfering with the accessory action of the pectoral muscles.

Disproportion in strength between protagonists and antagonists does not necessarily produce deformity; therefore aggravating factors must be present: either deliberate and continued overaction as in the case described, or emotional overaction from prolonged tension in the muscle of a highly emotional patient, when a strong biceps predominates and unrestricted use of the limb in the supine position is allowed. The prevention and ease of correction of such a flexion deformity in the early stage suggests that functional overaction may play some part in its production, perhaps by aggravating the dysfunction produced by pain and incoördination.

A typical example of biceps resistance was in an adult male R.A.M.C. orderly, who was very concerned about the outcome of the disease. He developed biceps resistance on passive extension of the elbow beyond 90°. After a few days' treatment, by engaging him in conversation, the elbow could be passively extended. On drawing his attention to the elbow, however, the muscle resistance reappeared. Later the resistance completely disappeared, but it is of interest, in connection with the other phenomena, that he had pain on abducting the shoulders beyond 80°, and that straight leg raising was limited to 30°, with a positive Lasègue sign. This patient also had a partial lower-limb paresis.

Deformities due to hysterical contracture of muscle were seen in a female patient admitted six weeks after an illness originally diagnosed as poliomyelitis. It was stated that she had developed complete flaccid paralysis of the left arm and leg, but that subsequently "muscular spasm" had appeared and produced deformities. On admission it was noted that an increase in tone and resistance to stretch was present in both flexor and extensor muscles of the left arm and leg. The elbow was maintained in acute flexion and the hand in the "main d'accoucheur" position. The knee was held in full extension and the foot in equinovarus. Tendon-reflexes were increased n the leg, and Babinski's sign was negative.

(3) *Pain* was present in all the cases of muscle resistance o stretch. After generalised limb pains had subsided, pain occurred only on attempted active or passive movement of the limb. Muscle biopsies in man have failed to show any significant pathological change in the muscles (Clawson 1948, Jungeblut 1950). The site of pain must therefore be between the myoneural junction and the dorsal roots. Inflammatory changes have been found at necropsy in the region of the dorsal roots and meninges (Bodian 1948). Possibly the increased resistance to stretch in muscles such as the upper-limb flexor adductor groups could be an exaggerated muscle guarding in response to pain originating in the dorsal roots or meninges, contributory factors being incoördination resulting from internuncial neurone lesions and emotional overactivity of muscle.

Recently two patients were seen who demonstrated mild muscle-movement resistance of special interest and similarity. Both were healthy adult males of stable mental make-up. The muscle resistance was of minor degree and only present for a few days, after which it completely disappeared. In both cases there was some connection with movements of the cervical spine and the production of muscle resistance.

The first patient on examination showed a mild tendency to biceps stretch resistance which was easily overcome. The shoulder was then passively abducted to 100°, when the patient complained of pain radiating down the forearm, and the biceps contracted, resisting full extension by 30°. When the arm was brought down to the side, the pain and biceps contraction disappeared. When the arm was brought down to just below the pain-producing angle, the pain could be reproduced by lateral flexion of the neck towards the opposite side—this latter sign has since been found in several patients with limitation of upper-limb abduction but was not looked for in previous cases.

The second patient, who was reported as tending to develop deformities, had been propped up in bed with pillows because of respiratory difficulty. He had severe neck stiffness, and overaction of the biceps and shoulder adductors maintained his arms flexed and adducted. When he was placed supine, all the resistance in the muscles disappeared, allowing a full range of passive movements. The neck stiffness disappeared the following week.

CONCLUSIONS

The limitation of straight leg raising and shoulder abduction is considered to be due to pain arising from residual inflammatory changes in the region of the dorsal roots or meninges. In these cases muscle resistance to stretch is guarding in nature.

The greater resistance to stretch found occasionally in muscles such as the biceps cannot be explained by a guarding action alone. Muscle incoördination plus emotional overactivity of a strong or relatively unaffected muscle over a weaker affected muscle may exaggerate the underlying guarding mechanism.

These conclusions have been reached from clinical observations, and I agree with the opinion of Magoun and Rhines (1947) that "further investigation of the pathophysiology of spasm in poliomyelitis would appear necessary before it can be stated definitely to be either an exaggerated stretch reflex or tension maintained reflexly or voluntarily in response to pain or to have some as yet unanticipated etiology."

SUMMARY

Deforming factors appearing in the early stage of poliomyelitis are defined as: (1) limitation of straight leg raising; (2) limitation of shoulder abduction; and (3) muscle resistance to stretch.

Clinical observations are reported which suggest that pain is the main cause of the onset of deforming tendencies in the early stage. Resistance to stretch is guarding in nature. Incoördination and emotional overactivity or tension in a muscle may play a part in the production of the more severe deformities.

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SALT-LOSING NEPHRITIS

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THE importance of maintaining the sodium and chloride reserves of the body and of recognising the clinical features resulting from the deprivation of salt as opposed to water was emphasised by McCance (1936) and again by Marriott (1947). Marriott pointed out that sodium depletion presented an easily recognisable syndrome, whose prominent features are weakness, fatigue, giddiness, fainting, muscular cramps, anorexia, nausea and vomiting, and, later, hypotension and coma.

Sodium occurs so plentifully and widely that inadequacy is seldom the result of a simple deficiency of intake, unless it is due to a salt-free diet too strictly prescribed or too conscientiously followed and aggravated perhaps by the sodium diuresis induced by mercurial drugs (Soloff and Zatuchni 1949). A more common cause of a low sodium state is excessive loss, either from the skin by sweating or from the alimentary tract by vomiting, diarrhœa, or fistulæ. Finally, too much sodium and chloride may be excreted by the kidneys. This loss may be the result of functional changes in the renal tubules, when a deficiency of adrenal cortical hormones induces failure of tubular absorption, as in Addison's disease; or when, as in certain chronic illnesses, in the absence of any apparent renal lesion the ability to retain sodium and chloride is impaired (Winkler and Crankshaw 1938). It is evident also that an addisonian picture could, in theory, result from disease of the renal tubules. Although Peters et al. (1929) described excessive urinary loss of chlorides in certain cases of nephritis, Thorn et al. (1944) were the first to demonstrate what they called "salt-losing nephritis" as a clear clinical picture.

These workers described two cases, both young adults without previous history of renal disease. One was admitted to hospital in a drowsy state, collapsed (blood-pressure 64/46 mm. Hg), vomiting, and suffering from cramps; the other was nearly comatose (blood-pressure 35/0 mm. Hg). In both cases the sodium and chloride levels were grossly lowered in the serum and normal in the urine. Neither patient was pigmented, but adrenal cortical failure was diagnosed because no cells or casts were found in the urine of either, and only a trace of albumin in one. Treatment with large doses of deoxycortone acetate and adrenal cortical extract was ineffective, however, and only the administration of sodium chloride corrected the addisonian symptoms and raised the blood-pressure. The salt-losing tendency appeared to be a transient phase in the disease, and later it ceased, the patients finally succumbing in 2 and $4^1/_2$ years from uræmia and hypertensive heart-failure. At necropsy the kidneys in both cases were reported to show the changes of chronic nephritis, while the adrenals were quite normal.

Only four other cases of salt-losing nephritis have been described (de la Balze and Oñátivia 1947, Borst 1950, Sawyer and Solez 1949, and Nussbaum et al. 1952). In addition Rosenheim (1951) referred to this disorder and briefly cited another possible case. Nevertheless it is possible that similar cases have been reported previously as examples of Addison's disease with hypertension or Addison's disease complicated by chronic nephritis, particularly when such diagnoses have not been confirmed at necropsy. We acknowledge the undoubted authenticity of certain of these cases of combined renal and adrenal failure, however (Ravreby and Sawyer 1948).

We have found no original descriptions of this condition in the literature of this country, but it has been the subject of an annotation (*Lancet* 1952). In presenting a further three cases, therefore, we hope to draw attention to an important differential diagnosis of Addison's disease and one whose treatment should, in most cases, be at least temporarily rewarding. Case 1 reported here cannot be considered to be established beyond doubt and is presented as being of historical interest, for, although the disease was not proved to be a salt-losing one, the account of the clinical and pathological findings accord well with the original description of Thorn et al. (1944). All three cases were investigated and treated at Guy's Hospital.

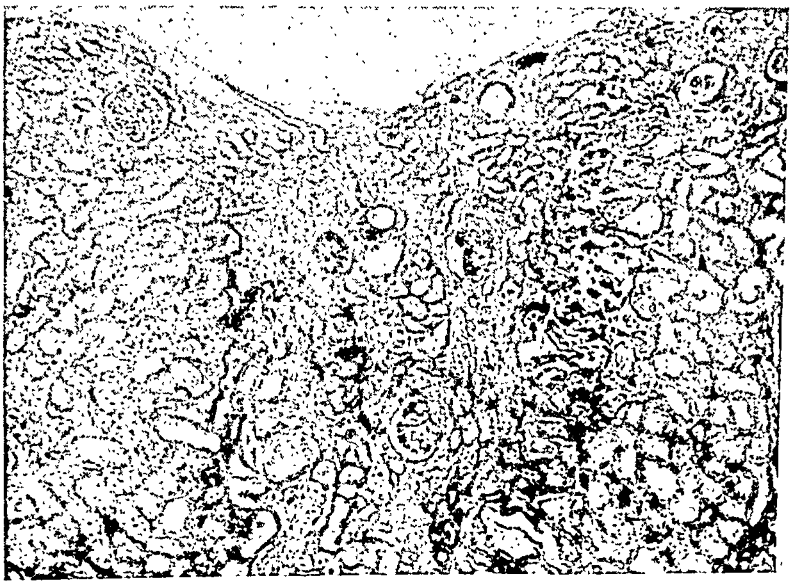

Fig. 1—Depressed cortical scar, tubular dilatation, and glomerular sclerosis of chronic pyelonephritis (case 1). (Van Giesen × 26.)

CASE-RECORDS

Case 1.—A girl, aged 20, was admitted on June 30, 1930, under the care of *Dr. John Ryle*. She complained of being easily tired, "slack," weak, and irritable since an attack of influenza two years previously. She had noticed bronzing of the skin for about a year, and amenorrhœa for 4 months. Until the age of 17 she had had nocturnal enuresis, and since then had had considerable frequency by day and night. At the age of 9 months she had had pneumonia, and at the age of 13 months scarlet fever and diphtheria. She had had other childhood ailments, including two operations on tonsils and adenoids. One sister had recently died from tuberculosis.

On examination she weighed 6 st. $4^1/_2$ lb. and appeared somewhat younger than her

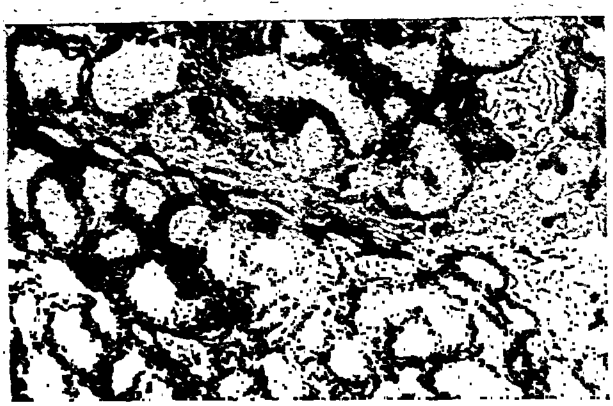

Fig. 2—Calcification of basement membrane of hypertrophied and dilated tubules (case 1). (Von Kossa × 74.)

years. Her skin was "bronzed," and her nipples were deeply pigmented. There was additional darkness over pressure points, and some small pigmented spots were seen in her mouth. Her blood-pressure was 100/70 mm. Hg., but no abnormality was detected in any other system. Her urine, sp. gr. 1·016, showed a trace of albumin. A blood-count showed Hb 7·2 g. per 100 ml., red cells 2,650,000 per c.mm., colour-index 0·92, and white cells normal. A test-meal was likewise normal. Radiography of the chest showed infiltration at the right apex. Dr. Ryle thought her condition most like that seen in Addison's disease.

Progress.—The patient rapidly deteriorated, and by July 9 was much worse, complaining of great lassitude and malaise, and her blood-pressure was 79/57 mm. Hg. On July 10 she was almost comatose, her reflexes being only just obtainable, and her pupils reacting poorly to light. Her blood-pressure then was 69/48 mm. Hg. By the afternoon she became unconscious, her pupils ceased to react to light, and shortly after this she died.

Necropsy findings.—Both adrenal glands were large and completely healthy. The kidneys were small (18 g. and 31 g.) and the capsules stripped easily, showing a mottled surface with some depressed scars. Section showed that the cortex was narrowed to 9–10 mm., and the corticomedullary junction ill differentiated. The skull was thickened and soft, resembling that seen in Paget's disease. Some tuberculous infiltration was found at the apex of the right lung. The other organs were normal, the parathyroid glands not being noted to be enlarged. On histological examination (Dr. J. B. Enticknap) the kidney changes were seen to be those of healed pyelonephritis (fig. 1), with evidence of a recent exacerbation. Calcification was seen in the tubules (fig. 2). The adrenal glands were of normal structure.

Case 2.—A man, aged 27, was admitted on July 27, 1951, with several weeks' history of weakness and tiredness and about 6 hours' history of pain in the left loin and inability to micturate. His family history was irrelevant. At the age of 18 months he had a tuberculous gland excised from his neck. At the age of 20 years his right kidney was found to be tuberculous and was subsequently removed surgically. At that time his blood-pressure was 150/90 mm. Hg and some impairment of renal function was noticed even postoperatively, the blood-urea remaining raised at 48 mg. per 100 ml. in July, 1945, and 60 mg. in February, 1946. He continued to pass tubercle bacilli in his urine. In 1948, at the age of 25, miliary tuberculosis of the lungs was discovered and treated with streptomycin and rest, with good result, but the blood-urea level reached 200 mg. per 100 ml. at this period. There was a decline from this high level, but shortly before admission to hospital in 1951 it still stood at 120 mg.

On examination the patient was thin but of good colour. His blood-pressure was 115/80 mm. Hg, and the only significant physical abnormalities detected were pyrexia (103°F), pulse-rate 100, and tenderness on palpation of the left loin. His urine, however, contained protein 2 g. per litre besides pus cells and acid-fast bacilli.

Progress.—The pain in the loin subsided within a few hours, and the patient micturated freely. Within 3 days his temperature had fallen to normal, but a week after his admission there was a bout of anuria lasting nearly 24 hours. Even before this his general condition started to deteriorate. Cramps developed in his legs and hands, his appetite was poor, and he was weak, listless, and at times faint. His blood-pressure dropped but did not reach the levels seen in addisonian crisis, the systolic pressure never falling below 100 mm. Hg. Estimations of the serum-electrolytes now revealed a gross depletion of sodium, at 266 mg. per 100 ml. (115 m.eq. per litre), and of chlorides at 396 mg. per 100 ml. (114 m.eq. per litre), while the blood-urea level was considerably raised. Although the tongue and skin were dry and he vomited occasionally, he continued to pass considerable quantities of urine of a very low specific gravity, which nevertheless contained relatively large quantities of sodium chloride (see table). Treatment with sodium chloride by mouth was started, and later, because he did not tolerate this well, large quantites of physiological saline solution were given per rectum and intravenously. On the 14th day after admission, the serum-sodium level still being grossly depressed, the patient was given intramuscular injections of 10 mg. of deoxycortone acetate daily, but without clinical or biochemical improvement (see table). The renal function steadily deteriorated until on the 25th day the blood-urea level was 330 mg. per 100 ml. and the blood-uric-acid 17 mg. per 100 ml. The patient died in coma 31 days after admission.

Necropsy findings (Dr. D. H. Osborne).—The body was sparsely covered, with little subcutaneous fat. The heart was not enlarged, weighing 350 g. In the apices of both lungs were small areas of caseation surrounded by scar tissue, the remainder of both lungs being normal. The alimentary system was normal except for a suppurative swelling of the left parotid gland. The left kidney weighed 232 g., and several yellowish-white areas bulged through the capsule. On section a considerable amount of renal parenchyma was found to have become caseating masses, some of which communicated with the pelvis. The intervening tissue was mottled by more recent tuberculous lesions. The pelvis and ureter were moderately dilated and both were inflamed. The ureter was thickened and in its lower third would just admit a probe. The bladder showed slight congestion only, and the prostate and seminal vesicles showed evidence of tuberculosis. The adrenal glands were normal, and no abnormality was seen in the brain.

BIOCHEMICAL FINDINGS IN CASE 2

—	Aug. 3, 1951	Aug. 7, 1951	Aug. 23, 1951	Aug. 27, 1951
Serum-sodium (mg. per 100 ml.)	266 (*115*)	269 (*116*)	283 (*124*)	253 (*110*)
Serum-potassium (mg. per 100 ml.)	16 (*4·1*)	16 (*4·1*)	15·3 (*3·9*)	22·5 (*5·8*)
Serum-chloride (mg. per 100 ml.)	396 (*114*)	359 (*102*)	435 (*112*)	370 (*106*)
Plasma-bicarbonate (vols. per 100 ml.)	57·6 (*26*)	63·6 (*28·8*)	48·1 (*21·8*)	41·3 (*18·6*)
Blood-urea (mg. per 100 ml.)	147	150	126	330
Uric acid (mg. per 100 ml.)	..	..	..	17
Urine sp. gr.	1003	1004	1009	..
Urine sodium chloride content (mg. per 100 ml.)	..	272	212	..

Figures in parentheses represent m.eq. per litre.

Histological examination of the kidney showed widespread caseous tuberculosis (fig. 3) and in the areas not so affected changes that probably represent antecedent healed pyogenic pyelonephritis (fig. 4).

Case 3.—A boy, aged 18, was admitted in April, 1951, with a month's history of generalised cramps, weakness, and unsteadiness, and several months' history of mottled pigmentation of the face. There was no relevant family history, and he had worked as a farm labourer since the age of 14. He had always been very fit until the age of 16, when he had an attack of tonsillitis, followed by puffiness of the eyes and headaches. He first noted cramps soon after this illness. They were confined to his calves, and occurred after exercise and at night. He had always tanned easily in the summer, but the tan that he acquired in the summer of 1950 faded very slowly, leaving brown blotches on his face throughout the winter of

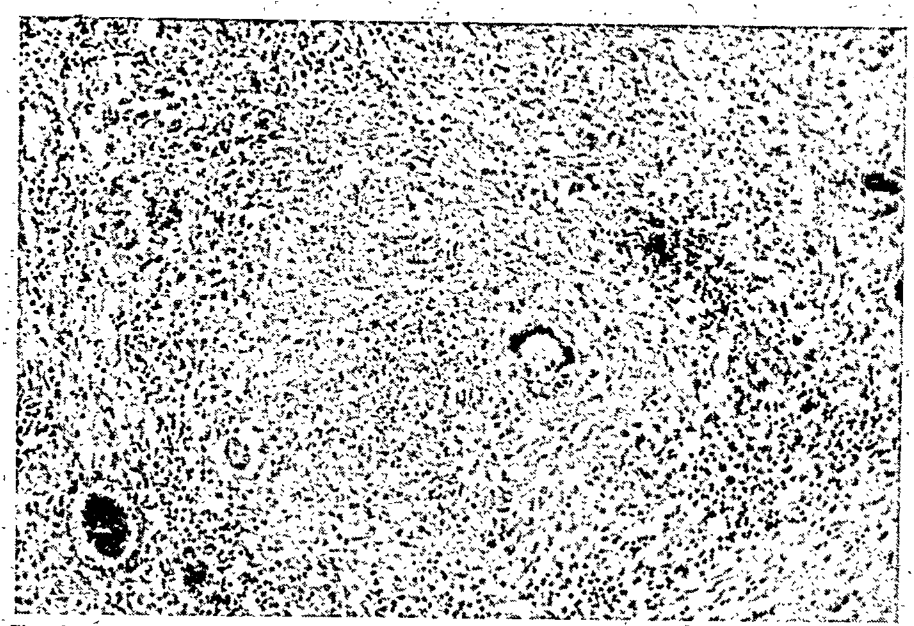

Fig. 3—Tuberculous granulation tissue, caseation, and interstitial inflammation (case 2). (Hæmatoxylin and eosin × 174.)

1950–51. In March, 1951, he noticed that he was rapidly becoming tired and breathless and had palpitations while doing the work to which he was accustomed. He also developed cramps of the hands and feet, and some shakiness. On one occasion he fainted. He was seen by his family doctor, who prescribed sodium chloride 16 g. daily by mouth, after which the cramps and unsteadiness were much improved, although he still felt weak and listless.

On examination patches of brown pigmentation were seen over his face and arms, but not on his buccal mucosa. Muscular twitching was noted during the examination. His blood-pressure was 140/65 mm. Hg, and his heart was not enlarged. All his reflexes were very brisk. His urine was of low specific gravity, seven specimens being below 1·010, and contained 2 g. of protein per litre. No formed elements were seen.

Treatment and progress.—It was thought that the diagnosis lay between Addison's disease and chronic nephritis, and the extra salt which had been prescribed was stopped for an observation period. He was given a normal diet, but with no added salt, and after 8 days the serum-sodium level had fallen to 302 mg. per 100 ml. (131 m.eq. per litre). On the 10th day he complained of weakness and nausea, and later began to vomit. His blood-pressure fell to 80/50 mm. Hg, but he rapidly improved when given salt by mouth. He continued to take sodium chloride 4 g. four times daily throughout his stay in hospital.

Investigations.—The blood-urea level was 205 mg. per 100 ml.; the blood-sugar 100 mg. per 100 ml.; the alkali reserve 26·2 vols. per 100 ml. (11·8 m.eq. per litre); the serum-calcium 8 mg. per 100 ml. (4 m.eq. per litre); the serum-phosphate 4 mg. per 100 ml. (1·25 m.eq. per litre); and the 17-ketosteroid excretion 7·95 mg. in 24 hours. After 10 days on 16 g. of salt daily, the serum-sodium level was 357 mg. per 100 ml. (156 m.eq. per litre) and the serum-chloride 367 mg. per 100 ml. (104 m.eq. per litre).

Discharge.—It was felt that the probable diagnosis was salt-losing nephritis, and that in view of the acidosis, and their response to salt, the cramps were due to the lack of sodium chloride rather than calcium. The patient was discharged, and recommended to continue to take 16 g. of salt daily.

Follow-up.—After his discharge he attended as an out-patient twice—in June, 1951, when he seemed in excellent health, and in January, 1952, when he said that he felt very well but had reduced his extra salt intake to 8 g. daily on advice from his doctor, who had noticed slight œdema of his ankles. He appeared much less pigmented than before, and his blood-pressure was 160/120 mm. Hg. The serum-sodium level was 350 mg. per 100 ml. (152 m.eq. per litre); the serum-chloride 340 mg. per 100 ml. (96 m.eq. per litre); the alkali reserve 42·4 vols. per 100 ml. (19·1 m.eq. per litre); the serum-potassium 19 mg. per 100 ml. (5 m.eq. per litre); and the blood-urea 110 mg. per 100 ml. The urine, sp. gr. 1·010, contained protein.

Readmission.—The patient was readmitted on March 16, 1952, having felt quite well until the end of February, 1952, when he noticed that his legs had become swollen up to the thighs: 2 days before admission he had developed a headache and vomiting.

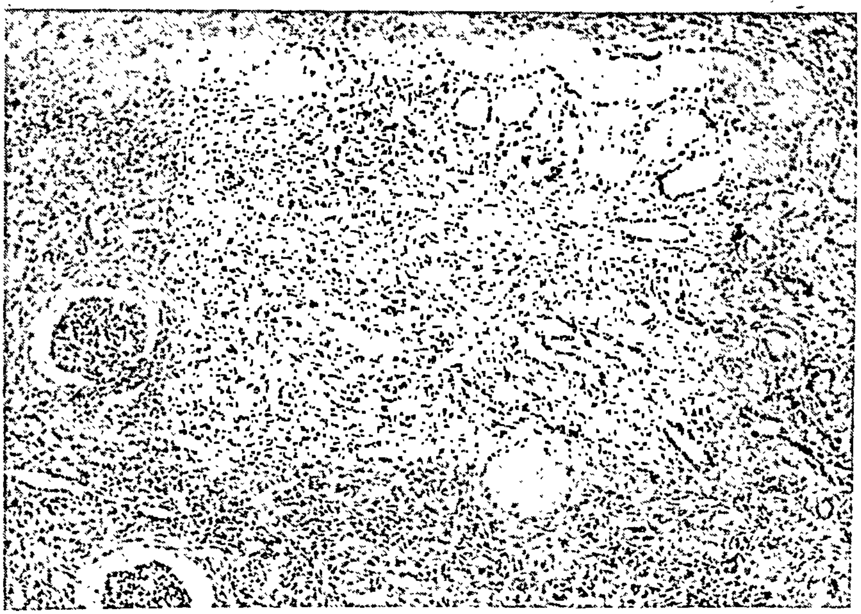

Fig. 4—Another part of the same kidney as in fig. 3, but distant from the tuberculous lesion; showing glomerular hypertrophy and sclerosis, interstitial scarring and inflammation, and tubular dilatation and hypertrophy, probably due to antecedent pyogenic pyelonephritis (hæmatoxylin and eosin × 104.)

On examination no cutaneous pigmentation was now visible. The blood-pressure was 180/130 mm. Hg, and a presystolic triple rhythm was audible in the heart. There was œdema of both ankles, and a small sacral pad, but the neck veins were not raised, and there was no pulmonary congestion. All the tendon-reflexes were very brisk, and Chvostek's sign was elicited. The urine, sp. gr. 1·010, contained protein 4 g. per litre and numerous granular casts. The serum-sodium level was 325 mg. per 100 ml. (142 m.eq. per litre); the serum-chloride 340 mg. per 100 ml. (96 m.eq. per litre); the alkali reserve 33·8 vols. per 100 ml. (15·7 m.eq. per litre); the blood-urea 150 mg. per 100 ml.; the serum-calcium 4·4 mg. per 100 ml. (2·2 m.eq. per litre); the serum-phosphate 4·26 mg. per 100 ml. (1·33 m.eq. per litre); the serum-potassium 17·1 mg. per 100 ml. (4·4 m.eq. per litre); the serum-creatinine 14·4 mg. per 100 ml.; the serum-alkaline-phosphatase 8·1 King-Armstrong units, and the serum-protein 6·15 g. per 100 ml. (14·9 m.eq. per litre).

Progress.—The patient rapidly developed generalised œdema, and on the

8th day (April 3) began to vomit. Over the next 2 weeks his persisted, and he developed gross muscular twitchings nd weakness. On the 32nd day (April 17) a pericardial riction rub was heard, and he died in uræmic coma on April 19, 34 days after admission.

Necropsy findings (Dr. J. B. Enticknap).—The adrenals were enlarged (20 g. each). Both kidneys were small, the left weighing 7·8 g. and the right 25 g. The left renal pelvis was larger than the kidney, and both ureters were dilated to a diameter of ·2 cm. (fig. 5). The right kidney was about four times as big as the left, but was still markedly reduced in size, and showed gross scarring of the surface. Perinephric adhesions were present on both sides, and section showed the cortex to be narrowed to about 2 mm. Histologically there were present changes typical of chronic pyelonephritis. The heart was enlarged (460 g.), and there was a recent fibrinous pericarditis. There was hæmorrhagic ulceration throughout the gut. The parathyroid glands and all other organs were normal.

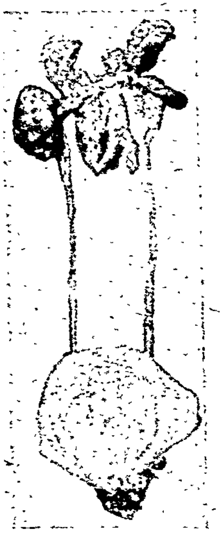

Fig. 5—Bilateral contraction of kidneys, left being much more affected than right and associated with dilatation and hypertrophy of pelvis and ureter (case 3).

DISCUSSION

Clinical Features

The six cases of salt-losing nephritis that have been previously reported comprise a clearly defined clinical group. The patients are usually young adults and, except for Thorn's patients, who experienced polyuria, have no history of renal disease or any symptom suggesting renal insufficiency. The illness presents with any or all of the symptoms of Addison's disease, including tiredness, weakness, anorexia, nausea and vomiting, cramps, collapse, and coma. All six of the reported cases and two of the three presented here (cases 1 and 3) were at one time diagnosed as adrenocortical failure, and this diagnosis was seriously considered in our other patient (case 2). In one patient carcinoma of the stomach was entertained as a possible diagnosis (Nussbaum et al. 1952).

Pigmentation of the skin, which has now been seen in three patients (Sawyer and Solez 1949, and the present cases 1 and 3), and the almost invariable absence of casts and cells from the urine make the diagnosis even more difficult. Some cases may be recognised by their failure to respond to deoxycortone acetate and adrenocortical extract or by the unusual degree of nitrogen retention and acidosis that exists. The diagnosis, if correct, can easily be confirmed by renal-function tests, which show gross impairment. Conversely, adrenocortical function, as shown by carbohydrate metabolism, 17-ketosteroid excretion, and response to adrenocorticotropic hormone (e.g., Thorn's test), will be found to be normal; whereas, tests of adrenal function that depend on intact renal tubules (e.g., the Kepler-Power test) are invalid in this condition.

Treatment by replacement of the lost sodium and chloride by doses of up to 20 g. of salt daily has enabled some patients to spend the rest of their lives in fair health. The longest recorded survival period has been 1½ years (Thorn et al. 1944). Correction of acidosis by sodium bicarbonate (15 g. per day) has been tried by Sawyer and Solez (1949), but Nussbaum et al. (1952), who used sodium acetate, observed that a restoration of the alkali reserve of their patient was associated with clinical deterioration and subsequent death.

The two common causes of death seem to be collapse in a state of salt depletion (de la Balze and Oñátivia 1947, and the present cases 1 and 2) and hypertensive heart-failure with uræmia (Thorn et al. 1944, and the present case 3), a fate which seems to await those in whom the salt loss has been successfully treated. In addition, these patients, like all nephritics, are ill equipped to overcome the other hazards of existence. One is reported to have died after a surgical operation (Sawyer and Solez 1949); another suddenly, possibly as the result of retention of potassium (Nussbaum et al. 1952); and a third from pulmonary tuberculosis (Borst 1950), a disease which two of our three patients had (cases 1 and 2). It is recognised indeed that in case 2 the picture of renal salt loss was complicated by the concomitant tuberculosis, which, for example, led to the appearance of pus cells and considerable amounts of protein in the urine. Further, it is arguable that the illness was in some degree due to active tuberculosis. These reservations are valid, but nevertheless we consider on clinical and biochemical grounds that sodium depletion was the most important feature of his illness.

Pathological Features

The biochemical findings in this type of nephritis are those of loss of salt and water together with nitrogen retention and acidosis. It is evident that these patients must all be in negative sodium, chloride, and water balance, although these crucial observations have never been recorded.

Kidneys.—Necropsy findings have been reported in five previous cases. Chronic glomerulonephritis was seen in three (Thorn et al. 1944, Sawyer and Solez 1949); polycystic disease, with apparent specific tubular damage, in one (Borst 1950); and pyelonephritis in another (Nussbaum et al. 1952). Two of the present cases showed chronic pyelonephritis (fig. 1), and one tuberculosis and chronic pyelonephritis (figs. 3 and 4). In case 1 (fig. 2) calcification of the tubules was seen, a finding previously reported by Thorn et al. (1944) and Sawyer and Solez (1949). The functional impairment is of the whole kidney, but the special features of this condition suggest that the tubules are specifically damaged. This is to some extent supported by the anatomical observations already cited, and further by the observations that the tubules do not respond to deoxycortone acetate, parathyroid, or pituitary extract (Thorn et al. 1944, Borst 1950), or to cortisone (Nussbaum et al. 1952), and that renal secretion of ammonia is decreased (Thorn et al. 1944).

Serum changes.—Thorn et al. (1944) graphically demonstrated that the abnormality of serum-electrolytes is due to failure not of production of adrenal cortical hormone but of tubular response. This principle of "target organ" failure has recently been recognised in other conditions—e.g., pseudohypoparathyroidism (Albright et al. 1942). The derangement of renal function underlying nitrogen retention is better understood (Fishberg 1939) than are those which cause acidosis and loss of salt and water. Platt (1951), however, has shown that in most cases of chronic renal failure sodium balance is still maintained, and that, because glomerular-filtration of sodium is diminished, this must imply a decrease in reabsorption of sodium by the tubules. In a few patients (Platt 1950) sodium loss was noted, and these may be regarded as potential salt-losing nephritics. Attention may also be drawn to the work of Pitts and Alexander (1945), who showed that the cells of the renal tubules can exchange hydrogen ions for sodium ions from the glomerular filtrate, and thereby eliminate acid and conserve base. Should this mechanism fail, acidosis together with excessive loss of salt and water would result, a condition similar to that seen in "salt-losing nephritis." Bull et al. (1950) have observed electrolyte loss in the recovery phase after prolonged anuria, when the tubules are specifically damaged, but this is a further acute episode in the course of a dramatic renal illness, and clinically distinct from "salt-losing nephritis." In this connection it may be noted that case 2 had two short periods of anuria (6 hours and 24 hours). His blood-pressure was not, however, very low during either episode, and we do not feel that they were causally related to his salt loss.

If the state of acidosis were of sufficient duration, sources of base other than sodium would have to be found. Albright and Reifenstein (1948), basing their calculations upon results obtained by Shohl (1939), conclude that 49% of the calcium in the skeleton is available as a source of base. This might eventually be drawn on and, should the drain be excessive, the picture of renal osteodystrophy result. This point has been fully discussed by Snapper (1949), but it is interesting to note that in case 3 the serum-calcium level was reduced to 4·4 mg. per 100 ml. (2·2 m.eq. per litre), and that the skull in case 1 resembled that seen in Paget's disease, being thickened and soft, a finding common in renal osteodystrophy. A further point of resemblance is the metastatic calcification noted by Sawyer and Solez (1949). Excessive excretion of calcium might explain the calcification which these workers found in the glomeruli and tubules. Tubular calcification was seen in case 1 (fig. 2).

Pathological pigmentation of the addisonian type has once previously been recorded in this condition (Sawyer and Solez 1949). In the present case 1 it was classical, involving the buccal mucosa, pressure points, and normally pigmented areas. In case 3 it was not characteristically addisonian, but the brown blotches on the face were very striking when the patient was first seen in 1951. This finding too is common in renal osteodystrophy (Maddox 1932). No explanation is offered for the occurrence of addisonian pigmentation in salt-losing nephritis, but it seems unlikely that adrenal medullary failure plays a part in its production.

SUMMARY

Three new cases of salt-losing nephritis, with necropsy findings, are reported.

The previously recorded cases are briefly reviewed.

The clinical features of the condition are summarised.

Two further cases showing pathological pigmentation of the skin are recorded.

The pathology of the condition is discussed.

Certain points of resemblance to renal osteodystrophy are noted.

We wish to thank Mr. W. D. Doherty and Dr. K. S. MacLean under whose care cases 2 and 3 were admitted; Dr. J. B. Enticknap for the histological reports and photomicrographs in all three cases and for the necropsy report in case 3; and Dr. J. C. Houston for helpful criticism and advice.

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THE CONDITION OF THE KIDNEYS IN SALT-LOSING NEPHRITIS

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Thorn et al. (1944) reported 2 cases of a clinical syndrome which closely resembled Addison's disease and in which pathological changes were found only in the kidneys, the adrenal glands being normal. Several similar cases have since been reported by other workers (table I). The condition has recently been reviewed by Joiner and Thorne (1952a), who present 3 further cases seen at Guy's Hospital. Specimens from these patients were much alike, a fact which prompted a review of the pathological features of all the 8 cases hitherto reported.

MATERIAL AND METHODS

The published reports of the first 5 cases have been extracted and summarised, wherever possible in the author's own words. In 4 of these 5 cases the descriptions are full and detailed, but none of the reports includes a photomicrograph. For case 6 the original necropsy report was available together with paraffin blocks of one kidney, one adrenal gland, and a piece of skull. The necropsies in cases 7 and 8 were personally observed, and the relevant material was examined histologically by conventional methods.

RESULTS

These are summarised in the accompanying tables, and the last 3 cases have been illustrated by Joiner and Thorne (1952a). All the kidneys were affected by generalised disease, but in case 7, who had had a unilateral nephrectomy, much of the remaining kidney was destroyed by tuberculous pyelonephritis. The description of this organ both in the text and in the table is mainly concerned with the parts of it apparently unaffected by this process, in which it was thought that changes were present that had probably antedated the tuberculosis. Even if they did not they so closely resembled those due to pyogenic infection that the main argument is unaffected. While it is impossible to dogmatise on the lesions present in the first 5 cases, the published reports show that they are very similar to those found in the last 3.

Macroscopically (table I) these diverse kidneys had several common features. Ten of the twelve kidneys in which it was possible to make an estimate were contracted, and the presence of multiple cysts in the remaining two makes it unlikely that the weights are a measure of the amount of functioning renal tissue. In 5 of these 6 cases the contraction was bilaterally asymmetrical. Capsular adherence was common, the normal pattern was usually destroyed, and in all the cases but one the thickness of the cortex was reduced to less than 3 mm. The surfaces of the kidneys were granular, and cysts were seen in several cases. Some abnormality was present in the pelvis in all the 7 cases in which it was described.

Microscopically (table II) there were again numerous features in common. Reticular or radial scarring is specifically mentioned in 5 cases, in 2 no relevant comment is made, and in the remaining case the kidney was grossly distorted by the presence of multiple cysts.

The *interstitial tissue* in all the cases showed various amounts of fibrosis and was infiltrated by cells denoting chronic inflammation.

The *glomeruli* were variably affected in the different kidneys, but in none were the changes of active glomerular nephritis seen, and all the descriptions suggest or emphasise the fact that the changes were not evenly distributed. Capsular thickening was present in all the cases, but in only 1 were adhesions to the tufts described.

The *tubules* showed changes in all the cases. Some dilatation was present in them all, and the descriptions of the other features of the first 5, although varying in detail, were compatible with the presence of the lesion that was seen in the last 3: focal hypertrophy producing an epithelium of variable depth in dilated subcapsular tubules that alternated with scarred areas in which the tubules were atrophied. The so-called colloid casts were present in 5 cases, and hyaline and granular material in another. Pus cells were present in the tubules in 4 cases, but 1 of these was the case with renal tuberculosis. Calcification of the tubular basement membrane was seen in 3 cases, and focal glomerular calcification in 2.

Other Findings.—In 2 of the cases there was hypertrophy of the parathyroid glands, but in only 1 of these and in 1 other in which they were normal was there any osteomalacia. There was also a tendency to hypertrophy of the adrenal glands, the weights in the 3 patients for whom they are recorded being above the normal mean, and hyperplasia being described in another case.

Diagnosis.—In 4 of the 7 cases in which a definite pathological diagnosis was made the condition was said to be pyelonephritis.

DISCUSSION

These findings suggest that chronic pyelonephritis is the condition commonly responsible for this syndrome; so it becomes important to define this term. As used here it is almost synonymous with the chronic interstitial nephritis of the older descriptions, a term which might well be applied to all the kidneys referred to. Its main feature is the presence of a chronic inflammatory exudate in the interstitial tissue causing renal contraction that is commonly greater on one side than the other. Microscopically a reticular type of fibrosis (Russell 1929) is seen, and the most typical lesion is a radial band extending from the pelvic region to a coarse depressed stellate scar on the surface. Parenchymal lesions are mainly confined to these bands of scar tissue, in which tubular atrophy and glomerular hyalinisation together with arteriolar sclerosis and hyalinisation are commonly found. In between these scars tubular hypertrophy and dilatation are present, and in many cases this proceeds to the stage of formation of small cysts in which the so-called colloid casts may be seen. Eventually numerous large cysts may develop, a condition much more commonly due to interstitial fibrosis than to the parenchymal inflammation of a predominantly glomerular nephritis (Weiss and Parker 1939). Numerous smaller points of differentiation have been described but are not sufficiently exclusive to be of real diagnostic value.

I have discussed elsewhere (Enticknap and Joiner 1952) whether the term "chronic pyelonephritis" is the best name for the condition present in kidneys showing these appearances, and have provisionally concluded that it is. In such cases that present, as these subjects did, with some form of renal failure, the disease has probably developed from repeated minor attacks of hæmatogenous renal infection following asymptomatic transient bacteræmias. It is becoming increasingly recognised (see Enticknap and Joiner 1952 for references) that this condition is perhaps the commonest single form of Bright's disease; hence it is not surprising that several of the cases in the present series were so diagnosed and that they were the ones more recently published. The first 4 cases may therefore be re-examined to see whether they too are not examples of a similar condition. Cases 1 and 4 and cases 2 and 3 will be discussed together because they present similar appearances.

Cases 2 and 3 both have much contracted kidneys from which nearly all pathognomonic changes have disappeared, and it is perhaps unwise to attempt to diagnose them too precisely solely from the condition of the kidneys. Clinically case 2 had only a trace of protein in the urine, whereas case 3 had none, and in neither case were casts found, findings quite unlike those of the terminal stages of chronic glomerular nephritis. A further point is that case 2 had hypertrophy of one parathyroid gland and softening of the ribs. Gilmour (1947) showed that secondary hyperparathyroidism in acquired renal

TABLE I—MACROSCOPIC APPEARANCES OF KIDNEYS

Case no.	Reference	Original author's diagnosis	Kidney weights (g.)		Capsule	Surface	Normal pattern	Pelvis
			R	L				
1	*Thorn et al.* (*1944*): Case 1	None given	140	140	Adherent	Finely granular and showing numerous cysts	Destroyed by cysts, cortex reduced to a few mm.	A few submucosal hæmorrhages
2	Case 2	Diffuse glomerulonephritis in the final state	60	42	Adherent and thickened	Finely granular with a few cysts	Destroyed, a few cysts present, cortex 1·0–2·5 mm. thick	A few hæmorrhages and some increase in fat
3	*Sawyer and Solez* (*1949*)	Severe chronic glomerulonephritis	70	70	Adherent	Finely granular	Poorly demarcated, cortex 3 mm. thick	Submucosal hæmorrhages
4	*Borst* (*1950*)	Bilateral cystic disease	Combined weight 770		..	..	Innumerable cysts, from pinhead size to 3 mm. in diameter	..
5	*Nussbaum et al.* (*1952*)	Acute superimposed on chronic pyelonephritis	80	110	Adherent	A few cysts	Cortex of normal thickness	Purulent exudate
6	*Joiner and Thorne* (*1952a*): Case 1	Chronic pyelonephritis	18	31	Stripped fairly readily	Granular with depressed scars	Not present	Small papilloma
7	Case 2	Tuberculous pyelonephritis	..	232	..	Mottled with yellow areas	Distorted by tuberculosis	Slightly dilated, ureter thickened
8	Case 3	Chronic pyelonephritis	25	8	Adherent to kidney and perinephric tissue	Coarsely granular with depressed scars and a few cysts	Destroyed, a few small cysts present, cortex 1–2 mm. thick	Dilated to twice the normal size on side of smaller kidney; a few hæmorrhages

disease was found almost exclusively in chronic pyelonephritis, a finding which agrees with experience in this hospital (Joiner and Thorne 1952b). Finally it may be pointed out that the label "glomerulonephritis" attached to these cases by the original American workers does not necessarily preclude their being examples of chronic pyelonephritis as defined, for it may merely reflect the absence of agreement on the significance of the terms used in renal pathology. It is therefore concluded that these 2 cases are examples of contracted kidneys in the sense that the term has been used elsewhere (Enticknap and Joiner 1952); and, although the question of their origin must be left undecided, it was found in the investigation referred to that such kidneys occurred most commonly in patients thought clinically to have chronic pyelonephritis.

Both cases 1 and 4 had kidneys containing multiple cysts and accordingly of normal or increased weight. In case 1, not diagnosed by Thorn et al. (1944), there can be little doubt from the description that the condition was inflammatory and almost certainly due to chronic pyelonephritis. Much parathyroid hyperplasia was again present. The weight of the kidneys in case 4 makes this diagnosis much less likely, but the description given is fragmentary. Probably the correct diagnosis is congenital polycystic disease, but the fact that this patient was not hypertensive makes this uncertain. In any event such kidneys commonly show evidence of superadded infection, fibrous replacement of renal parenchyma following repeated attacks being the probable morphological basis of ultimate renal failure, and much proliferation of interstitial connective tissue is emphasised in the description. Case 1 is then almost certainly one of chronic pyelonephritis, and case 4, although probably having some other renal abnormality as well, shows changes that strongly suggest the presence of the same condition.

TABLE III—OTHER FINDINGS

Case no.	Para-thyroid glands	Bones	Adrenal glands	Other necropsy findings	Urine
1	5·7 g.	Normal	16·5 g. and 24 g.	..	No proteinuria and no casts
2	1 of the 3 found was larger than normal	Ribs soft	7·5 g. and 8·8 g.	..	Trace of protein and no casts
3	Normal	Normal	Hyperplasia	..	No protein and no casts
4	..	..	Normal	Hilar node, pulmonary and miliary tuberculosis	..
5	..	..	Normal	..	..
6	..	Skull soft but histologically normal	Normal	..	..
7	Normal	Normal	Normal	Previous unilateral nephrectomy for tuberculosis	..
8	Parenchyma weight 105 mg.	Normal	Large, about 20 g. each	..	..

Extensive tubular changes, giving rise in most cases to cyst formation, are a uniform feature of the histology of these kidneys. This is of interest in view of the conclusion of Joiner and Thorne (1952b) that the tubules are the site of the biochemical abnormality.

In summary it may therefore be said that 4 of these

TABLE II—MICROSCOPIC APPEARANCES OF KIDNEYS

Case no.	General appearance	Interstitial tissue	Glomeruli	Glomerular capsules	Tubules	Casts and tubular contents	Calcification of tubules
1	Extensive scarring widely separating cystic tubules and atrophied glomeruli	Hyaline fibrosis with plasma cells, mononuclears, and lymphocytes	Mostly hyalinised; preservation of single tufts in a few only	Pericapsular fibrosis	Dilated; flattened epithelium	"Colloid" casts	Present
2	..	Numerous lymphocytes	Mostly hyalinised; remainder hypertrophied; a few capillary thrombi	Adenomatous proliferation of epithelium; a few hyaline crescents	Dilated and hyalinised proximal tubules	Hyaline, granular, pus-cell, and "colloid" casts	..
3	..	Increased connective tissue; round cells	Reduced in number; mostly hyalinised, some lobulation and calcification	Thickened and adherent to tufts	Patchy distribution of atrophy and hypertrophy	None	Prese
4	Multiple cysts	Much proliferation of connective tissue	Those present are intact	..	Severe degenerative changes, especially inconvoluted tubules; 2nd c.t. dilated	2nd c.t. contain hyaline and granular material	..
5	Patchy scarring	Increased fibrous tissue, with lymphocytes and plasma cells	Some degeneration	Thickened	Hypertrophy and dilatation	"Colloid" casts and pus	..
6	Reticular fibrosis with changes most marked in the radial scars	Gross fibrosis and some pus cells	Some hypertrophied and others with focal capillary hyalinisation and calcification	Some pericapsular fibrosis	Atrophy dilatation and hypertrophy; a few cysts 1–4 mm. in diameter	"Colloid" casts and some pus cells	Presen
7	Radial areas of tuberculosis; radial scarring	Fibrosis and round-cell infiltration	Hyalinisation in radial scars only	Some fibrosis	Dilated and hypertrophied between scars in subcapsular region; destroyed elsewhere	Pus cells	..
8	Reticular scarring and gross distortion	Increased fibrous tissue and lymphocytes	Mostly hyalinised	Thickened	Atrophy, dilatation, and hypertrophy	"Colloid" casts	..
			A few grossly contracted glomeruli within dilated capsules showing plicated endothelium				

cases had chronic pyelonephritis in association with the salt-losing syndrome. In 2 further cases there was present in addition another serious renal condition, tuberculous pyelonephritis in one, and a form of cystic disease in another. In the remaining 2 patients inflammatory fibrosis had caused such gross distortion of the kidneys that it was impossible to be certain of the initial condition, which may well, however, have been pyelonephritis. In view of these findings it may be questioned whether salt-losing *nephritis* is the best possible name for this very important syndrome, and I suggest that, until the biochemical abnormality responsible is elucidated, it is better to use a circumlocution such as "urinary salt loss due to renal disease" or, perhaps much more neatly, "Thorn's syndrome."

SUMMARY

The renal findings in the 8 published cases of the salt-losing nephritis syndrome of Thorn et al. (1944) are described.

Chronic pyelonephritis was certainly present in 4 of them, probably present in 6 of them, and may well have been present in all 8 cases.

Since this condition is the only common pathological feature of these cases, the syndrome is probably an unusual response to it and the term "salt-losing *nephritis*" is not an accurate description.

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RETARDATION OF GROWTH ASSOCIATED WITH HIRSCHSPRUNG'S DISEASE

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ALTHOUGH for the past thirty years neuromuscular dysplasia or incoördination has been accepted as the cause of congenital megacolon (Hirschsprung's disease), and has supplanted the theory of valves or kinking of the colon at the rectosigmoid junction as the result of fæcal loading, a better understanding of the pathogenesis of the condition has been given by the work of Bodian et al. (1949) and Swenson et al. (1949).

Sir Arthur Keith (1915) was aware that much could be learnt of the pathology of the colon by a study of the "Auerbach tissue," as he called the functioning complex of ganglia and nerves lying within the muscle of the gut. He investigated its anatomy and pathology when Arbuthnot Lane was doing colectomy for intestinal stasis, and the discovery of some abnormality in the neuromuscular complex was anticipated as corroborative evidence in support of such treatment. Keith did not claim that the genesis of stasis had been solved:

> "Although my investigations have not succeeded in finding a pathological basis for impaired mobility of the colon, they may be of service in another way, by drawing attention to our considerable ignorance concerning both the anatomy and physiology of the great bowel."

Surgical textbooks of the day—e.g., Miles (1923)—always pointed out that there were two types of megacolon: one in which dilatation and hypertrophy extended from the anus upwards, and another in which various lengths of the rectum appeared normal in every respect. It is in this second type that Bodian et al. (1949) have shown an abnormality of "Auerbach tissue" in the seemingly normal portion of the rectum—namely, absence of ganglion cells, with some increase in size of the nerve-fibres. Swenson et al. (1949) have also demonstrated this abnormality and confirmed it by the manometric recordings of peristalsis. However, they do not suggest that there is absence of ganglion cells in all cases of congenital megacolon. Until this work, attention had always been focused on the dilated and hypertrophied portion of colon.

In view of these recent observations it has been suggested that the term congenital megacolon should be restricted to the second of the above-mentioned types, which usually manifests itself shortly after birth, the other types of megacolon with achalasia of the anal sphincter being excluded (Stephens 1951). Although this conception is based upon the time of onset of the disease in the life of the patient, together with the histological findings, it is really necessary to have proof of absence of some structure or of some function of the anal canal before such a distinction can be made permanently. Congenital weakness or imbalance may not show itself in the first few years.

The life history of these unfortunate victims who are deprived of the means of normal rectal and colonic evacuation is chequered with constipation and crises of such a degree of fæcal retention and impaction that, besides the effect of toxin absorption, peritonitis and death may result from perforation of stercoral ulceration. The least discomfort that the patient can have to endure is a rectal washout every week or so, and periodic manual evacuation of the rectum superimposed upon the obstinate constipation. If the lesion is more than a few inches from the anal canal, such conservative measures as rectal dilators and rectal washouts have little or no chance of permanent success compared with those cases of achalasia of the anal sphincter which Hurst (1924) declared could be treated in this way. Spinal anæsthesia (Telford and Simmins 1939) may be effective if given early enough in the life of the child, but a permanent result cannot be expected where "Auerbach tissue" is absent.

What is the quality of the life of one who suffers from this absence of "Auerbach tissue" and what is its duration? The quality is poor, being probably due to the absorption of toxins from the colon, for the general health is not good and the body is thinly covered and undernourished. The duration may be as short as a few weeks; but, even if early crises are survived, death may come from perforation or from intercurrent infection in adolescence. Adult life is rarely attained. Published reports give little or no information about the effect on physical and mental development or on endocrine balance that the condition may have if the patient survives; and no worker has reported such a remarkable delay in development, followed by an even more remarkable transformation after colectomy, as in the case described here.

CASE-RECORD

The patient was born in 1931. At the age of 11 days he was admitted to hospital with vomiting and signs of intestinal obstruction, and this early crisis was overcome with conservative measures. For the next 3 years the boy was in and out of various hospitals with attacks of obstruction. At the age of 3 years he was brought to the Children's Hospital, Birmingham, and there diagnosed as a case of Hirschsprung's disease. Admission was advised, but while he was on the waiting-list he had a further attack of obstruction. This time the distension and colonic impaction of fæces were so severe that a hard core of fæces was protruding through the anus. One of us (F. A. R. S.) did a cæcostomy and manual evacuation of the rectum as an emergency device to afford relief. Later on in his 3rd year the boy underwent presacral sympathectomy and section of the lumbar colonic nerves; but no permanent relief was obtained, and his abdomen remained grossly distended. Yet there was some improvement, and because of this, and because of the war, he was lost sight of until he was aged 18, when he was admitted to Queen Elizabeth Hospital, Birmingham, for further investigation and treatment because he never had a spontaneous bowel action, fæcal impaction being prevented by enemata every other day. He had found that he could sometimes pass flatus if he lay steeply inclined with the pelvis high, so that the sigmoid could straighten out by gravity. He sought advice because his abdominal distension caused increasing breathlessness on exertion.

On examination he was very small, like a child aged 10 years rather than 18; his voice had not broken, his genitalia were undeveloped, and he had no pubic or axillary hair. His abdomen was enormously distended (fig. 1), and peristaltic waves were visible, often preceded by pain sufficient to make him cry out.

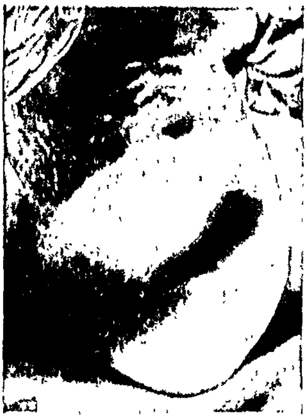


Fig. 1—Enormous distension of abdomen, tiny chest, and flaring of ribs.

Investigations.—The blood-pressure was 100/60 mm. Hg. Blood-count: hæmoglobin 30%, red cells 3,500,000 per c.mm.—a severe microcytic hypochromic anæmia.

Radiography of the chest was normal. The report on the abdomen was: "One can only call the fæcal accumulation fabulous." The report on the epiphyses was: "The bones are slender with wide marrow cavities. The union of the epiphyses to the shafts is a little delayed. That for the radial head should have fused at puberty; that at the distal end of the humerus should just be fusing."

Progress.—Even while enemata were being given to remove the accumulation of fæces the patient developed obstruction with vomiting and increase in the distension, but the crisis was overcome by further washings, and during the following fortnight enormous stools were obtained. The abdomen became much softer, but the large hypertrophied colon could easily be felt. It was decided to do a laparotomy to see if anything, possibly a colectomy, could be done to help the patient.

Operation (F. A. R. S.).—On July 18, 1949, the abdomen was opened through a left paramedian incision. Gross hypertrophy and dilatation of the ascending, transverse, descending, and sigmoid colon were found. The mesocolon and mesosigmoid were enormously thickened. The cæcum was normal. At the rectosigmoid junction the bowel suddenly narrowed, and the lumen appeared constricted for half an inch, at which point there seemed to be an increase in the circular muscle fibres; distal to this point the bowel was narrow (fig. 2). It was decided that a colectomy was contra-indicated by the patient's poor condition and by his patulous anal sphincter, which would probably leave him incontinent after a colectomy with anastomosis of the ileum to the rectal stump. It was suggested that a plastic procedure like that used in Heller's operation for cardiospasm or in the Fredet-Rammstedt operation for pyloric stenosis in infancy could be tried. This plastic procedure at the site of constriction was undertaken, and longitudinal and circular muscle-fibres were divided vertically for three inches, and the incision was deepened until the mucosa began to pout through the incision. The rectum was not opened, but the bared area with pouting mucosa was covered by overlapping the appendices epiploicæ from each side; a pelvic drainage tube was inserted as a safety measure in case of leakage. The abdomen was closed.

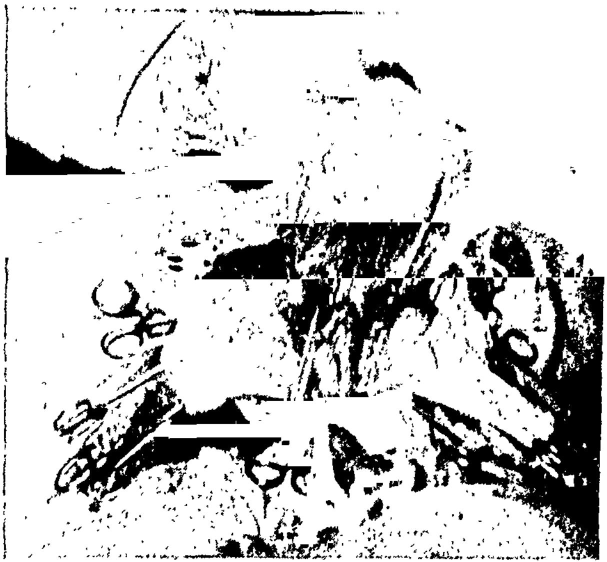
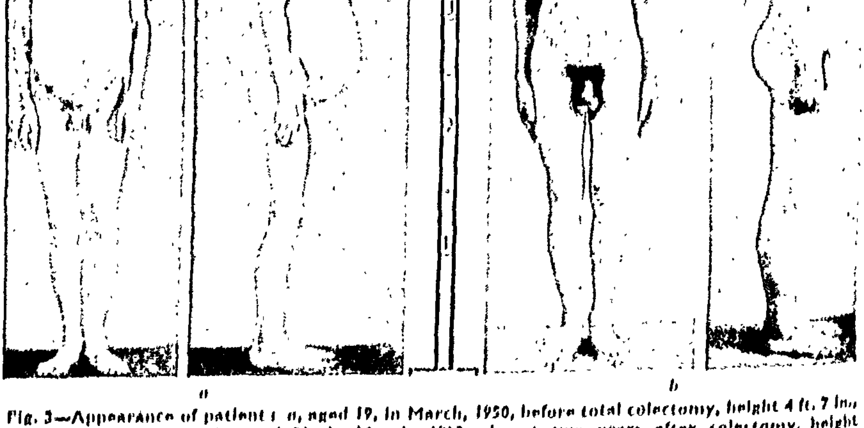


Fig. 2—Thickened dilated sigmoid colon joining apparently normal rectum found at plastic operation.

Postoperatively the patient could pass flatus through the tube, and 4 days later he had a spontaneous bowel action. From then on he had several actions of good amount each day, and his general condition was much improved. He was delighted, because this was the first time in his life that he had ever had a spontaneous action.

On discharge his hæmoglobin had risen from 30 to 60%, his abdomen was considerably less distended, and he was learning abdominal exercises so that the muscles could regain their tone after being continually overstretched.

Relapse.—After 3 months of spontaneous bowel actions constipation recurred, and in 6 months the patient was admitted to another hospital as an emergency case with



a *b*

Fig. 3—Appearance of patient: *a*, aged 19, in March, 1950, before total colectomy, height 4 ft. 7 in., weight 5 st. 11 lb.; *b*, aged 21, in March, 1952, almost two years after colectomy, height 5 ft. 4 in., weight 8 st. 7 lb. Note recovery of stretched abdominal muscles in spite of operation scars.

obstruction of the large bowel. This obstruction was temporarily relieved by enemata, and after this he was admitted once more under one of us (F. A. R. S.). This time it was decided that total colectomy with anastomosis of the lower ileum well down on to the apparently normal rectum offered the only chance of success. The patient was now aged 19 and still looked as poorly nourished and infantile as before, and the distension of his abdomen was considerable (fig. 3*a*). His hæmoglobin was 46% and red cells 3,000,100 per c.mm. Repeated blood-transfusions were given before operation, raising the hæmoglobin to 86% and the number of red cells to 4,700,100 per c.mm. The serum-chloride and serum-protein levels were normal.

Total colectomy (F. A. R. S.).—On April 4, 1950, laparotomy was done through a midline incision, and the huge colon was found with many adhesions over the cæcum. The bowel at the rectosigmoid junction, where the previous plastic operation had been done, was found to be dilated, and below this the rectum appeared normal in size and on palpation. The site of the plastic operation was almost obliterated by scar tissue. Total colectomy was done (fig. 4). The distal ileum was anastomosed end-to-side with the rectum after the upper cut end of the latter had been closed by invagination.

Postoperatively the patient's general condition was good, but in the first 2 days he had severe abdominal colic, and it was noticed more than ever how child-like the patient was in his response to the pain and considerable discomfort. On the 3rd day he passed fæces and flatus; on the 4th and 5th day he had diarrhœa, having his bowels open five and seven times a day; on the 6th day his bowels were opened twice; and subsequently, although the motions were loose, he had no more than two or three actions daily until he was discharged on April 22, 1950.

Pathological report on the apparently normal area below the dilated sigmoid: "Ganglion and nerve-fibres present in the position of Auerbach's and Meisner's plexuses. The muscularis of the colon below the stricture shows infiltration with lymphocytes and plasma cells."

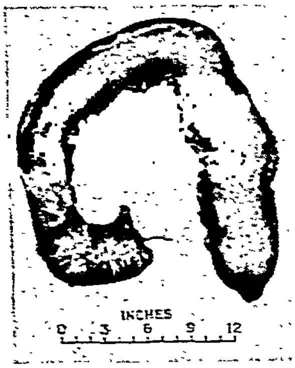


Fig. 4—Colon removed at second operation. Note foot rule and size of appendix, which escaped dilatation and hypertrophy.

Follow-up.—Two years have gone by since the colectomy: and in that time, besides maintaining spontaneous rectal evacuation from once to three times a day with no looseness or diarrhœa, the patient has been physically and mentally transformed. He is now aged 21, with a healthy agile mind and body (fig. 3*b*), looking forward to hard work and a good future. He is an engineering apprentice and in his spare time enjoys cycling and a great deal of ice skating. In April, 1952, he was 5 ft. 4 in. in height (4 ft. 7 in. before colectomy) and 8 st. 7 lb. in weight (5 st. 11 lb. before). The genitalia have developed, and all secondary sexual characteristics are present. His hæmoglobin is 92%, and radiography of the long bones shows (Dr. J. F. Brailsford) "evidence of some delay in ossification. The appearances suggest that the skeleton temporarily retarded has established its potential growth. The main epiphyses have now fused. There is no indication of giantism."

DISCUSSION

Diagnosis

The history of obstinate constipation from birth, with failure of spontaneous bowel action until the plastic operation at the age of 18, the crises of fæcal impaction, the failure of more conservative operations, together with the typical appearance shown by a fractional barium enema and the findings at operation (fig. 2), mark the patient as having congenital megacolon with dysplasia of the apparently "normal" segment of the rectum.

Rationale of Operation

For the extreme distension of fæcal impaction in a small child cæcostomy is a life-saving operation, overcoming obstruction and preventing perforation from stercoral ulceration; and the consequent improvement in the patient's condition makes it possible to empty the large bowel with less risk. There is no doubt of the good effect obtained in the present case.

Some operations become popular as the result of experimental work on a particular subject, and this was true in the early 'thirties of presacral neurectomy and section of the lumbar colonic nerve following the contributions of Learmonth and Markowitz (1930) and Rankin and Learmonth (1930) to the understanding of the autonomic system in the pelvis. Sympathectomy had just made its début, and reports of its application and results were beginning to come in (Stammers 1932). In the present case, however, there was no striking improvement. The plastic operation of 1949, done on the same lines as that for achalasia of the cardia or for congenital hypertrophic pyloric stenosis, was attended with some, though only temporary, success, for it was after this that the patient had the first spontaneous bowel action of his life. The cause of the failure may have been, just as it can be with rectosigmoidectomy, that the operation was not carried past the affected area of rectum. Had this been done, success might have lasted longer, though it must be observed that in the temporary period of 6 months of success there was no improvement in growth and development.

Total colectomy and not rectosigmoidectomy was done because the colon had been dilated and hypertrophied for 19 years and was involved right up to the cæcum; toxic absorption from the colon was causing delay in growth and development; and total colectomy in one stage for ulcerative colitis is not considered dangerous provided that the water and electrolytic balance of the patient is maintained. Colectomy for intestinal stasis on the grounds that it causes absorption of toxins was advocated and practised by Lane (1915) and Ward (1915).

The remarkable result that attended total colectomy in the present case supports the theory of toxic absorption (Mutch 1915), for some factor must have entered the body from the colon to retard growth and development to such an extent. One may wonder whether the same result would have been obtained by rectosigmoidectomy, by which operation the affected area of apparently normal rectum would have been excised but the proximal colon would have been retained. This may well be doubted, since no such change followed the plastic operation, although spontaneous bowel actions occurred.

Little is known of the toxins that can be absorbed from the bowel or be responsible for such a condition. Although such absorption is held to be the cause of a sallow-skinned and poorly developed body with equivalent mental features, as is often seen in those who have prolonged obstinate constipation, this patient's mind and agility were of a high standard considering the stress imposed by the protuberant abdomen. Some other "toxin" must have been absorbed which had a direct effect on the pituitary gland.

In the last few years interest has been focused on necessary growth-promoting substances, such as vitamin B_{12}, and their association with bacterial activity and antibiotics. Perhaps in megacolon the absorption of these substances is prevented by the effects of stagnation in the dilated large bowel, effects which may even cause severe retardation of endocrine function. The more recent discovery of the rôle of pantothenic acid as an enzyme in the formation of acetylcholine may provide further impetus for research in Hirschsprung's disease. Although Swenson et al. (1949) have shown that the ganglion cells were absent in some of their cases, they state that this is not always so, this point being borne out in the case reported here. Perhaps an upset of the normal bacteriology of the colon, with incomplete synthesis of pantothenic acid and the failure to absorb growth-promoting substances, may be responsible for much of the pathology of Hirschsprung's disease. Though this is conjecture it is an additional pointer to the fact that the pathology of Hirschsprung's disease is not yet completely known.

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TREATMENT OF THE ADRENOGENITAL SYNDROME WITH CORTISONE

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THE manifestations of the adrenogenital syndrome in girls and women at or after puberty respectively are hirsuties, acne, enlargement of the clitoris, and amenorrhœa or irregular scanty menstruation. Although some of these patients may have a daily excretion of 17-ketosteroids within average limits (5–15 mg.), if the output of 17-ketosteroids is followed over a long period it can be shown in many instances to exceed 20 mg. daily. This increased excretion is intermittent and varies in amount; it has been reported by Koets (1949) to be greatest in the phase of ovulation, and by Merivale (1951) to be maximal in the luteal phase. The recognition that cortisone depressed adrenocortical function soon led to its use in conditions of adrenocortical excess. Wilkins et al. (1951, 1952) have described its use in eleven children for 5–17 months, and Bartter et al. (1951) have described the results of treatment in three patients. Bishop et al. (1952) and Simpson (1952) have reported its use for a short time in two patients with adrenocortical hyperplasia.

In the case reported here a girl, aged 19, with virilism, was studied for ten months, during the last five of which she was treated continuously with cortisone.

CASE-RECORD

The patient, who was referred to me from the dermatological department of the Derbyshire Royal Infirmary by Dr. P. D. C. Kinmont for investigation of hirsuties, complained of an excessive growth of hair on her face since the age of 15, more marked on the cheeks than on the lip and chin (see figure). She shaved three or four times a year. Her menses started at the age of 13 and were irregular during the first two years, with periods of amenorrhœa lasting three or four months. From the age of 15 to that of 17 the intervals between periods were about a month, but during the last year usually 31–33 days.

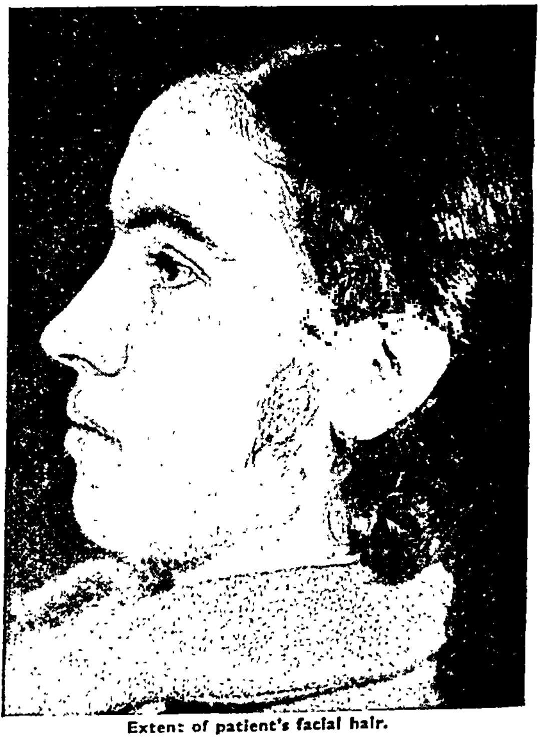
On examination the patient had a few hairs round the areolæ of the nipples and a male distribution of hair on the abdomen. The growth of hair on the back and on the legs was excessive. There was a moderate amount of acne on the face and back. The labia minora were reported by a gynæcologist (Mr. N. L. Edwards) to be hypertrophied, and the clitoris to be enlarged.

Investigations.—A tumour of the adrenal cortex was excluded, and the usual endocrine functions were investigated and found to be within average limits except in two aspects. The urinary excretion of 17-ketosteroids was intermittently greater than usual. In 25 estimations done in five months the average daily excretion was 15·2 mg. per twenty-four hours, the lowest figure being 7·0 mg. and the highest 33 mg. per twenty-four hours. It could not be determined that the rise or fall of 17-ketosteroids was related to definite intermenstrual phases, nor were the highest levels associated with the increase of pregnanediol in the luteal phase. The other abnormal finding was that on 6 out of 23 occasions the serum-potassium level was lower than normal; the lowest of these six readings was 12·2 mg. per 100 ml. (3·1 m.eq. per litre), and the average 14·5 mg. per 100 ml. (3·7 m.eq. per litre). On three of these occasions the serum-sodium level was above normal: 334, 340, and 344 mg. per 100 ml. (145, 147, and 149 m.eq. per litre). The plasma-chloride level, the alkali reserve, and the urinary output of sodium, potassium, and the chlorides were invariably within accepted average limits. The eosinophil-count was always between 200 and 500 per c.mm.

Treatment.—The patient was first given a week's treatment with 100 mg. of A.C.T.H. daily. This produced an eosinophil-count averaging 60 per c.mm. (ten counts), and an excretion of 17-ketosteroids averaging 24·0 mg. per twenty-four hours (six estimations). The day-time output of urine in the five days preceding A.C.T.H. therapy was 182 oz. (daily average 36·4 oz.) and the nocturnal output 93 oz. (nightly average 18·6 oz.). In the first four days of A.C.T.H. therapy the day-time output was 84 oz. (daily average 21 oz.) and the nocturnal output 144 oz. (nightly average 36 oz.). The daily average serum-potassium level in the first four days of A.C.T.H. therapy was 13·9 mg. per 100 ml. (3·6 m.eq. per litre). In the last two days of the week of A.C.T.H. therapy the serum-potassium level was normal and the ratio of diurnal to nocturnal urine was corrected. At the end of five weeks, and before cortisone therapy was started, the patient's cheeks were shaved and the hair removed was weighed. This was repeated at the end of four further five-week periods, during which the dose and method of administration of cortisone varied (see table).

RESULTS OF TREATMENT

These findings confirm the therapeutic results obtained by Wilkins et al. in adrenocortical hyperplasia in children. Cortisone will suppress the excessive androgenic activity of the adrenal cortex, and Wilkins et al. suggest that, to sustain an optimal therapeutic effect, the excretion of 17-ketosteroids should be kept less than 8 mg. per twenty-four hours. In the present patient with varying dosage this level was maintained for periods of no longer than two weeks, and a detailed examination of the records suggests that this level might be permanently


Extent of patient's facial hair.

RESULTS OF CORTISONE THERAPY

—	First 5 weeks	Second 5 weeks	Third 5 weeks	Fourth 5 weeks	Fifth 5 weeks
Average daily dosage of cortisone (mg.)	Nil	50 (1)	25 (2a & b)	40 (3a & b)	40 (4a, b & c)
Weight of hair removed (mg.)	99	50	70·8	68	58
Average daily excretion of 17-ketosteroids (mg.)	20	10·3	11·5	10·5	10·4

Method of administration :

1, 25 mg. by injection twice daily.
2(a) 2 weeks, 50 mg. orally (? = 25 mg. by injection).
(b) 3 weeks, 25 mg. by injection daily.
3(a) 1 week, 25 mg. by injection twice daily.
(b) 4 weeks, 50 mg. by injection on alternate days.
4(a) 2 weeks, 50 mg. by injection on alternate days.
(b) 2 weeks, 25 mg. twice daily.
(c) 1 week, 100 mg. on alternate days.

sustained with a daily injection of 50 mg. or an injection of 100 mg. on alternate days. The same dose by mouth was ineffective, and Wilkins et al. advise that, for an equal suppressive action, the oral route requires two or three times the amount given by injection.

It will be seen from the table that there is a rough correlation between the amount of hair growth, the dose of cortisone, and the amount of 17-ketosteroids excreted. It is shown that the rate of excessive hair growth can be about halved, but that it can be completely suppressed by cortisone therapy is as yet uncertain.

MODE OF ACTION

It is assumed that cortisone suppresses adrenocortical activity by opposing the action of A.C.T.H. Bartter et al. suggest that the androgenic excess may be due to a relative insufficiency of 11,17-oxysteroid production (which is the major opponent and regulator of A.C.T.H. secretion) with a consequent excessive secretion of A.C.T.H.

The present patient showed no evidence of 11,17-oxysteroid insufficiency (including her response to a water load, to intravenous insulin, and to stress). Moreover, though A.C.T.H. 100 mg. daily produced an effect on 17-ketosteroid output and serum-potassium levels of the same order as had appeared intermittently in the preliminary control periods, it produced in addition a profound and sustained eosinopenic response. Clearly 11,17-oxysteroid production was not deficient in this patient either under ordinary conditions or in response to A.C.T.H.

DISTURBANCE OF ELECTROLYTES

It has long been recognised that adrenocortical hyperplasia in infants may be accompanied by excessive loss of sodium and that, though this is corrected as the child grows older, it tends to recur during infections. In Cushing's syndrome a low serum-potassium level is sometimes seen; and this may be sufficiently severe to produce the hypochloræmic alkalosis which is now recognised to follow a potassium deficit. It is assumed that this hypokalæmia is due to the excessive production of a steroid with a deoxycortone-like action. In this patient the low serum-potassium levels presumably resulted from the same cause.

Occasionally this hypokalæmia was accompanied by a serum-sodium level above normal; but, although examined on scores of occasions, no reduction of plasma-chloride level and no increase of CO_2-combining power beyond average limits were recorded. The hypokalæmia was not accompanied by fatigue, muscle weakness, or electrocardiographic change. This lack of correlation is now widely recognised. Since this observation of hypokalæmia in the adrenogenital syndrome has apparently not been made before, great care was taken to ensure that these results were accurate. They were checked against estimations made on other patients on the same day, they were frequently estimated by different methods, and they were usually duplicated in two laboratories.

In another patient with adrenocortical hyperplasia now being investigated a similar hypokalæmia has been observed:

A school-mistress, aged 24, complained that a considerable growth of hair had been present on her face since adolescence. She had a male distribution of hair on her abdomen. Her menarche was at the age of 18, and her menses are scanty, short, and irregular. Her breasts are normally developed, and her clitoris is moderately enlarged. Her average daily excretion, determined each day for 23 days, was 21·3 mg., the lowest daily value being 11 mg. and the highest 30 mg. The average daily serum-potassium level in a month was 14·3 mg. per 100 ml. (3·7 m.eq. per litre), and the average of seven daily serum-potassium levels obtained in another laboratory in the same period was 14·4 mg. per 100 ml. (3·7 m.eq. per litre).

POSSIBILITIES OF THERAPY

Though the treatment of adrenocortical hyperplasia in childhood, whether in female pseudohermaphroditism or in macrogenitosomia præcox in boys, is undeniably first-class therapy, it is uncertain whether adrenocortical hyperplasia occurring at puberty and after justifies continued treatment with cortisone. The suppression of the signs of virilism—hirsuties, menstrual disturbance, acne, and so on—may seem to be an inadequate reward for the frequent injections of a potentially hazardous substance. On the other hand, few conditions cause more distress to girls in adolescence and in young womanhood than does virilism, and, when cortisone is more freely available, such therapy, carefully controlled, may justifiably be practised. This condition is by no means rare and, since its effective treatment will require about 20 g. of cortisone a year, such therapy is not immediately practicable.

SUMMARY

The treatment of a patient with the adrenogenital syndrome (virilism) with cortisone for five months is described.

The amount of cortisone required for the suppression of excessive androgenic activity was about 50 mg. daily. This dosage slowed the rate of facial hair-growth by about half.

The finding of intermittent hypokalæmia in this patient and in another with the adrenogenital syndrome is reported. This parallels the potassium deficit which sometimes occurs in the adrenocortical (Cushing's) syndrome.

This paper is the report of a great deal of investigation, much of it here unrecorded, conducted by several technicians. The chemical investigations were made in the laboratory of the Derbyshire Royal Infirmary (Dr. G. R. Osborn) by Mr. J. A. Allen, Miss A. Matthews, B.SC., and Miss J. Pegg, B.SC. The duplication of the potassium estimations was done in the laboratory at the Sheffield Royal Infirmary (Dr. A. Jordan) by Mr. D. A. Podmore, A.R.I.C., Miss K. P. M. Groocock, B.SC., and Miss M. C. O'Connell, B.SC. The estimation of 17-ketosteroids was done by Mr. F. Mitchell, B.SC., in the laboratory of the Jessop Hospital for Women, Sheffield (Dr. G. C. Paine). To all these chemists my thanks are due. Dr. Harold Tulloh and Dr. Barbara Green, my house-physicians, and Miss L. M. Edwards, my ward-sister, gave me much help. I am indebted to the Medical Research Council for the A.C.T.H. and the cortisone.

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THIOPENTONE FOLLOWED BY NITROUS OXIDE AND OXYGEN FOR ANÆSTHETISING OUTPATIENTS

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UNTIL recently a blind eye was turned on the unsatisfactory conditions associated with general anæsthesia for ambulant patients. In no other type of anæsthesia were anoxia and poor operative conditions permitted, but in the casualty department these were looked on as inevitable. Bourne (1951) tried to prevent anoxia and struggling by using cyclopropane instead of nitrous oxide, and was impressed by the results. Rook (1952) emphasises the advantages of a short-stay ward attached to the casualty department; outpatients can then be given full premedication followed by adequate general anæsthesia. Franks (1952), however, points out that very few hospitals possess a short-stay ward, and that the length of stay in hospital required by this technique is a disadvantage.

In busy outpatient departments rapid recovery and early return home are outstanding considerations, and this is why nitrous oxide still remains the most commonly used anæsthetic agent for outpatients in this country. Though in many cases patients can be anæsthetised satisfactorily with nitrous oxide, in others it fails badly. In anæsthetic-resistant patients a smooth anæsthesia with good operative conditions cannot be obtained unless the gas-and-oxygen is reinforced or superseded by a more potent agent. It is over the choice of the potent agent that disagreement arises.

DISADVANTAGES

The disadvantages of various techniques of general anæsthesia for outpatients are as follows:

Nitrous Oxide—Air.—Adequate oxygenation cannot be maintained, and length of administration is limited.

Nitrous Oxide—Oxygen.—It may be impossible satisfactorily to anæsthetise resistant patients. Anoxia may be unavoidable.

Nitrous Oxide—Oxygen—Trichlorethylene.—This is a very useful technique but may produce breath-holding or a bout of coughing in heavy smokers.

Cyclopropane—Oxygen.—The main disadvantages of this method are that it is inflammable and cannot be trusted to the novice. Postoperative nausea and vomiting may be troublesome.

Intermittent Thiopentone.—Recovery may be slow and be associated with disorientation. The practice of shortening the recovery period by *routine* injection of an analeptic does not appear rational.

Full Premedication and General Anæsthesia.—A short-stay ward is essential, and the patient's stay in hospital is very long after even minor surgical procedures.

THIOPENTONE—NITROUS OXIDE—OXYGEN

Various methods of general anæsthesia have been tried in the casualty department of the County Hospital, Bedford, and that described below has been found the most successful. It is not a new technique; its use in resistant dental cases has been described by Macintosh and Pratt (1940). It has been used here in more than two hundred consecutive and unselected adult outpatients, and has shown its best results in the anæsthetic-resistant and in the poor-risk patients in whom anoxia is particularly undesirable. This method allows optimal oxygenation of the tissues and thus enables nitrous oxide to produce its best degree of muscle relaxation (Guedel 1951). It is assumed that, if 17–20% oxygen is administered throughout the major part of the anæsthesia, anoxia is either minimal or absent.

The method consists of a sleep-dose of thiopentone followed by nitrous oxide/oxygen anæsthesia. It is based on the synergistic action between these agents shown by Organe and Broad (1938), who observed that administration of about 85% nitrous oxide and 15% oxygen halved the amount of barbiturate required to produce anæsthesia.

Premedication.—Atropine gr. $^1/_{100}$ is used in all the cases to prevent excessive salivation and to reduce thiopentone-irritability of the larynx.

Assessment of Patient.—Each patient is classified according to age, physique, occupation, habits, &c., as "frail," "average," or "resistant," and the dose of thiopentone varied accordingly.

Sleep-dose of Thiopentone.—The amount needed by most patients is 2–5 ml. of the 5% solution (0·10–0·25 g). This amount is, of course, inadequate to produce anæsthesia. In making the injection 0·5 ml. is given and, after a slight pause during which the patient is asked if he feels any discomfort, the remainder of the selected dose is injected *rapidly*.

Inhalational Supplement.—As soon as the patient has become unconscious, several breaths of pure nitrous oxide are given, after which oxygen is introduced in increasing concentration. Gas-and-oxygen is administered for about two minutes before the operation begins, so as to produce some degree of nitrous oxide saturation in the tissues. After the skin incision, &c., the oxygen can usually be increased to, and maintained at, 17–20% without reflex movements or other signs of lightening anæsthesia. The Walton III machine has been used without rebreathing, the percentage of the inspired gases being read off from the dial directly.

Recovery.—Consciousness is regained well within a minute, but sometimes a patient appears to remain asleep at the end of this time; he will, however, open his eyes if addressed loudly and soon begins to talk rationally. There seems to be little tendency to fall asleep again unless the dose of thiopentone has been excessive. There is a striking absence of excitement on coming round. Nausea and vomiting are uncommon, as indeed are other ill effects. A few patients complained afterwards of headache, but in these the dose of thiopentone was probably excessive. Many patients remarked on the pleasantness of the anæsthetic. Most patients were able to leave hospital in about half an hour by public transport, often unaccompanied.

Range of Use.—The technique has been used for all the common outpatient operations, except those on the face. The length of the operations varied from $1^1/_2$ to 28 minutes. The technique is indicated especially in anæsthetic-resistant and poor-risk cases.

RESULTS

This method has been used in more than two hundred consecutive adult patients, and data have been collected in the last hundred of these. Of these hundred patients 14 were classified as frail, 71 as average, and 15 as resistant. Their ages varied from 18 to 89, and twelve patients were over 70. The average dose of thiopentone was 3·75 ml. of the 5% solution, with a range of 1·5–7·0 ml. Only 2 patients required more than 5 ml. The average oxygen proportion for the major part of the anæsthesia was 19%, and the average time to leave hospital was $28^1/_2$ minutes, with a range of 15–50 minutes. 55% went home unaccompanied and without incident. The post-anæsthesia vomit-rate was 6%. In no case was there regurgitation after the thiopentone. This was prevented by giving the patient's stomach plenty of time to empty before induction, by keeping his head slightly elevated on a pillow, and by using only very small doses of thiopentone. Operative conditions were excellent in most cases, and satisfactory even in resistant patients. Anoxia seemed to be either absent or only slight.

I wish to thank Dr. M. D. C. Hosford, consultant anæsthetist to the Bedford group of hospitals, for his very helpful

criticism and advice in the preparation of this paper; and the casualty staffs for their coöperation.

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TETRAETHYL LEAD POISONING

REPORT OF A NON-FATAL CASE

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THE following history is typical of tetraethyl lead (T.E.L.) poisoning.

The patient was foreman of a gang of men employed to remove the T.E.L.-containing sludge from large storage tanks which had contained leaded petrol, and although he seems to have been familiar with the stringent safety precautions required in such work he apparently omitted to observe some of them.

A brief account is also given of another five men similarly exposed to the same hazard.

CASE-RECORD

Case 1.—A man, aged 26, had cleaned petrol tanks since December, 1949. He worked about thirty-five hours each week with frequent short daily rest periods in the open air. Inside the tank he wore protective boots and gloves and an oilskin suit, but admitted that sometimes he had not worn the positive-pressure air-line respirator provided as an essential part of his equipment. He explained that it made manual work uncomfortably hot, and slower for his gang than his ambition to prove himself an efficient foreman would permit. He claimed to have observed all the other precautions required in his occupation, such as washing before meals and after work each day, bathing and changing his clothes regularly, and drinking a pint of milk each day; but he admitted that his unprotected face was sometimes splashed by the sludge. He was twice clinically examined by local doctors, on Aug. 24, 1950, and Feb. 12, 1951. On both occasions he was found healthy, and on the latter occasion was told that no signs of lead absorption were detected.

The following history was compiled with the help of the patient's diary. In early February, 1951, he first experienced difficulty in falling asleep and in concentrating on the administrative side of his work. He was worried about his wife's health and about debts resulting from excessive beer-drinking. Later the same month he abruptly stopped drinking. By March 9 he was so despondent that he decided to absent himself from work for a few days, but he was recalled the same evening. The next day he heard that one of his men had become insane; and on his own initiative he stopped work and took his men to London, where he reported to his employers. On March 11 the gang left for another site, and that evening he overheard the men debating whether or not to tell him of the sudden death of one of their workmates, allegedly from a brain tumour. They had apparently noticed that he was depressed and listless and did not wish to upset him further. He immediately became very anxious and wished to visit a church. Instead he went to see a doctor, who reassured him and sent him back to his lodgings. Anxious to be with his wife, who was then on holiday 100 miles away, he set out to walk to her, without any idea of the appropriate route. A lorry driver picked him up, soaked to the skin, and drove him to London, where he found his way to his own home. Subsequently he was taken by his wife to a hospital where, after an examination, he was reassured and sent home. On March 15 his employers, who suspected T.E.L. poisoning, arranged for him to be admitted to the Middlesex Hospital.

On admission he was obviously worried and talked about himself for two hours, quoting extensively and haphazardly from his diary. He was anxious about his wife's health, and explained that he felt that he was responsible for the death of one, and the illness of another, of his men by failing to insist on precautions which he had known were necessary in their work. He said that for 2 weeks he had experienced twitching of the nose, a feeling of something stuck in the throat, a creeping sensation in the region of the right ear and shoulder, transient blurring of vision, and episodes of what appeared to have been experiences of *déjà vu*. He had also had insomnia, relieved by hypnotics, for over 3 weeks, and since admission he had experienced panicky feelings of instability. He complained of halitosis and a metallic taste in his mouth for a few days. His appetite had become voracious, but he claimed to have lost about 14 lb. in weight during the last month. He had recently complained of a mild sore throat and occasional headaches but had had no fits or faints and no disturbance of bowel habit. The family and past medical history revealed nothing which seemed relevant.

On examination he appeared intensely anxious, but the physical signs usually associated with anxiety were strikingly absent. His temperature was 97·4°F; pulse regular, rate 68 per min.; and blood-pressure 105/45 mm. Hg. His palms were warm but dry; there was no tremor of his outstretched hands; and his pupils were not dilated. His tendon-reflexes were symmetrically brisk, and there was no "lead line." There were no other physical signs of disease, except a large blister on the left big toe—evidence of his long walk. He weighed 164 lb.

Examination of the blood showed Hb 13·3 g. per 100 ml., red cells 5,000,000 per c.mm., colour-index 0·95, white cells 7400 per c.mm. (neutrophils 45%, lymphocytes 44%, monocytes 5%, eosinophils 6%). No basophilic stippling of erythrocytes was seen.

Urine.—Tests for reducing substances, coagulable protein, and blood were all negative.

Lumbar puncture produced clear cerebrospinal fluid at a pressure of 105 mm. (rising freely to 185 mm. on jugular venous compression) and containing protein 30 mg. per 100 ml., sugar 61 mg. per 100 ml., chloride 692 mg. per 100 ml., and 1 lymphocyte per c.mm. A Pandy test was negative, and a Lange test gave 0000000000.

Liver-function Tests.—A colloidal gold test was negative. Thymol turbidity was 3 units. The serum-bilirubin level was 0·3 mg. per 100 ml. The alkaline phosphatase level was 2·7 King-Armstrong units, and the cholesterol level 174 mg. per 100 ml.

Urinary Lead *.—The corrected urine-lead levels were 0·36 mg. per litre on March 15; 0·24 mg. per litre on April 10; 0·23 mg. per litre on April 22; and 0·21 mg. per litre on April 23. The normal urinary excretion of lead is 0·06–0·08 mg. per litre (Kehoe et al. 1935).

Chest radiography and electrocardiography showed no abnormality.

Electro-encephalography and abdominal radiography are discussed below.

Treatment was entirely conservative. For the first week the patient was confined to bed, encouraged to drink five or six pints of fluid daily, and given phenobarbitone gr. 1 four times daily and 'Sodium amytal' gr. 3 at night. Subsequently he was allowed out of bed for progressively increasing periods, and the sedation was reduced. The phenobarbitone was omitted for two days before electro-encephalography.

Progress.—His symptoms gradually disappeared, and when he was discharged on April 14, 1951, he complained only of occasional creeping sensations in the right side of his head and insomnia when the sodium amytal was withheld. During his month in hospital he gained 10 lb. in weight, his pulse-rate was 60–80 per min., and his temperature 97°–98°F. His blood-pressure, known to have been 130/80 mm. Hg in February, 1948, averaged 90/50 mm. Hg during the first week, and increased to 120/60 mm. Hg on discharge.

Follow-up.—He was seen again on April 23 and 24, 1951, when he was admitted overnight for electro-encephalography,

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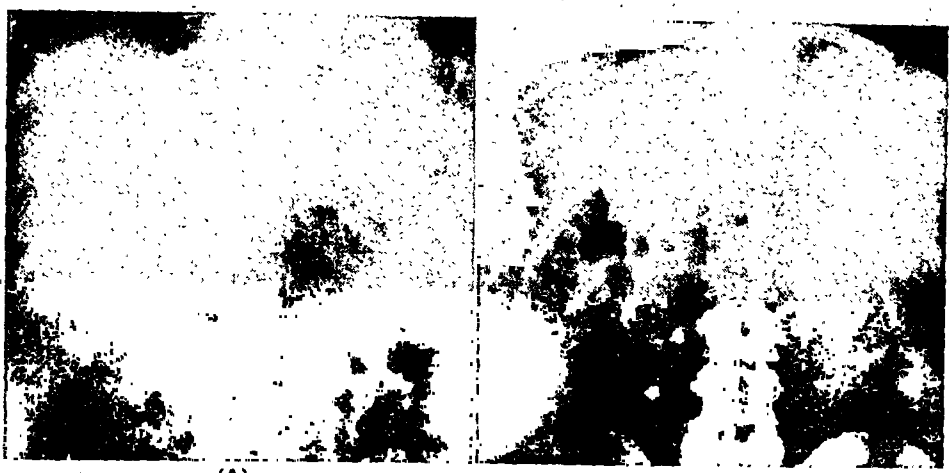
* Lead estimations were done by a short colorimetric method using dithizone on snap samples of urine, and the values obtained were corrected to a standard specific gravity of 1·014 by multiplying by 14/X, where X equals the last two figures of the specific gravity of the urine when the specific gravity of water is expressed as 1·000. This method was adopted to obtain comparable figures over long periods in individual workmen when only snap samples were available. The values it gives are roughly proportional to the rate of excretion of lead.



(A) (B)

Radiograph showing liver shadow of (A) patient and (B) control.

and again about 3 weeks later, after a seaside holiday. At this time he said that he felt very well but still required a hypnotic at night. He proposed to look for alternative employment.

RADIOGRAPHIC DEMONSTRATION OF LEAD IN THE LIVER

T.E.L. is highly lipoid-soluble, and Kehoe and Thamann (1931) showed that in laboratory animals it is concentrated in lipoid-rich organs, particularly the liver. Cassells and Dodds (1946) confirmed this in two fatal human cases, reporting values of 2·35 mg. and 2·5 mg. of lead per 100 g. of wet liver tissue. At the suggestion of Dr. D. Sutton that such lead concentrations in the liver might be demonstrable radiographically, the patient and three healthy medical students of similar girth were radiographed with identical exposures, and the plates were developed under identical conditions. The patient's liver shadow was denser than that of the controls (see figure). That this difference can be due to the presence of lead in the liver was confirmed by taking radiographs, under identical conditions, of a glass tank containing water, and then an aqueous solution of lead acetate containing 2 mg. of lead per 100 ml. The shadow of the lead solution was appreciably denser than that of the water alone. Lack of other patients has so far prevented extension of this work.

ELECTRO-ENCEPHALOGRAPHY

Electro-encephalography on March 27, 1951, showed a slow α rhythm of 8 per sec., which was disturbed in all areas by runs of 5–6 per sec. waves, seen most obviously in the central part of the right temporal lobe. Hyperventilation caused the appearance of paroxysms of 2 per sec. waves in both frontal regions and some 3 per sec. activity over the rest of the cortex.

By April 24, 1951, the record had changed considerably, the dominant frequency varying between 7 and 9 per sec., its voltage having doubled from 16 to 32 μ. In the first record the recordings from the parietal region were relatively flat and featureless, whereas in this record the 7 per sec. frequencies were predominant. In the temporal lobes the previous asymmetry was reproduced and, as elsewhere, had a higher voltage. The response to hyperventilation was also different: within half a minute low-voltage 2 per sec. waves appeared in both occipital regions. High-voltage generalised 3–4 per sec. waves first appeared at $1^1/_2$ min. and appeared paroxysmally for the rest of the exercise of $3^1/_2$ min. and for 20 sec. after it. They had not appeared in the previous record until 2 min. 20 sec., and on that occasion were not nearly so well marked.

We have not been able to find any published work on the electro-encephalogram in T.E.L. poisoning in man; but Hill and Parr (1950) mention the unpublished finding that the changes resemble those seen in the early stages of T.E.L. poisoning in cats, which Steinman and Thorman (1939) describe as a decrease in amplitude of cortical rhythm, with a tendency to cortical instability. Our findings, which conform with these, suggest that in man T.E.L. causes generalised suppression of cortical activity, with the appearance of non-specific slow-wave activity.

DISCUSSION

The anti-knock properties of T.E.L. were discovered by Midgley and Boyd (1922), and manufacture and blending with petrol began in America in 1924. The toxicity of the substance was not recognised until many workmen died, when manufacture was suspended for a year, pending the result of a government inquiry. It was resumed only after the enforcement of strict industrial and medical controls which made the industry safe. There have been no deaths since manufacture and blending started in England in 1940. Apart from isolated cases, such as those reported by Cavallazzi (1946), where poisoning followed exposure to an insecticide, and those of Bini and Bollea (1947), where workers cleaning clothes with leaded petrol were involved, the only cases reported recently in America and Western Europe have occurred in tank cleaners. These men work in small parties and, in spite of supervision, have in each incident relaxed the precautions necessary for their safety. Such an outbreak in England was reported by Cassells and Dodds (1946).

T.E.L. is absorbed chiefly through the skin and the respiratory tract, and waterproof clothing and respirators of various types afford complete protection. Hence, when proper equipment is available and is in working order, tank cleaning should be entirely safe, outbreaks of poisoning being due to the negligence of the workmen.

The clinical picture of T.E.L. poisoning was reviewed by Machle (1935). The symptoms are referable chiefly to the nervous and alimentary systems. Insomnia, lassitude, irritability, and unpleasant dreams appear early, and may be followed by weakness, tremor, and headache. Anorexia and loss of weight are common, and nausea, morning sickness, and diarrhœa may occur. In severe cases a toxic psychosis develops, with hallucinations, delusions, and excitement which may terminate fatally in delirium. If recovery takes place it is usually complete, and sequelæ are uncommon. The characteristic physical signs are pallor without anæmia, low temperature, bradycardia, hypotension, and brisk tendon-reflexes. In severe cases collapse and encephalopathy are found. Lead line, neuropathy, and basophilic stippling of the erythrocytes are rare in contradistinction to inorganic lead poisoning.

The diagnosis is established from a history of exposure, the clinical picture, and urinary lead estimations. Mild cases give urinary concentrations of about 0·2 mg. of lead per litre, and severe cases up to 4 mg. per litre. The clinical picture, however, does not always run parallel with the urinary excretion of lead.

The most widely accepted treatment is conservative. Good nursing, sedation, and the maintenance of a high intake of fluid are essential. R. Kehoe (personal communication) states that there is little evidence that the course of the disease has been materially influenced by he use of dimercaprol. No results have so far been published on the effect of di-sodium phosphate, recommended by Proctor and Kahn (1950) to accelerate the excretion of lead in inorganic lead poisoning.

The development of symptoms within a few days of stopping heavy drinking of beer, noted in case 1, was also noticed by Benassi (1939) in his fatal case. No explanation is offered.

NOTES ON OTHER CASES

Case 2.—A single man, exposed in a similar fashion to case 1, after a few days of insomnia and restlessness, became confused, deluded, and aurally hallucinated, and was certified insane on March 9. On admission to a mental hospital his temperature was 97·6°F and his blood-pressure 105/80 mm. Hg. No physical signs of organic nervous disease were found, but moderate albuminuria and hæmaturia were present. His mental condition gradually improved, and he was fit for discharge after 6 months.

Case 3.—A man, who had twice sought medical advice for insomnia and weakness, collapsed on March 7 and was admitted to hospital. He was very agitated and complained bitterly of a sore throat, although only minor faucial injection could be seen. 2 days later he became hallucinated and increasingly restless and died after a convulsion. At the time of his death his occupation seems to have been unknown, and the diagnosis of T.E.L. intoxication was not considered. The history of exposure and the subsequent clinical picture, however, strongly support the possibility of T.E.L. poisoning, although confirmatory biochemical evidence is not available.

Three other men, who had minor symptoms of sleeplessness and restlessness but no physical signs, were found to have an abnormally large amount of lead in the urine and undoubtedly had mild T.E.L. poisoning.

SUMMARY

A non-fatal case of tetraethyl lead poisoning in a petrol-storage tank cleaner is reported, with notes on other affected men.

Observations are made on the electro-encephalographic changes and on the increased density of the liver shadow demonstrated radiographically.

We wish to thank Prof. A. Kekwick for his encouragement and permission to report the case, which was under his care; Dr. D. Sutton, who suggested and provided the facilities for the liver radiography; Dr. G. Parsons Smith, who interpreted the electro-encephalograms; and Dr. W. T. Earlam, under whose direction the urinary lead was estimated.

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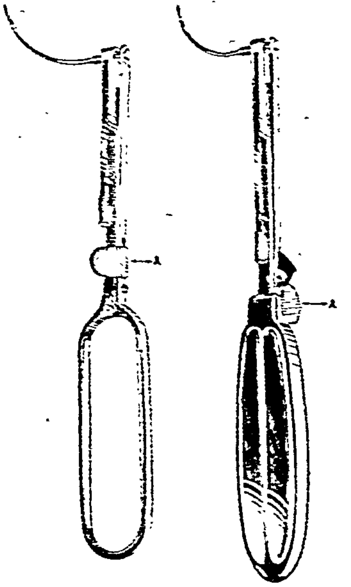
"Some people think that the philosophy a scientist accepts is not of very much importance: his job is to observe the phenomena. This is a gross oversimplification, and it involves the subsidiary hypothesis that all scientists are fully equipped with serendipity. A sensible philosophy controlled by a relevant set of concepts saves so much research time that it can nearly act as a substitute for genius; it may be that this is what we mean by genius. Thus equipped we avoid the pseudo-problems or, more correctly, the problems that are real in adjacent fields but pseudo in our own. A scientist can have no more valuable skill than the ability to see whether the problem he is investigating exists and whether the concepts he is using are applicable. But the lure of a concept that clarifies another field is strong and many of us follow it, like the music of the Pied Piper, to our scientific detriment."—N. W. PIRIE, F.R.S., *Science News,* 25, 1952, p. 20.

New Inventions

MODIFICATION OF BONNEY-REVERDIN NEEDLE-HOLDER

FOR the surgeon who uses the Bonney-Reverdin needle-holder, here is a modification which should be found useful. The essential difference is that the needle eye is opened by means of a separate press-button (shown at point A) instead of by compressing the handle.



The chief reason for altering this well-tried instrument is the tendency of the needle eye to be opened by accidental compression of the handle when the needle is being inserted in or withdrawn from tough tissues such as the rectus sheath. The needle either breaks or becomes fouled in the tissue and soon needs repair.

The two needle-holders shown are exactly the same except that one has a solid handle and the other a loop. They are made by Heaton Grogan Co. Ltd., of Clerkenwell.

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Reviews of Books

William Smellie

The Master of British Midwifery. R. W. JOHNSTONE, C.B.E., M.D., HON. LL.D., professor-emeritus of midwifery, University of Edinburgh. Edinburgh: E. & S. Livingstone. 1952. Pp. 139. 20s.

FOUR boys destined to inscribe their names indelibly on the scroll of medical history were born within a period of thirty years and a distance of thirty miles of one another in the county of Lanark—William Smellie (1697), William Cullen (1710), William Hunter (1718), and his brother John (1728). Smellie is almost best known by the pithy and eminently quotable lampoons written by jealous colleagues. How many medical readers remember that he was said to have "monstrous hands fit only to hold horses," but can recall little about his great place in the history of obstetrics? He used his big hands most dexterously, and by his teaching and practice greatly helped to improve the conditions of poor lying-in women, and the clinical teaching of midwifery to midwives and medical students. This short biography is a modern assessment of his work. The author claims that no other man advanced in his lifetime the knowledge and practice of midwifery to an extent in any way comparable with that achieved by Smellie, and in circumstances which would have discouraged someone less heroic. Without powerful friends to help him, without the advantages of a hospital clinic, he attended and taught in the homes of the poor; and by so doing, and by his writings, raised himself to the foremost position in his profession. His case-notes are freely quoted. As the narrative proceeds, describing one difficulty after another, Smellie's personal character emerges. A man of good will, he was kindly and tolerant towards all except those who were pretentious, insincere, or false; and his unselfish devotion to his patients' interests and his great skill and thoughtfulness are recalled. The remarkable fortitude of his patients is astonishing. Indeed, to us, with our analgesics and our wide choice of anæsthetics, the sufferings which child-bearing women underwent in the 18th century whenever there was any obstetrical complication are almost unimaginable, and show the reasons that inspired James Young Simpson's unwearied search for a safe anæsthetic for childbirth.

The technical details in this important book will fascinate modern obstetricians and midwives, and there is much that will delight the ordinary reader.

An Explaining and Pronouncing Dictionary of Scientific and Technical Words

W. E. FLOOD, M.A., PH.D., lecturer in education (science method) in the University of Birmingham; MICHAEL WEST, M.A., D.PHIL. London: Longmans, Green. 1952. Pp. 397. 12*s.* 6*d.*

ILLUSTRATED with 1300 thumb-nail sketches and diagrams, 10,000 scientific and technical words in fifty subjects (including such things as building and architecture) are here explained as to a person knowing little or nothing about them. The idea is good but the execution poor. The selection of terms for explanation is uneven, with many omissions and some naïve and even unacceptable definitions ("dog watch . . . 4–6 evening, 6–8 morning"; "diptera . . . insects with two pairs of transparent wings"; "Chagas disease . . . carried by bed-bugs"; &c.). Moreover, the phonetic representation is irritating for two reasons: the accent does not mean that the syllable before it is accented but the syllable after it; and the letter R is entirely disregarded except when it comes before a vowel or H. On the other hand, this dictionary is a useful one to have on the shelf because it is likely to list words not contained in some other dictionaries.

The Art of Marriage

MARY MACAULAY, M.B., J.P. London: Delisle. 1952. Pp. 97. 7*s.* 6*d.*

THIS is yet another book in a field where supply must surely soon outpace demand. It is sensible and accurate, but adds to the long list of similar works which are neither exceptional nor exceptionable. The half-quotations from older books (extending as far as Ovid's *Art of Love*) which somehow stick in the mind of sex educationists are all here; so is a good deal of sound advice based on experience. The book has in it most of the factual matter which patients need, and it is at least fully convinced that sexual relationships can and should be pleasurable. For general counselling use it is probably fully adequate.

Medicinal Chemistry

(In 2 volumes.) ALFRED BURGER, associate professor of chemistry, University of Virginia. New York and London: Interscience Publishers. 1951. Pp. 1084. 80*s.* each vol.

THIS work surveys in detail the whole field of the chemistry of medicinal agents for the advanced student of this branch of chemistry or of pharmacology. Interested medical readers will find it full of information on the effect of chemical structure on pharmacological action.

After some general chapters Professor Burger deals with drugs grouped according to their therapeutic uses. Structural chemistry is presented in detail; syntheses and derivatives are given great prominence, derivatives especially being used to display the relationship between graded changes of molecular structure and alterations in therapeutic or other biological effects. Modes of action and metabolic fate are discussed and methods of testing outlined; but comments on therapeutic use are brief, and, on occasion, somewhat ill expressed. The major chapters—on such things as analgesics, drugs acting on the cardiovascular system, and antihistamines—are replete with formulæ of active substances, including all the newer derivatives. References, in footnotes, are ample (up to 1951). Some shorter chapters (those on parenteral fluids, expectorants, and antacids, for instance) are rather sketchy, being insufficiently backed with data from modern organic synthetic chemistry.

In the second volume, which deals with hormones and chemotherapy, the steroid hormones are described chemically in great detail, while sex-hormone therapy occupies less than a page. The sections on sulphonamides, antimalarials, organic arsenicals, antibiotics, and antiseptics are full of facts, and theories of their action are well discussed. Drugs used in the chemotherapy of tuberculosis occupy a 20-page section, and the chapter on antiseptics offers a complete survey and ends with a particularly full account of the quaternary ammonium compounds.

It is a notable achievement for a single author to assemble, in two compact volumes, such an enormous amount of relevant chemical information, and to present it in such a pleasing lucid style.

Surgical Gynecology

J. P. GREENHILL, M.D., professor of gynæcology, Cook County Graduate School of Medicine, Chicago. Chicago: Year Book Publishers. 1952. Pp. 350. $8.50.

IN his preface the author states that he has tried to show in as simple a way as possible how to carry out nearly all the gynæcological operations that are being done today. In this he has succeeded most admirably. His text is clear and his exposition definite. Over 100 beautiful pen-and-ink illustrations define each step in the various operative procedures. In addition to the usual operations associated with gynæcology, he describes how to repair injuries to the bladder, ureter, and bowel, and gives an account of the surgical treatment of hæmorrhoids and the repair of inguinal and femoral herniæ. Pitfalls and dangers are mentioned just where they may occur. The book has been carefully prepared and is suitably indexed. It is limited to its title and is not too lengthy. In a future edition the author might consider inserting on each plate of illustrations the name of the operation being described.

Diseases of the Heart and Circulation (2nd ed. London: Oxford University Press. 1952. Pp. 472. 35*s.*).—In its second edition, Dr. A. A. Fitzgerald Peel's useful students' textbook has undergone considerable revision, and—as too often happens with new editions—enlargement. It retains its original merit of correlating clinical cardiology with anatomy and physiology. Unfortunately, its approach to therapeutics is not so commendable. No attempt has been made to differentiate between the treatment of supraventricular and ventricular paroxysmal tachycardia; and to suggest that amyl nitrite may be of value as a hypotensive agent in hypertension is, to put it mildly, asking for trouble. It is unfortunate, too, that trade names for drugs should be used so profusely, when other teachers are striving to induce their students to restrict themselves to official or approved names. These are minor blemishes in an otherwise commendable book.

Autopsy Diagnosis and Technic (3rd ed. New York: Hoeber. London: Cassell. 1951. Pp. 471. 45*s.*).—The first edition of this book by Dr. Otto Saphir appeared in 1937, the second in 1946. It was written, in the form of a working manual, to provide a diagnostic outline of the gross lesions most commonly encountered at necropsy. Modifications of the techniques of Rokitansky and Virchow are well described and illustrated, while there is a special section devoted to the examination of stillborns and infants. The chapter on the necropsy permit shows the differences in law and custom between the U.S.A. and the United Kingdom, both in the ordinary and the coroner's examination. These differences—together with the American vogue for embalming the dead—account for the concern of the American pathologist to make use of limited and inconspicuous skin incisions. Dr. Saphir rightly charges the prosector, when he has completed his examination, with the task of explaining the clinical picture in the light of his findings, and of explaining in terms of morphology the various laboratory data collected during the patient's lifetime. The technical parts of the book are very good, but the accounts of the abnormalities found at post-mortem examinations are of questionable value for students, being given more fully in textbooks of systematic pathology. Those with some practical experience of necropsies who are revising pathology, however, may benefit from this form of presentation.

THE LANCET

LONDON: SATURDAY, SEPT. 6, 1952

What of General Practice?

To many students and young doctors the idea of going into general practice makes no notable appeal. For this there are many reasons; but commonly these include ignorance and prejudice. The medical student, trained in scientific method, naturally measures the general practitioner's opportunities by the precise yardstick of science—and shakes his head. What may escape him is that the good family doctor laces science's cold portion with the warmer stuff of humanism. Some of this humanism is being formalised in the doctrine of social medicine, which is finding its way into curricula; but, even so, the general practitioner's twofold technique remains essentially empirical, and only those who have tried know the difficulties and satisfaction of applying it. The ivory hospital of the medical school gives little clue to the medical life beyond its walls. As one practitioner puts it in a letter that we print this week:

> "There are many who can think only of the team around the bed in the great teaching hospital, where the personal onus of care is not so heavily on one man, where the relatives are not watching each move and action, and where the patient's friends do not have to be met and spoken to each day."

The student's prejudice against general practice derives partly from the influence of his teachers. Last week, in his good-natured tilt at academic training, Dr. Bromley [1] observed that this is the age of the medical don. Dons, especially those who pursue scientific disciplines, are not remarkable for their tolerance of the empirical; and thus, unknowingly, academic teachers may turn their students against a career beyond the university or large hospital.

The upshot is evident from an article that appeared a week or two ago in our unconstrained Points of View series. Here an anonymous correspondent [2] outlined in darkest colours his conception of general practice. Now others of his generation may not see the picture so black; but we believe that many see it in varying tints of grey. Our correspondent hinted at this. "So it is," he concluded, "that the queue for specialisation grows and grows, and those that at last sink into general practice are bitter and frustrated near-specialists, hating themselves and their job."

Such hostility is best eradicated by giving the facts; and an increasing number of medical schools are shrewdly enabling students to meet practitioners and to see practices.[3] The sort of information that such contacts may yield is indicated in the letters that we publish this week in reply to our correspondent's, perhaps deliberately, provocative arguments. Conditions for the practitioner are far from perfect; but they are not nearly so inimical as some have supposed. Together, these letters show that general practice is emphatically a live concern; and Dr. Ball suggests that the National Health Service Act, far from hastening its end (as many with keen *Schadenfreude* have proclaimed), has in some ways given it new strength. For example, the shadow of fees no longer inhibits doctor or patient; the heavy task of buying a principal's place no longer weighs on the young doctor; and clerical work is, if anything, lighter than before. Furthermore it seems that the rift between hospital and practitioner is being partly bridged by an increasing number of hospitals that are wisely opening their investigation departments to the family doctor, who thus retains more patients continuously in his charge. Then again, the Danckwerts award at last promises adequate pay. Though this alone will not bring suitable candidates, it is one important factor.

We believe that more good candidates will come forward—and come forward eagerly—if students are convinced of the importance of general practice to our society. Unfortunately, general practitioners, who already appreciate this, seldom say so—our correspondence columns this week provide a welcome exception. A college or faculty of general practice [4] could do much to attract to this indispensable and rewarding work a fair share of the profession's best skill.

Isoniazid Trials

A few weeks ago, discussing bacterial resistance to isoniazid, we suggested that there seemed no justification for using this substance alone in preference to streptomycin and *p*-aminosalicylic acid (P.A.S.), except in planned clinical trials.[5] Grace and his colleagues [6] now suggest that it should not be used alone even for large-scale clinical tests. As such tests are at present being carried out by the Medical Research Council in this country, by the Veterans Administration and the Public Health Service in the U.S.A., and by the National Association against Tuberculosis in Sweden, this view needs to be carefully considered.

The evidence on which it is based is derived almost entirely from laboratory experiments. Grace et al. point out that isoniazid is the only commercially available antibacterial agent, apart from streptomycin, against which bacteria can become almost completely resistant in a single step. Furthermore, in vitro, resistance to isoniazid originates about 1000 times as rapidly as resistance to streptomycin. The advantages of administering more than one antibacterial substance are evident in many diseases; and mutation to resistance against two drugs given together is theoretically the product of the individual mutation-rates. In the case of isoniazid and streptomycin it has been calculated that a volume of bacteria almost as great as that of the human body would be necessary for the finding of a cell simultaneously resistant to both agents. Grace and his colleagues predict the early and widespread appearance of resistant strains if isoniazid continues to be used alone, and this will largely neutralise "one of the most hopeful developments in the recent history of tuberculosis therapy"; trials of isoniazid alone are "nothing short of catastrophic."

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[1] Bromley, J. F. *Lancet*, Aug. 30, 1952, p. 393.
[2] *Ibid*, Aug. 16, 1952, p. 332.
[3] See leading article, *Ibid*, 1952, i, 495.
[4] See leading article, *Ibid*. p. 139; Hunt, J. H. *Ibid*, p. 1303.
[5] Leading article, *Ibid*, p. 1293.
[6] Grace, E. J., Bryson, V., Szybalski, W., Demerec, M. *J. Amer. med. Ass.* 1952, 149, 1241.

This argument seems to be based on several assumptions: that isoniazid is a very effective agent against tuberculosis in man, that resistance to it is clinically significant and permanent, and that combination with other drugs will prevent resistance. None of these assumptions has so far been proved. The original reports on isoniazid suggested that it is remarkably effective against tuberculosis in man; but this has not been conclusively demonstrated. Furthermore, the clinical significance of resistant strains emerging during treatment is difficult to determine. The emergence of variants highly resistant to streptomycin tends to worsen the prognosis; but strains of relatively low resistance may have little or no clinical significance.[7] Although highly isoniazid resistant strains can be produced in the laboratory, the resistance of strains so far reported in the sputum during treatment has been relatively low.[8] Highly resistant variants will probably be found as investigation continues, but it cannot be assumed that they will necessarily have the same significance as with streptomycin. Certainly there is already a hint that isoniazid resistance may be of some importance, since the number of bacilli in the sputum begins to increase after its appearance [8]; but this feature has been observed during streptomycin treatment, even when the variants which have emerged show such low resistance that this in itself may be clinically insignificant.[9] Furthermore, in vitro, resistance to isoniazid is certainly not permanent. Strains which appear resistant can become sensitive when grown in isoniazid-free media [10]—a reversion which does not take place with streptomycin-resistant variants. As Grace and his colleagues point out, there is still no indication that this reversion occurs in the body when isoniazid is stopped; but there is also no evidence that it does not occur. Very little is known about combinations of isoniazid with other drugs. Exposure of tubercle bacilli in vitro to isoniazid with streptomycin apparently delays or averts bacterial resistance to both [11–13]; but we do not know whether other combinations behave similarly.

In the absence of so many essential facts we cannot accept the conclusions of Grace and his colleagues. But, supposing that the dangers they foresee are real, can continuation of the trials still be justified? An effective, relatively cheap drug that can be administered for long periods by mouth would be of immense value. Treatment with streptomycin and P.A.S. is still expensive, and, except under close supervision, difficult to carry out in the patient's home. In large areas of the world the only chance of helping the great majority of patients is by developing a form of antibacterial therapy readily obtainable by all. It seems right, therefore, to explore fully the potentialities of isoniazid even in the face of early reports of bacterial resistance and knowledge of what this might signify. Without controlled trials of isoniazid alone the efficacy of this drug cannot be proved, nor can its effect be measured against the known action of others. The action of streptomycin and P.A.S. alone and combined has been fully investigated, particularly by the Veterans Administration in the U.S.A. and by the Medical Research Council in this country. Because of the planned continuity of the M.R.C. investigations it may perhaps be possible to compare the effects of isoniazid with those of streptomycin and P.A.S. alone and combined. Such basic knowledge would have much value. Grace and his colleagues suggest that administration of isoniazid should be combined with, for example, streptomycin and P.A.S.; but the immediate clinical effect of the three drugs together is unlikely to be much greater than that of streptomycin and P.A.S. only. Thus to show the differences convincingly would require very large numbers of patients with long delay in completing the trials. Moreover, the important question whether isoniazid can be used effectively by itself would remain unanswered. Only properly conducted clinical trials can quickly and convincingly prove that isoniazid should not be used alone. Warnings based on *a priori* reasoning are unlikely to prevent the widespread use of such a simply administered, cheap, and plentiful drug in a disease such as tuberculosis. Facts are required; and these can come only from efficiently conducted clinical trials.

At the same time, on the evidence so far brought to light, the potential dangers of bacterial resistance are real enough to justify a very strong warning against its indiscriminate use in ordinary practice, either alone or with other antibacterial drugs. Streptomycin and isoniazid together are already being investigated under controlled conditions, and we hope that isoniazid and P.A.S., which form an attractive combination because of its easy administration, will also be tested in this way. Until the results of these trials are known it seems reasonable to give it together with, rather than instead of, streptomycin and P.A.S. Voluntary restraint in the exploitation of this new and probably valuable drug can prevent any serious dangers from bacterial resistance.

Atropine Alkaloids

Physicians, no less than metaphysicians, must often wonder why the vegetable kingdom contains well-defined chemical substances with specific actions on man and animals—actions which can often be turned to good therapeutic account. Many vegetable drugs still hold their own. We are hard put to it to improve on morphine, ergometrine, digoxin, and emetine, to mention only a few. Pharmacists spend a good deal of time and energy (to say nothing of money) in trying to improve on Nature. Their purpose is to enhance the therapeutic usefulness of a drug and at the same time to diminish its side-effects. Whether they succeed or fail they usually throw new light on the action of the drugs they investigate.

The deadly nightshade, *Atropa belladonna*, is a good example. Some of its actions have been known for centuries, but modern developments in the chemistry and pharmacology of its alkaloids date from the isolation of atropine by Mein in 1831. The structure

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12. Szybalski, W., Bryson, V. *Ibid*, p. 768.
13. Knox, R., MacLean, K. S., Robson, J. M. *Brit. med. J.* 1952, i, 1081.

of the atropine group of alkaloids offers almost unlimited scope to the chemist. They are esters formed by the union of an aromatic acid (tropic acid) with organic bases (tropine or scopine). The substitution of other acids and bases has yielded a crop of synthetic compounds, many of which have come to the notice of doctors in recent years. Yet, although many of these new drugs have established their claim to official recognition, the indications for their administration in preference to atropine or hyoscine are rather limited. Moreover, existing atropine substitutes are likely to be constantly challenged by new arrivals. Homatropine (tropic acid plus mandelic acid) has, however, almost certainly come to stay—at any rate among ophthalmologists—and in the United States eucatropine, the mandelic acid ester of a polymethyl piperidine derivative, is put to similar uses. Other synthetic compounds have been designed to give maximum relaxation of smooth muscle with minimum effects on the eye, the salivary glands, and cerebral function. One of this group is amprotropine phosphate (' Syntropan ') (the tropic acid ester of 3-diethylamino-2, 2-dimethyl-1-propanol), which is intended to relieve painful spasm in the hollow viscera—the intestine, bile-duct, bladder, and ureters. The structure of ' Trasentin ' is a new departure, for it contains neither tropic acid nor tropine, but retains simply the form of an ester and the tertiary amino base. Here again the aim is to produce an antispasmodic drug acting on involuntary muscle and having no perceptible effects elsewhere. In fashioning these new compounds to produce particular effects, chemists start from the fact that the activity of atropine on the autonomic nervous system is centred in the tropic acid radical, and that the tropine base is practically inert. The essential reaction that they use is the esterification of tropic acid with a tertiary amino alcohol.

The atropine group of drugs are thought to act on the effector cells in the distribution of the cholinergic fibres of the autonomic system by blocking the acetylcholine effect; but it is by no means certain that the same mechanism accounts for their action on the brain. The contrast between the effects of atropine and hyoscine on cerebral function suggests that their pharmacological actions can hardly be identical. Meyers and Abreu [1] have compared the central and peripheral effects of atropine, hyoscine, and some of the synthetic atropine-like compounds. They emphasise the importance of working on the living animal. In studies of the effects of the atropine group of compounds on the colon of the unanæsthetised monkey, they found that none of the synthetic drugs, except homatropine, compared with atropine in their ability to produce complete and sustained inhibition of motility of the large bowel. No-one would give these drugs by injection for their ocular effects, but it is of considerable academic importance that synthetic compounds which powerfully inhibit the alimentary canal were found to have a negligible effect on the pupillary reflexes. The action of these compounds on cerebration appeared to be biphasic, varying with the dose: small doses were apt to produce only lethargy; larger amounts were followed by hyperpnœa, excitement, motor weakness, and then drowsiness. Meyers and Abreu claim that doses can be chosen which produce a persistent excitement, lasting for as long as forty minutes in the case of hyoscine and for a shorter time in the case of the synthetic drugs. They emphasise that " except for differences in potency as shown by the different dose required to produce the same effects no differences between atropine and scopolamine were observed." The subject is complex and is full of pitfalls for those who attempt its simplification. Although atropine and scopolamine are known to act in the same way on the peripheral autonomic nervous system, there are quantitative differences and peculiar contrasts in regard to the susceptibility of various tissues to the effect of the two drugs. On the heart, intestine, and bronchioles atropine has a much stronger and longer action: on the other hand, scopolamine is a more powerful blocking agent for the iris, ciliary body, and certain secreto-motor fibres (sweat, salivary, and bronchial glands). In clinical practice one complicating factor is the biphasic character of the response. This depends on the concentration of the drug in the tissues; and thus very small doses may evoke actions which are the very opposite of those following large doses. This biphasic response has been carefully studied by Dr. W. F. Anderson,[2] whose work is particularly important for its emphasis on the fact that tissue cells exposed to attack by powerful drugs may react differently according to whether they are, so to speak, suddenly overwhelmed by a high concentration of molecules or, on the other hand, given time to adapt to solitary invaders. As regards the atropine group, the biphasic response was observed by Meyers and Abreu as an evanescent bradycardia, which they attributed to preliminary medullary stimulation; but usually this feature is likely to be obscured by the rapid onset of the drug's predominant action.

The newcomers among the atropine substitutes include ' Banthine,' which chemically resembles ' Panparnit ' and ' Trasentin.' Here the objective seems to have been to evolve a more satisfactory drug for the treatment of diseases of the alimentary tract accompanied by spasm. Chapman et al.[3] have carried out kymographic studies in healthy adults who had received 100 mg. of banthine. The effect was compared with that of tincture of belladonna; but it is noteworthy that the doses here were conservative—0·4 and 0·6 ml., equivalent to 0·12 mg. and 0·18 mg. of alkaloid. Banthine, it was found, caused a striking decrease in propulsive and total contractions and a slight to moderate decrease in tone. Banthine acted more rapidly and inhibited motility to a greater degree than did tincture of belladonna in either dosage. Chapman et al. observed more dryness of the mouth after banthine than after tincture of belladonna, and also tachycardia—which did not occur in the tests with belladonna. This contrast in side-effects again raises doubt as to the adequacy of the doses of belladonna. Banthine was used by Levy and Zweifler [4] in 100 cases of infantile colic and vomiting. The result was classed as good in 68%, as moderately good in 12%, and as poor in 20%. It would be interesting to know what results might have been obtained from doses of belladonna large enough to produce minor side-effects.

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[1] Meyers, F. H., Abreu, B. E. *J. Pharmacol.* 1952, 104, 387.

[2] Anderson, W. F. *Lancet*, Aug. 9, 1952, p. 255.

[3] Chapman, W. P., French, A. B., Hoffman, P. S., Jones, C. M. *New Engl. J. med.* 1952, 246, 435.

[4] Levy, H., Zweifler, B. M. *J. Pediat.* 1952, 40, 570.

Annotations

DIURNAL EXCRETORY RHYTHM

Soon after birth a daily cycle of behaviour is established in relation to sleeping, waking, and feeding with subsidiary patterns of diurnal rhythm affecting other physiological functions. These include body-temperature, white blood-cell population in peripheral blood, carbohydrate metabolism, renal excretion of adrenocortical steroids, and renal excretion of water and electrolytes.

The excretory cycle of water and electrolytes has been known and investigated since 1877.[1] During the night there is a diminution in the renal excretion of water, sodium, potassium, chloride, and bicarbonate with a fall in urinary pH and a rise in urinary ammonia and titrable acidity.[2] In the morning there is an "alkaline tide" in the urine; this is unrelated to the gastric secretion of hydrochloric acid since it occurs despite achlorhydria or fasting. In addition there is a rising output of water and electrolytes, which reaches a peak about midday with a subsequent fall and a minimum output during the night. This complex cycle depends on fluctuations in renal tubular transfers of ions, since in the normal person there is little or no change in renal hæmodynamics (renal blood-flow and glomerular filtration-rate) or plasma-ion levels throughout the twenty-four hours.[3] While one might be tempted to ascribe the diurnal rhythm to a cycle of adrenocortical activity, as evidenced by diurnal variation of eosinophils in peripheral blood and of urinary excretion of adrenocortical hormones, the evidence is against this possibility.[4] The diminished pulmonary ventilation associated with sleep, and the resulting acidæmia, may be the factor determining the cycle of renal tubular function.[2] It is well known that, in acute experiments, hyperventilation and the resulting alkalæmia produce pronounced changes in renal ion clearances, though these are not quite comparable to the altered ion clearances brought about by waking.

Attention has lately been focused on the reversal of the diurnal rhythm of water and electrolyte excretion in congestive heart-failure accompanied by œdema and cirrhosis of the liver with ascites.[5] In such patients, however, it is noteworthy that there is an associated diurnal rhythm in renal hæmodynamics with maximum renal blood-flow and glomerular filtration-rate at night.[6] This may possibly be related to changes of posture or activity during the twenty-four hours. Such a renal hæmodynamics cycle, rather than an altered cycle in hormonal control of renal tubular ion transfers, may account for the reversal of diurnal rhythm of water and electrolyte excretion.

Our knowledge concerning the mechanism of the normal diurnal rhythm and its reversal in disease states is still incomplete. Will further research provide clues to that all-important problem—the unknown mechanism that controls the volume of extracellular fluid?

ADVANCES OF SCIENCE

Scientists must recall with sympathy the plight of that wrecked sailor who had so many things that he wanted to do that whenever he thought he would like to begin he couldn't, because of the state he was in. Luckily for us, or possibly unluckily, they have not stumbled on his masterly solution—which was to do nothing but basking until he was saved. Members of the British Association for the Advancement of Science, now meeting in Belfast, have so much to tell each other, and on such very different topics, that opportunities for basking must be strictly limited, despite the indulgent and excursive hospitality of their hosts, and the fact that the Mountains of Mourne are performing their well-known feat only a short drive away.

But, indeed, it is doubtful whether scientists are in the mood for basking. A hundred years ago their forerunners could carry their calling lightly, looking confidently forward to a benefited world. Today, as Prof. A. V. Hill, F.R.S., the president of the association, said of their ethical dilemma, "science finds itself unexpectedly and without those centuries of tradition and experience in a position no less important to the community than medicine: and its ethical principles have not yet clearly emerged." There seems, he concluded, to be no simple answer. Scientists are naturally as anxious about this as the rest of us; but they have accepted the duty of using their minds as well as they can to discover the nature of the universe, and like the rest of us they take refuge in their work.

Certainly they have plenty to occupy them. Their programme at Belfast contains no specifically medical section, but various sections touch on medicine—notably those on chemistry, zoology, physiology, psychology, and agriculture. Subjects of interest to doctors include such things as the control of the movements of the alimentary canal, the chemistry of bread-making, the assessment of personality, and Britain's food-supplies. In speaking of the problems of parthenogenesis, Prof. A. D. Peacock, D.SC., was not perhaps discussing a subject of immediate concern to us, but he raised some interesting speculations. In the last year, he recalled, G. Pincus and his associates have been responsible for the development of seven rabbit parthenogones; all were female, five were born alive, and one has since produced a litter of nine after normal mating. Pincus sees a possible application of the principle in stockbreeding: if cows could be made to breed females by parthenogenesis it would be extremely convenient.

VALVULOTOMY VERSUS SHUNT

Cyanotic congenital heart-disease is nowadays treated surgically in centres all over the world as a result of the pioneer work of Blalock and Taussig[1] in Baltimore. Because these unfortunate patients can now be relieved, partly or completely, of their disabilities, interest has quickened greatly. The rapid advances in such techniques as cardiac catheterisation and cardioangiography have made it possible to reach an accurate preoperative diagnosis in almost every case; but there remains the question of which operation will afford the best result.

The shunt operation of Blalock is ideally suited to cases of severe pulmonary atresia or of tricuspid atresia. Pure stenosis of the pulmonary valves, however, clearly invites a more direct approach to widen the stenosed opening; and this Brock[2 3] has most successfully practised. The problem now before the cardiologist and cardiac surgeon (for it is imperative that they work together) is which patient will derive most benefit from a subclavian-pulmonary anastomosis, and which from a direct valvulotomy or infundibular resection[4] of the stenosed area. Pure pulmonary valvular stenosis (i.e., not associated with an interventricular septal defect) is best treated by Brock's direct attack on the stenosed opening with a valvulotome.[5 6] A Blalock shunt is contra-indicated since sooner or later right-sided heart-failure develops because the strain on the obstructed right ventricle is unrelieved. On the other hand, with atresia of the tricuspid valve so little blood enters the right ventricle that this is largely functionless, and pulmonary valvulotomy will be useless. In such patients

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1. Quincke, H. *Arch. exp. Path. Pharm.* 1877, 7, 115.
2. Stanbury, S. W., Thomson, A. E. *Clin. Sci.* 1951, **10**, 267.
3. Sirota, J. H., Baldwin, D. S., Villarreal, H. *J. clin. Invest.* 1950, **29**, 187.
4. Rosenbaum, J. D., Ferguson, B. C., Davis, R. K., Rossmeisl, E. C. *Ibid*, 1952, **31**, 507.
5. Jones, R. A., McDonald, G. O., Last, J. H. *Ibid*, p. 326.
6. Baldwin, D. S., Sirota, J. H., Villarreal, H. *Proc. Soc. exp. Biol., N.Y.* 1950, **74**, 578.

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1. Blalock, A., Taussig, H. B. *J. Amer. med. Ass.* 1945, **128**, 189.
2. Brock, R. C. *Brit. med. J.* 1948, i, 1121.
3. Brock, R. C., Campbell, M. *Brit. Heart J.* 1950, **12**, 377.
4. Brock, R. C., Campbell, M. *Ibid*, p. 403.
5. Blalock, A., Kieffer, R. F. *Ann. Surg.* 1950, **132**, 496.
6. Potts, W. J., Gibson, S., Riker, W. L., Lemiger, C. R. *J. Amer. med. Ass.* 1950, **144**, 8.

venous and arterial blood are mixed in the left ventricle and only an anastomosis between the systemic and pulmonary circulations—i.e., a Blalock or Potts operation—will allow the blood to enter the lungs and so relieve the cyanosis. Possibly there is one other group in whom a shunt type of operation must be carried out—those with such extensive pulmonary atresia that direct attack is impracticable.

Between these two groups of cases, in which the indications for either a shunt operation or valvulotomy are fairly precise, there lies a large number in which the decision may be difficult. Where a surgeon is more experienced in arterial anastomosis, he will naturally find himself treating most of his patients in this way. Others will favour the direct relief afforded by valvulotomy, and as they gain greater experience in its execution will find more cases to which it can be successfully applied. A recent report by Brock[7] is particularly illuminating. Of his first 223 cases of pulmonary stenosis, 112 were treated by anastomosis and 111 by direct operation; but in the first 50 there were 2 direct operations and 48 anastomoses, whereas in the last 50 there were 36 direct operations and only 14 anastomoses. Of these 14, 5 were cases in which a direct operation could not be done for reasons stated above.

The direct relief of pulmonary stenosis seems, therefore, to be technically possible in about two-thirds of the cases. It is certainly an attractive solution, since it largely restores to normal the mechanics of the heart, adds no new strain, and does not call for an artificial ductus with its potential risk of infection. Nevertheless only continued close study of patients treated by these alternative techniques will establish their relative values.

GETTING INTO STEP

THOSE of us who find irksome even the mild regimentation of contemporary civilian life will readily sympathise with the soldier who is "out of step." Usually he is a young man who finds that soldiering does not agree with him and that the consequences of kicking over the traces of discipline can be more unpleasant in the Army than in civil life. He may have wanted to be a driver, not an infantryman; if he could not be a driver he wanted to transfer to the Navy or the Mercantile Marine. He, and his like, find it hard to conform. They have not learned to swallow small injustices, and they almost inevitably run foul of the authority of the orderly room; and their "crimes" may range from personal neglect ("dirty rifle") to absence without leave. Sometimes their offences, though still not of a kind to get them into real trouble in civil life, are more serious and may vary from making Donald Duck noises on parade to throwing a bucket of whitewash over the regimental sergeant-major.

In 1941 the Army established at Pontefract a camp at which the training was to be "specially framed with a view to reclaiming young soldiers from a career of crime and converting them into good soldiers." Mr. Joseph Trenaman, who shared in the educational side of the venture, has described[8] the men who came to the camp, and how they fared there. Physically the men were weaker, feebler, and more ill-nourished than the ordinary run of young soldiers. They were a little below the average level in innate intelligence, but not obviously subnormal; emotionally they were immature. For the most part they came from poor and overcrowded homes. Only some 14% had been apprenticed to a skilled trade in civil life, and many had been in police trouble there; 36% had been convicted of indictable offences before joining the Army. But Trenaman believes that parental neglect was the "probable major factor" responsible for delinquency, with psychopathic states a poor second. Among the minor factors he lists, in order, physical deficiency, poverty at home, broken home, and invalid parents. Sir Cyril Burt, who contributes a stimulating preface to the book, does not like the term "psychopathic." It was a label bestowed by the psychiatrists who saw the men; but, as Burt says, different psychiatrists interpret the term in different ways.

Not all the men were enamoured of the new venture. It would have been overoptimistic to have expected otherwise. Some made it plain that they took a poor view of this latest outcropping of reforming zeal. The Glasgow youngster was probably not alone when he wrote across one of the early questionary forms, "none of your bissness." But the important thing is that the method seemed to bring results. The records of these lads were much better after treatment in the unit than they had been before.

ISOTOPES IN BRITAIN

DURING the late war British scientists heard with admiration—and not a little envy—of the remarkable developments in America as radioactive isotopes became available for biological research. These developments flowed directly from the brilliant work by American physicists in setting up cyclotrons and the first chain-reacting pile. After the war came a period when the United States with great generosity provided British workers with supplies of isotopes and information about the technique of their use in biological research. But these supplies were necessarily limited and could not in any case include the shorter-lived isotopes. It was therefore a great relief when the pile at Harwell came into action and home supplies were to be had. Now a wide range of isotopes can be obtained by British workers, and in addition Harwell carries on a thriving export trade.

With several years' experience now behind them, British workers can give a good account of themselves, as is shown by an issue of the *British Medical Bulletin* devoted to this subject.[1] A comprehensive review of this sort provides an opportunity for assessing the value of this fascinating and still novel application of physics to biology and medicine. The tale of what has so far been achieved has to be set against a background of the many technical problems that had to be overcome before any results at all were possible. Although nearly all isotopes are now prepared by neutron bombardment of suitable material in the pile, the actual production and isolation of each one involves an individual problem if material of the desired specific activity is to result. Isotopes are only useful to the biologist if they are present in the chemical form which he requires. For this reason the radiochemical centre at Amersham was set up. Here the necessary chemical manipulations can be carried out on highly radioactive substances: the compounds which the centre can supply include some forty labelled with C^{14}. In the subsequent handling of radioactive materials stringent precautions are needed, according to the type of radiation and the half-life of the isotope concerned.

In the measurement of radioactivity in tissues or whole organs there are many pitfalls for the unwary. The research-worker has to adjust himself to the new habits of thought required for the interpretation of experiments involving isotopes. He first has to become used to the idea that all his measurements are subject to an inevitable (but always calculable) error due to the random nature of atomic disintegrations, over and above any errors which may result from his manipulations. Then he must realise that his measurements only enable him to follow the fate of a small parcel of labelled atoms, introduced into his biological preparation at a particular time; rapid passage of a batch of labelled atoms through a given organ does not necessarily mean that large quantities of the corresponding unlabelled substance are passing through that organ all the time. A small sample of raw material may pass rapidly through a factory and be converted into the finished product; but if raw material is scarce the factory's total output may be low. Again, compounds neatly labelled by the introduction of a radioactive atom may be introduced into the body; but it cannot be assumed that the label will remain permanently in place. Finally a careful watch must be kept on the radiation received by the tissue under study, lest radiation damage should vitiate the result.

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[7] Brock, R. C. *Ann. Surg.* 1952, 136, 63.

[8] Out of Step. JOSEPH TRENAMAN. London: Methuen. 1952. Pp. 223. 21s.

[1] *Brit. med. Bull.* 1952, 8, no. 2–3.

The technical and intellectual difficulties involved in work with isotopes are formidable: the compensating advantages are equally great. Where conventional chemical methods are too inaccurate or too laborious, or insufficiently delicate, isotopes often make possible an estimation that could not otherwise be effected. Studies on the metabolism of penicillin and vitamin B_{12} (described by E. Lester Smith) and on antigen-antibody reactions (A. Wormall) are good examples. Isotopes are particularly useful (as A. Neuberger shows for various proteins) in determining the average length of stay of the various component parts of large molecules incorporated in animal tissues. Then again, isotopes can be used efficiently in combination with another modern technique—paper chromatography. Gross and Pitt-Rivers demonstrate this elegant method in identifying a new iodine-containing compound in the blood of patients treated with radio-iodine.[2]

Thus isotopes make possible a new and more refined biochemistry, which is already reaping its harvest in many other fields. They can be used, for example, in clinical investigation, as C. H. Gray shows in his review on porphyria. But isotopes do not merely replace or extend chemical tests. They can be used, for instance, to label red blood-cells as well as molecules, and thus facilitate the estimation of blood-volume (E. B. Reeve). They can be used in conjunction with histology to show the location of elements within tissues (S. R. Pelc and A. Howard). Perhaps the most striking departure from traditional methods is in the detection and measurement of γ-emitting isotopes by external counters. Measurement of thyroid function in this way (described by N. B. Myant) may become a routine clinical test for thyrotoxicosis. The rate of disappearance of radiosodium, or its appearance elsewhere, after injection into the tissues or blood-stream, can give valuable information about rates of movement of ions into and within the blood (H. Payling Wright, E. M. McGirr) and even about the viability of the plastic surgeon's skin grafts (J. N. Barron and N. Veall).

Therapeutically, isotopes have great possibilities in the destruction of unwanted tissue. If that tissue is presented with a radioactive substance which it specifically concentrates, it can be bombarded from within, without risk to other tissues. Unfortunately this condition is still fulfilled in only a few instances. The thyroid gland is the clearest example. As E. J. Wayne and others show, thyrotoxicosis can be successfully treated with radio-iodine. The same is true of those thyroid cancers which concentrate iodine, though the differential concentration is nothing like as great as in thyrotoxicosis, and therapeutic bombardment is consequently more difficult to achieve (R. Paterson and others). The presentation to cancerous tissue in general of an effective isotope in a chemical form which would be concentrated specifically is very much in the minds of those working on the subject, but its achievement is not yet in sight. For the present we must be content with bringing the radioactive material into as close contact as possible with the tissue which needs to be destroyed. This has been done with some success in the case of bladder tumours by introducing balloons containing solutions of radioactive sodium or bromine (R. J. Walton and W. K. Sinclair). Some relief can be achieved in malignant pleural and peritoneal effusions by partial replacement of the fluid with suspensions of colloidal radio-gold.

In summary, the isotope technique has already made major contributions to fundamental biology. It is proving useful in clinical investigation and has had sufficient therapeutic success to justify hopes of better things to come. Owing to the technical complexities and health hazards, the handling of isotopes is best left to research-workers for the time being. But it is well that the rest of the profession should know what is going on in this field, for the potentialities of the method are so great that its applications might, in the future, be the concern of us all.

STREPTOCOCCI AND RHEUMATISM

THE generally accepted view that recent streptococcal infection is the underlying bacterial cause of acute rheumatism leaves unexplained many of the baffling problems in this group of diseases. Clinically acute rheumatic fever resembles serum sickness quite closely, and many workers have suggested that the clinical features of rheumatic fever are due to an antigen-antibody reaction at special situations in the body.[1] This hypothesis has been too vague to carry us very far. Many different kinds of antigen have been tested, ranging from streptococcal "toxins" to hypothetical antigens from the patient's own tissues; and lesions resembling those of rheumatism have been produced by various experimental procedures. But there is still no really convincing explanation of the specificity of the lesions or the relative parts played by the streptococcus and the patient's own tissues in determining this specificity.

Dr. Glynn and Dr. Holborow have investigated these problems in some new experiments, which they describe in this issue. It is now recognised that the specificity of a protein can be profoundly modified by chemical combination with non-protein substances known as haptens. By suitable combination of a bacterial protein with, for example, a polysaccharide, a new antigen can be created which has the specificity, not of the original protein, but of the polysaccharide which has been attached to the protein. Glynn and Holborow, using β-hæmolytic streptococci (group A, type 4) as source of bacterial "protein" and a solution of chondroitin sulphate from human costal cartilage as polysaccharide, prepared a chondroitin sulphate streptococcus vaccine. Rabbits received intravenous injections of this vaccine, a control vaccine of the same streptococcus not treated with chondroitin sulphate, and a solution of the chondroitin sulphate alone. Five out of six rabbits which received the chondroitin sulphate streptococcus vaccine showed evidence of joint lesions—some with acute synovitis—and the serum of all these animals gave a positive precipitin reaction with chondroitin sulphate solution. Control rabbits that received either the streptococcal vaccine or the chondroitin sulphate alone showed no comparable joint lesions, and neither these nor normal rabbits showed any precipitin reaction with chondroitin sulphate.

The combination postulated by Glynn and Holborow may possibly occur in a slightly different way: instead of the streptococcus providing the protein and the patient's tissues the hapten, the rôles may conceivably be reversed and the streptococcus provide a hapten which converts tissue proteins into "auto-antigens" with a new specificity. There is some experimental support for this concept. For example, Goebel and Avery[2] showed that a pneumococcal polysaccharide which acts only as a hapten when injected into rabbits can be made fully antigenic by conjugating it artificially with a suitable protein, whereas a pneumococcal polysaccharide which is non-antigenic when injected into rabbits is fully antigenic by itself in mice and men.

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[2] See Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766; *Ibid*, 1952, i, 439, 593. Gross, J., Pitt-Rivers, R., Trotter, W. R. *Ibid*, p. 1044.

[1] See Fischel, E. E. *Amer. J. Med.* 1949, 7, 772.

[2] Goebel, W. F., Avery, O. T. *J. exp. Med.* 1931, 54, 431. Avery, O. T., Goebel, W. F. *Ibid*, p. 437; *Ibid*, 1938, 58, 731.

The discovery of the dramatic effects of adrenocorticotropic hormone has given a new impetus to the study of the rheumatic diseases; and the possible interrelation of hormonal factors, of the allergic state, and of an extrinsic bacterial agent poses some intriguing questions. The experiments described by Glynn and Holborow are interesting and suggestive; and we hope that these will be followed by further work on similar lines.

SEX-HORMONE METABOLISM IN LIVER DISEASE

CERTAIN clinical manifestations of liver disease have been thought to result from altered intrahepatic metabolism of steroid hormones with consequent disturbance of the normal balance between œstrogens and androgens.[1] In the male the most important clinical features of this sort are gynæcomastia, testicular atrophy, and loss of libido. Cutaneous spider nævi, palmar erythema, and loss of hair on the chest have also been attributed to a similar mechanism. Experimental data leave little doubt that the liver plays an important part in inactivating œstrogen; and observations in the rat have shown convincingly that this function may be impaired by malnutrition.[1] On the other hand, it now seems doubtful whether these results apply to other species. Zondek and Brzezinski,[2] for example, found that inactivation of œstrone was unimpaired in women with severe vitamin-B deficiency, while Hooker et al.[3] found that in primates the result of intrasplenic implantation[4] was the same as with administration by any other route. Direct evidence of hepatic inactivation in man has, however, now been described by Evans et al.[5] 9 patients receiving œstrogen therapy for carcinoma of breast or prostate were chosen because of their high blood-œstrogen levels. These levels were determined in samples taken simultaneously from the hepatic vein and the femoral artery. In 6 cases evidence of significant inactivation by the liver was detected. In the 3 cases where inactivation was insignificant the patients were severely undernourished.

Several attempts have been made to establish by assay of the hormones in the urine that such conditions as gynæcomastia arising in chronic liver disease result from impaired hormone metabolism. Rupp and his colleagues[6] found an increase of urinary œstrogen in 16 out of 25 cases of hepatic disease with gynæcomastia, but the over-all correlation was poor. Dohan et al.[7] also found no apparent correlation between the severity of the hepatic disease and gynæcomastia, or between gynæcomastia and the absolute values of urinary œstrogens. A further study of this problem by Dohan and his colleagues[8] provides, however, a possible explanation of such inconclusive results. 17 men with diffuse liver disease and 5 normal controls were included in this study. The severity of the disease was assessed by clinical examination, liver-function tests, and biopsy specimens. Hormone excretion was estimated on specimens of urine collected over several days, to minimise errors due to daily fluctuation; the estimations included the free and conjugated forms of œstradiol, œstrone and œstriol, and gonadotropin, all by biological assay, while total neutral 17-ketosteroids were estimated by a colorimetric method. Increased excretion of total œstrogen and decreased output of ketosteroids and gonadotropin was found to run approximately parallel with the severity of the disease. Urinary œstrogen was significantly correlated only with the serum-bilirubin and bromsulphalein retention—i.e., with tests of excretory function. Presumably the decreased ability of the diseased liver to excrete œstrogens accounts for the increased output by the kidney. The liver's ability to conjugate the steroids with glycuronic acid is apparently unaffected, since the increase of the combined form of the hormones in the urine is usually far greater than that of the free forms. The total œstrogen excretion, and still more the œstrogen-ketosteroid ratio in the urine, were significantly greater in the four cases with stable gynæcomastia than in those with regressing breast changes or no such changes at all. Dohan and his colleagues emphasise the importance of differentiating cases with persistent gynæcomastia from those in which the breast changes are reverting to normal, and suggest that failure to mark this distinction is the cause of previous failure to establish the relationship between the breast enlargement and the level of circulatory hormone as assessed by urinary excretion. The only test that could be correlated with spider nævi was that of free œstriol excretion; but a highly significant relationship was found between testicular atrophy with loss of libido and decreased excretion of gonadotropin.

These results confirm what has long been suspected, both on clinical grounds and from experimental work—that hormonal imbalance may result from impaired metabolism of hormones by the diseased liver. Excess of œstrogens is the most conspicuous result; but androgens may also be affected—a disturbance indicated by impotence associated with a fall in ketosteroid excretion due, at least partly, to diminished secretion of gonadotropin by the pituitary.

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1. Leading article, *Lancet*, 1952, i, 350.
2. Zondek, B., Brzezinski, A. *J. Obstet. Gynec.* 1948, 55, 273.
3. Hooker, C. W., Drill, V. A., Pfeiffer, C. A. *Proc. Soc. exp. Biol., N.Y.* 1947, 65, 192.
4. Biskind, M. S. *Vitam. & Horm.* 1946, 4, 147.
5. Evans, J. M., Young, J. P., Hertz, R., Tullner, W. W., Wilmer, G., Wood, O. *J. clin. Endocrinol.* 1952, 12, 495.
6. Rupp, J., Cantarow, A., Rakoff, A. E., Paschkis, K. E. *Ibid*, 1951, 11, 688.
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DEATH AFTER INOCULATION

MAINLY as the result of mass immunisation, begun in 1940, the extinction of diphtheria is in sight; and whooping-cough is now the most formidable acute specific respiratory disease of infants and very young children. A similar campaign against this disease, although long delayed by the need for large-scale controlled trials of vaccines made from numerous strains of *Hæmophilus pertussis* by different techniques,[1] is now in progress, and many thousands of children have already been inoculated without untoward effect other than an occasional transient local or general reaction caused by sensitivity to proteins of the dead organisms from which the vaccine is prepared. It is therefore disconcerting to learn of an inquest on a 2-year-old child who developed an abscess in the right upper arm after a second prophylactic injection of a whooping-cough vaccine and who later died of septicæmia—a sequel unique in the experience of the medical witnesses.[2] Since eight other children were inoculated with the same batch of vaccine, apparently without ill effect, the vaccine itself is clearly exonerated. Anyhow the tests for sterility by the manufacturers of this and other biological products for injection are so stringent that contamination of the contents of an ampoule before it is opened is extremely unlikely. At the inquest a pathologist expressed the opinion that death resulted from an accidental skin infection. Nevertheless, this tragedy should cause all who have to give parenteral injections to look to their technique.[3] The potential danger of infection of the needle-puncture from pyococcal skin lesions should also be borne in mind; and if such lesions are detected, prophylactic injections should be postponed.

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2. *Evening Standard*, Aug. 27.
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Public Health

THE NEED FOR AN OCCUPATIONAL HYGIENE SERVICE

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OCCUPATIONAL hygiene is the measurement of the industrial environment and its effects on workers' health. Though the advantages of this approach to industrial health problems have been appreciated in this country for many years, almost nothing has been done to apply it on a large scale. In the development of our industrial health services the emphasis has been on factory inspection—largely from a safety point of view—on the one hand, and health care by industrial medical officers on the other. In these aspects of occupational health, and also in factory legislation and notification of occupational disease, we have been pioneers and still have probably the finest services in existence. Unfortunately this is not true of our occupational hygiene facilities. Indeed no service of this kind exists and our country lags behind others.

AMERICAN PRACTICE

In the United States industrial health services developed rather differently. The great increase of production during the first world war resulted, as here, in outbreaks of industrial disease. To combat these, individual States set up divisions of industrial (or occupational) hygiene, usually as a branch of the State public-health department. These developed greatly between the two wars and now most States, and even some cities, have such divisions. They are based on a laboratory where physicians, engineers, chemists, and industrial nurses work together on occupational health problems. Each specialist lends his particular skill to the task. For example, a visiting factory inspector or nurse may be the first to discover a possible toxic hazard. The physician may then visit the factory and, by studying the environment, talking with management and workers, and making clinical and laboratory examinations of those likely to be affected, decide whether a health hazard exists. Chemists and engineers then survey the factory, taking air-samples in different parts, and measure the amount of toxic substance present in the air. If a health hazard is discovered the correct preventive action can be determined in the light of the known facts. In this the engineer, with his special knowledge of exhaust ventilation and other protective devices, plays a large part.

These laboratories carry a full range of equipment for assessing most physical hazards in industry. Thus they are able to analyse air and body-fluids for toxic substances, to perform dust-counts and analyses, measure radiation, and conduct lighting and thermal comfort surveys. An important point is that they are not organised for research, though research is of course done. Their main work is to help and advise industry in health. Much of the work is routine—for instance, repeated examinations in lead-works of air-samples, and urine and blood specimens. In this country there are no facilities for regular surveys of this kind, apart from blood-counts, except where the firms provide them. The occupational hygiene division also acts as an advisory centre on all matters of occupational health. Help is given to firms which wish to start their own medical services, and there is often an industrial nursing consultant who acts as focal point and adviser to all industrial nurses in the area.

Many other countries have developed such services —e.g., Canada, Finland, Peru, the Philippines, Sweden, the U.S.S.R., and Yugoslavia.

A FIRST STEP

I believe that there is a real need for a service of this kind. Anyone with access to a large number of factories, as we have at Slough, must come to realise that there is a great deal of occupational ill health which is never recognised, let alone notified. Through ignorance dangerous solvents and other toxic substances are used carelessly, and may cause disease which long remains undiagnosed. Men are also often exposed to high concentrations of the less dangerous solvents, and minor health impairments or worry over the effect of the fumes may lead to loss of production. Fettlers and grinders may work in confined spaces with high dust-concentration, their only protection a calico mask which they are expected to wear continuously. Often lighting, heating, or ventilation is poor, and recurrent though preventable eye injuries are found.

These situations arise because managements of small firms are not in a position to obtain advice on health matters. When advice is given in convincing form, they are usually anxious to coöperate and improve working conditions. A detailed survey of conditions, from medical and engineering aspects, figures for air-concentrations, and suggestions for action are far more effective in producing a positive response from management than mere verbal arguments.

The Factory Department of the Ministry of Labour and National Service has 16 medical inspectors of factories who are responsible for the whole of England, Scotland, and Wales. These inspectors have a wider knowledge of occupational hygiene than anyone else in the country, yet they have no technical assistants and no suitable laboratory behind them. Samples for analysis are sent to the Government Laboratory and, because only occasional samples can be analysed, few, if any, complete and repeated occupational hygiene surveys can be made. The situation would be very different could there be many more medical inspectors and regional laboratories, with engineers and chemists, to help them. The Medical Research Council's Unit for Research in Industrial Medicine has a fine laboratory and is able to undertake any kind of factory survey, clinical or environmental. It, however, exists primarily for research—and rightly so—and cannot carry out routine work or cope with the many small problems that exist up and down the country. Really serious hazards—such as instances of beryllium poisoning or the recent outbreaks of poisoning by dinitro-*ortho*-cresol—are dealt with immediately and effectively, yet the multitude of smaller problems cause greater loss of health and production.

Realising the need for this preventive approach to occupational health, the Nuffield Foundation and those working at Slough were responsible, in 1949, for sending an engineer, Mr. R. J. Sherwood, to Harvard to be trained in occupational hygiene techniques. After his return a small team was formed, consisting of myself as physician, Mr. Sherwood as engineer, and Miss Joan Bedford as chemist, to investigate occupational health problems at Slough and elsewhere. The foundation made a grant towards an occupational hygiene laboratory which has been set up at the London School of Hygiene and Tropical Medicine. Samples collected in the field are brought to this laboratory for analysis, counting, and so on. The laboratory is part of the occupational health sub-unit which also plays a part in teaching students of the D.P.H. (industrial elective) course and public-health engineers.

The number of requests for help which we have received has been greater than so small a unit can cope with. As well as the regular work at Slough on the discovery and control of toxic hazards, skin irritants, and uncomfortable working conditions, there have been requests for advice from managements who were about to instal new processes or who wished to check safeguards which they had installed. We have also had many calls for advice from industrial medical officers or direct from managements of firms in all parts of the country. Our experience has convinced us of the need for a service which can give technical help to industrial medical officers and, even more, to firms with no medical care. An occupational hygiene service to cover the entire country would need perhaps six or eight units, staffed with doctors, engineers, chemists, and physicists. If any industrial health service was later set up these centres could form an integral part of it.

A NATIONAL SERVICE

A precedent for these centres already exists in the Public Health Laboratory Service, which is administered by the Medical Research Council. There are 18 special or reference laboratories and a further 49 constituent laboratories in different parts of the country. Nothing like this number of occupational hygiene centres would be needed, but their administration by the Medical Research Council for the Ministry of Health following the pattern of the P.H.L.S. is a possibility.

There is also a strong case for the centres to become part of the Factory Department of the Ministry of Labour and National Service. This department has the necessary experience and a corps of medical inspectors who could act as leaders of the project. Further, the work of the service would be largely inspection, using every available scientific means, rather than research.

Another possibility is that industry itself should be encouraged to set up these centres. The National Coal Board, for instance, is already doing, and planning to do, preventive work based on research carried out by the Pneumoconiosis Research Unit of the Medical Research Council. The Industrial Hygiene Research Laboratory of Imperial Chemical Industries is an example of what a single large firm can do. Other large firms might do the same, but in many the hazards are not numerous enough to warrant such provision. Some industrial organisations, such as the Shirley Institute (cotton), the British Cast Iron Reserach Association, and the British Iron and Steel Research Association, already carry out some occupational hygiene investigations, though they are not primarily interested in health. Some of them are associated with the Department of Scientific and Industrial Research, which suggests the possibility of a combined private enterprise and Governmental approach.

Finally, some universities might consider it of value, from the point of view of teaching, to join in work of this kind, perhaps in coöperation with another agency such as the Factory Department. But whatever the form of organisation chosen, it is important that something should be started now. The health of our workers and the output of our factories should no longer be allowed to suffer for want of reasonable facilities in occupational hygiene.

I should like to place on record the names of those who foresaw the need for occupational hygiene at Slough and elsewhere in this country, and were responsible for sending the first engineer to train under Prof. Philip Drinker at the Harvard School of Public Health. They are Dr. A. Austin Eagger, Prof. J. M. Mackintosh, and Dr. M. E. M. Herford.

Poliomyelitis

In the week ended Aug. 23 notifications (uncorrected) of poliomyelitis in England and Wales were as follows (figures for the previous week in parentheses): paralytic 152 (170); non-paralytic 68 (88); total 220 (258). This brings the total for the 34 weeks since the start of the year to 2388, compared with the following totals for the same period in each of the five previous years: 1951, 1747; 1950, 4125; 1949, 2033; 1948, 1067; 1947, 3619.

According to the Weekly Epidemiological Record, issued by the World Health Organisation, there has been a definite recrudescence of the disease in Europe, and notably in parts of Western Germany, the Netherlands, and Belgium. In the U.S.A.[1] 2648 cases were reported during the week ended Aug. 9; this was an increase of 15% over the figure for the previous week. Up to Aug. 9 the cumulative total for the "disease year," which began with the week ended April 5, was 12,046; the corresponding figure last year was 7056. The incidence has also been increasing in Canada, particularly in the west, where quarantine restrictions have been imposed at two large military stations, from one of which 17 cases had been reported.[2]

International Certificates of Vaccination

The International Sanitary Regulations adopted by the Fourth World Health Assembly come into force on Oct. 1. New and simpler forms of certificates of vaccination against smallpox and cholera will then be used.

Persons going abroad, who are vaccinated against these diseases *after* that date, should have their certificates on the new forms, obtainable from the company arranging their passage. International certificates for vaccination done *before* that date remain valid for the period shown on them.

The international certificate of vaccination against typhus has been abandoned, because this vaccination is no longer required internationally.

Medicine and the Law

Murder and Abnormality

There is notoriously an unbridged gulf between the forensic and the medical view of insanity in relation to criminal responsibility. Two recent cases in the Court of Criminal Appeal show afresh how far the two are apart.

On the appeal of J. H. Godar,[1] convicted of murdering Maureen Cox, his counsel, Mr. G. D. Roberts, Q.C., conceded that at the trial the summing up had been full and fair and that there had been evidence on which the jury could properly find a verdict of guilty; in other words there were no grounds for an appeal. It appeared that Godar had in 1944, while serving in the Army, been found to be suffering from a disease of the mind amounting to defect of reason. This fact, however, was not mentioned as a matter for the appellate tribunal to consider; it was merely referred to by counsel, in passing, as one which the Home Secretary might perhaps take into account when advising the Crown as to the exercise of the prerogative of mercy.

On the other appeal, that of J. T. Straffen,[2] the apparent irrelevance of the appellant's mentality was even more striking. At his trial there had been evidence of his having been certified a mental defective, of his having formerly been found unfit to plead to a criminal charge, and of his having strangled two other little girls in addition to the 5-year-old Linda Bowyer whom he was accused of having murdered.[3] The Court of Criminal Appeal was not asked to note his obvious abnormality; it was irrelevant; the two grounds of appeal (technical questions of the admissibility of evidence, legally, no doubt, of great importance) ignored it. Even had the case found its way up to the House of Lords, his mental condition would still doubtless have been immaterial. Public opinion, as well as medical science, may be convinced of the irresponsibility of men like Straffen. The criminal law goes on its majestic way unconcerned.

"There are," wrote the late Sir Edward Troup, a former head of the Home Office, "a certain number of borderline cases in which the question whether a prisoner is insane,

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1. Morbidity and Mortality: Weekly report by the Federal Security Agency, Public Health Service. Washington, D.C., Aug. 15, 1952.
2. *Times*, Aug. 29.
3. *Ibid.*, Aug. 20.
4. *Ibid*, Aug. 21.
5. *Lancet*, Aug. 2, 1952, p. 239.

though negatived by the jury or not raised at the trial, has to be considered after conviction." If medical experts then certify the prisoner insane, "there is a consensus of legal authority for the view that it would be contrary to the common law to allow the execution, and the records which go back to 1840 show no exception to this rule." Accordingly on the advice of his panel of doctors the Home Secretary has recommended that Straffen should be reprieved. Thus, in the end, the medical opinion prevails over the judicial sentence after all. Sir Edward went on to give statistics showing that, over the 22 years from 1901 to 1922, out of 585 persons convicted of murder 517 were found to be insane, either before trial or by special verdict of the jury or on Home Office inquiry after conviction. If, as is probable, more recent totals show a not dissimilar proportion, is it not time for another review of insanity in relation to crime such as that which the Atkin Committee conducted thirty years ago? As Sir Russell Brain, P.R.C.P., has pointed out [6] the circumstances in which mental illness should mitigate criminal responsibility "is a question, not for lawyers or doctors, but for society to decide"; and he, too, thinks the question should be reconsidered, perhaps by a Royal Commission.

Points of View

CURE OF TOBACCO-SMOKING

LENNOX JOHNSTON
M.B. Glasg.

"How can I stop smoking?" I, who stopped many years ago, have often been asked. "By not smoking again," is the brutal correct answer; for every movement of smoking is voluntary. "But I have tried repeatedly and failed; I haven't enough will-power. Is there a way in which I can be helped to stop?" "Yes, there is a way," is the answer; and the purpose of this article is to show it.

The view that smoking can be stopped only by the exercise of will-power is almost universally accepted. Yet it is only part of the truth. For "knowledge is power" (or will-power) when acted upon. The greater the volume and more impressive the character of knowledge, the more insistently does it demand effective expression (in action). When knowledge is repressed, or is merely expressed in words unsupported by actions (when, for example, a smoker says, "I *know* that smoking is harmful" but continues to smoke), the power of knowledge is insufficient (usually because of insufficiency of knowledge) to compel its effective expression.

The urge to smoke is at first purely psychological —a desire. While it remains so, it is easy to give up smoking. As smoking proceeds, however, the urge becomes increasingly compulsive: the psychological urge has been reinforced by a pharmacological urge, the craving for tobacco.

PSYCHOLOGICAL URGES TO SMOKE

The desire to smoke originates from the advocacy of smoking by smokers, much of it unconscious. Each time a smoker lights up, he says in effect, "I am in favour of the smoking of tobacco, I approve of smoking"; and little weight attaches to any mere words he may utter in contradiction to his actions. Each proferred cigarette, each word of approval of smoking, written or verbal, is smoking propaganda. Every smoker is, in fact, whether he wills it or not, a living advertisement for tobacco, and there are so many smokers today, and they smoke and speak encouragement to smoke so often, that the persuasive pressure on non-smokers to commence or recommence smoking is powerful indeed. To this must be added the lavish scientific advertising of the tobacco combines. In the United States of America in 1945 it was calculated that almost 3000 non-smokers start to smoke every day.[1]

The initial desire to smoke is closely associated as a rule with one to appear grown-up or sophisticated, to imitate someone admired—usually Daddy or, nowadays, Mummy—or to be companionable or sociable. Later there is a recurring desire to perform the now largely habitual and often ritualistic actions of smoking, particularly at certain times—e.g., after meals—or to relieve boredom or nervousness. Freud drew attention to the possibility that oral-libidinal satisfaction—the association of smoking with the infantile pleasure of suckling—may also urge people to smoke.[2]

Psychological "infection" of the non-smoker is completed, as a rule, by the intimate persuasion of a smoker: "have a cigarette, old man"; "it'll do you good (or steady your nerves)"; "don't be so miserable (or a cissy)"; "one has to have a bit of pleasure (or comfort) these days"; or "one has to have one little vice; it doesn't do to be too good." Besides simple persuasion, reinforced by example and free samples, smokers use —though as a rule without realising it—less ethical methods of infecting non-smokers. Thus they suppress the facts, particularly the more damning facts, against smoking, and circulate in their place favourable untruths: in short, they use deception.

PHARMACOLOGICAL URGES TO SMOKE

Having established, on myself and 35 volunteers, that the repeated administration of nicotine is a satisfactory substitute for tobacco-smoking,[3] I decided to ascertain how long craving for a drug of addiction takes to develop.

> I was at that time somewhat addicted to nicotine, so I had to use another drug. I gave myself hypodermically, night and morning, cocaine hydrochloride, a drug I had not taken previously, in doses ranging from $^{1}/_{4}$ to 1 grain (16–64 mg.). About 5 min. after administering each dose, I experienced a curious sensation which I find impossible to describe: it was readily distinguishable from nicotine and codeine (whose actions are equally indescribable), but was not pleasurable. This occasioned me and a control volunteer to whom I administered several doses, some surprise—and, indeed, disappointment, for we had recently had considerable pleasure from experimental doses of nicotine. About 10 days after commencing the administration of cocaine, I found myself looking forward to the next dose with considerable satisfaction, and after 25 doses deemed it advisable to discontinue the experiment lest I became strongly addicted.

The slight craving I had acquired lasted several days, and could readily be recalled in fantasy for a much longer period. It must have developed as a side action of cocaine, and been built up cumulatively. With the craving came pleasure on its appeasement; and it seems clear that the pleasure derived from drugs of addiction arises mainly from the appeasement of craving, once such craving has been acquired. Pharmacological craving is clearly a specific, abnormal appetite for a drug, hostile (because of the drug's toxicity) to the normal, though not to the abnormal, functioning of the organism. Its development completes a vicious circle: administration gives rise, though not immediately, to craving, which leads to further administration. Once set in motion, this circle continues to turn without, as a rule, interference from the smoker's will.

Besides appeasing the craving of addicts, drugs of addiction have a further immediate specific pharma-

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6. *Times*, Sept. 1.

1. Clean Air. No. 39. April–June, 1948, p. 4.
2. Freud, S. Three Essays on the Theory of Sexuality. Translated by James Strachey. 1949; p. 61.
3. Johnston, L. *Lancet*, 1942, ii, 742.

cological action on both addicts and non-addicts. Smokers do not enjoy the pharmacological action of tobacco smoke at first—indeed, they usually dislike it. But as time goes on they find that, besides deriving positive pleasure from the appeasement of their craving, they have, if they be inhalers, an almost instantaneous general analgesic against life's little, or even big, stresses and vexations. The inhalation of cigarette smoke in moments of severe stress, in fact, is reminiscent of the inhalation of gas-and-air by a woman in labour. In pipe-smoking, the analgesic (or sedative) effect is delayed for about 10 minutes, since the absorption of nicotine is mainly alimentary. Unfortunately, the pleasurable analgesic action of nicotine (and of other drugs of addiction) is more than offset by after-depression and apathy. This cannot, of course, be demonstrated, since changes in mood are subjective; but I have observed that a striking and sustained uplift of spirits and of general interest almost invariably accompanies the giving up of smoking; and that heavy smokers seem as a class more depressed ("fed up") than non-smokers.

The effects of the psychological and pharmacological urges cannot be separately demonstrated, nor can their relative strengths be measured; only their combined effect on conduct is obvious. But interrogation of (I estimate) about 10,000 cured smokers over the past 24 years, and a personal analysis based on stopping smoking four times (twice experimentally), and on taking some 200 doses of nicotine by various routes, have convinced me that the pharmacological craving for tobacco though strongly compulsive, at first, is short-lived, at any rate in its acute form. It reaches its peak 24–36 hours after smoking has been stopped and thereafter sharply and steadily declines, though the initial steepness of the decline is not maintained: it takes several months, indeed, to reach zero.

Psychological urges to smoke, on the other hand, do not decline steadily when smoking is stopped, since most of the psychological stimuli which produce them persist. In my case, the desire for the general analgesic action of nicotine persisted, in times of particular stress, for more than a decade; so also did the less compulsive urge to smoke for companionable reasons. The desire for a plaything—the wish to perform the habitual actions of smoking—scarcely troubled me, and could in any case have been almost completely satisfied by performing the actions of smoking without actually lighting the cigarette. The longing of the recently cured smoker, after a meal, is not to perform the habitual actions of smoking, but to administer his postprandial dose of nicotine.

If, after he has smoked for some time, the smoker loses desire to smoke, and wishes to stop smoking, a conflict develops between opposing urges—the will to stop smoking, on the one hand, and craving for tobacco reinforced by various psychological urges, on the other. If the smoker's will prevails, smoking is cured temporarily or permanently. If, however, his involuntary urges prevail, he continues to smoke; but his smoking no longer expresses his will. He therefore tends to repress the whole conflict, for the outcome has been damaging to his self-esteem. He attributes his smoking solely to socially approved urges such as habit, the relief of boredom, or a simple desire for enjoyment. Smokers who have tried unsuccessfully to stop smoking, though they seldom realise or admit it, are unwilling smokers.

All smokers, willing and unwilling, however, encourage the spread of smoking and add to tobacco consumption. This has risen in Great Britain from 166 million lb. in 1913, costing £8,300,000, to 281 million lb. in 1948, costing £42,800,000. The increase in smoking has resulted in the progressive elimination of one non-smokers' sanctuary after another—drawing-room, bedroom, work-room, place of entertainment, conveyance, and finally, of late years, hospital ward and sanatorium, even when and where patients seriously ill from respiratory diseases are under treatment. The problem of sanctuary for those who claim (as I do) that the right to breathe clean air—air free, at any rate, from irritant fumes—is as basic, in a civilised country, as the right to drink clean water, has become today almost insoluble even when they are ill.

HOW TO STOP SMOKING

It is difficult to stop smoking—very difficult indeed if one is a heavy smoker of long duration. In order to stop, it is necessary to do much more than merely decide. Intellectual conviction that smoking should be abandoned is an essential preliminary, of course, to stopping, but it is only a preliminary. There must also be a build-up of resolution sufficient to withstand indefinitely all urges to smoke. As in war, the more overwhelming the preparatory build-up of strength (or resolution), the easier and more certain the victory; and conversely, irresolution tends to prolong the struggle and jeopardise success. Resolution not to smoke is born, as already indicated, of a sound and clear, though not necessarily extensive, knowledge of the action of tobacco smoke on the human organism.

The most difficult task, as a rule, is to make the break—to withstand the first surge of craving. Half the battle is over when the first day and night of non-smoking are completed. It is best, in my experience, to stop suddenly, abruptly, completely, ignoring all symptoms which might possibly be associated with tobacco deprivation. Detoxication, and hence improvement in health, begin directly smoking is discontinued, no matter how the smoker may feel; so he must follow his purpose without regard to his feelings. All thoughts about smoking should be rigorously excluded from consciousness, because craving precludes, for a time, objective thinking on this subject. It may help if he treats the craving contemptuously from the start, by carrying for a time (while resolution runs high) the paraphernalia of smoking. The more inflexible the determination to end smoking, the less the pain: as in grasping nettles, pain varies inversely with firmness. It is well to proceed silently, unobtrusively: the raillery of smokers is shrewdly calculated to undermine resolution. Acute affections, particularly respiratory affections, temporarily remove or greatly reduce all urges to smoke. A good time to stop, therefore, is when such an affection develops; or respiratory inflammation may be produced artificially, to some extent, by smoking very heavily the night before.

Psychotherapy consists in building up the patient's determination to end smoking by persuasion, encouragement, undeception, and re-education—patient and oft repeated when necessary—until, in favourable cases, its expression in non-smoking becomes irresistible. Fear, particularly of lung cancer (though this is a long-term risk) can be a potent psychotherapeutic agent, and the use of such intimidation is clearly justified when—as in this case—it is based on fact, or at any rate strong probability. A first, often difficult, task is to dispel defeatism born of previous, sometimes repeated, failure—failure almost invariably associated with ignorance of essential facts about smoking. Friends ought perhaps to be warned against irritability; but I believe I displayed none, and I suspect that it may in some cases be "laid on" by the smoker in the hope of getting his wife or fiancée to entreat him to recommence smoking, and thus shoulder some of the blame for relapse.

Unless psychotherapy has been extremely thorough, there is great risk, with so much psychological infection about, of relapse, particularly at times of lowered resistance—e.g., on sociable occasions, or in moments of stress. To avoid this, it is best to go over to the offensive: the oftener and the more remorselessly one attacks the smoking of others and exposes the falsity of arguments in favour of smoking (while doing one's best to avoid giving offence), the more finally is one committed to non-smoking, and the less one's danger of relapse. As cure is consolidated, and understanding of the harm caused by tobacco-smoking deepens, there develops gradually and unconsciously a hardening of one's attitude, or even hatred of tobacco-smoking, with pity for tobacco-smokers.

THE TOBACCO TABOO

Smokers dislike contemplating the ill effects of smoking, for some of which they cannot escape responsibility—the ash, the ends, the fumes, the fires, and the damage to the health, happiness, and economy of individuals and nations. They tend to repress them, and hence dislike hearing them spoken of. Thus they discourage serious discussion of the subject, imposing, in fact, a "drug taboo." Those who, in defiance of the taboo, speak out about the ill effects of smoking, are disapproved, derided, or ostracised in proportion to their outspokenness. Public lectures, including radio talks, which give *without compromise* the medical facts about tobacco-smoking are unheard of. The more winged the phrase, the more pointed the argument against smoking, the less the chance of their publication in the press. Even the medical press shows reluctance to publish uncompromisingly anti-smoking matter. The most remarkable manifestation of the tobacco taboo is the omission from all standard textbooks on medicine of any account of nicotinism.

SMOKERS' UNTRUTHS

Smokers' untruths are not as a rule intentional—they are rationalisations rather than lies, and are the more deceptive on that account. Moreover, liberties taken with the drug taboo, like those taken with sex and religious taboos, are a fruitful source of humour. Jokes about alcohol are, of course, legion, but there are also many about tobacco: references to cigarettes as "gaspers" or "coffin-nails" are examples. Most of us, hearing little about smoking except this language of untruths and jokes, grow up ignorant or deceived about the facts, and are psychologically infected by nicotinism in our 'teens or before.

After smoking has started, the development of craving for tobacco is evidenced not only in increasing application to the drug, but in increasing resistance to undeception. As a result, confirmed smokers are often largely inaccessible to the facts against smoking: the simple deception which took in the "pre-smoker" becomes, with development of craving, an increasingly fixed delusion of the smoker. But the inaccessibility varies. Some smokers are almost wholly inaccessible, refusing to concede the validity of even the most obvious fact against smoking; others listen with full attention, and concede verbally even the most hostile facts. Unless, however, words are supported by deeds, the sincerity of such agreement must always be in doubt. The fixity of smokers' delusions is doubtless related to the strength of their craving for tobacco, and in many cases this is so strong that the smoker projects his repressed self-criticism on to his would-be undeceiver, characterising him as a crank or fanatic, or at the least, as hopelessly biased.

Smokers usually refer to tobacco as something good or desirable which adds to the joy of living—not quite a necessity, but at any rate a luxury. Officially it is treated, in fact, almost as a necessity: even when our shipping position was at its worst during the war, space was found to bring us huge quantities. Yet tobacco is not a luxury; even on addicts, the whole action is not luxurious: coming out of their drug, smokers are depressed, like addicts of other drugs. If tobacco is a luxury, opium is an even greater luxury, and has an even stronger claim to be treated as such. Actually tobacco smoke contains various poisons, notably nicotine, pyridine bases, carbon monoxide, and arsenic,[4] and it is clearly asocial to pretend this toxic drug is a beneficent luxury. Addiction to tobacco, like addiction to opium, is a specific disease—an intermittent intoxication. An almost universal delusion is that smoking is a vice—a moral, not a medical, issue. Vice (or moral degeneracy) is merely a symptom common to all drug addictions. It is revealed in the common disregard of smokers of the moral rights of non-smokers. I have been in homes where the feeding and clothing of the children were deplorable, yet the parent or parents spent relatively large sums (perhaps £1 a week out of a weekly income of £7) on tobacco.

A common minor delusion of smokers is that they get their pleasure from purely psychological factors—playing with the cigarette or lighter, sucking the pipe or watching the smoke. Smoking, they say, is not enjoyed in the dark, or by the blind. In fact, of course, smoking in darkened cinemas is widespread, and the blind are just as strongly addicted to tobacco as the sighted. An undeniable advantage of smoking is its sociability; but actions which are sociable are not necessarily social. "Thick as thieves," we say, meaning, I take it, that thieving is often sociable; but it is also asocial, like drug taking.

The symptoms of tobacco-smoking become apparent to the sufferer only after the disease has been arrested, and he has given up smoking. An accession of high spirits, energy, appetite, and sexual potency, with recession of coughing, makes the chief symptoms of tobacco-smoking plain. Moreover, an increase in weight, often measurable in stones rather than pounds, in the course of a few months, shows that tobacco-smoking usually interferes with nutrition—a fact which should be sufficient in itself to cause smoking to be forbidden in sanatoria.

Tobacco-smoking is not, of course, usually a seriously incapacitating or a directly killing disease; but that does not mean its effects on health are negligible. Its protracted course, the enormous numbers affected, and spreading infection make smoking one of our most serious diseases. The extensive published work on tobacco-smoking as a predisposing cause of other disorders has recently been reviewed by Scott.[5] Wynder and Graham,[6] and Levin, Goldstein, and Gerhardt,[7] in America, and Doll and Bradford Hill[8] in this country, have established a strong probability that the development of carcinoma of lung is favoured by tobacco-smoking, and this probability was strengthened by the observations of Dungal.[9] Deaths from carcinoma of lung have risen from 612 in 1922 to 11,272 in 1949—a rise of 1740% in twenty-seven years, or 64% per annum. The work of Pearl[10] shows the total effects of smoking on mortality. Smokers of ten or more cigarettes a day aged 30–45 have a mortality from all causes considerably more than double that of non-smokers. This heavy toll of human life at a comparatively early age has not been sufficiently recognised.

These facts have failed to stir our profession to action. The reason is not far to seek: about 80% of us, I estimate, are smokers, and we behave collectively like an addict of tobacco. Radical cure of tobacco-smoking lies in its prevention; and tobacco-smoking is no more difficult to prevent than opium smoking. Our duty is plain.

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4. Dixon, W. E. *Brit. med. J.* 1927, ii, 719.
5. Scott, R. B. *Ibid*, 1952, i, 671.
6. Wynder, E. L., Graham, E. A. *J. Amer. med. Ass.* 1950, 143, 329.
7. Levin, M. L., Goldstein, H., Gerhardt, P. R. *Ibid*, p. 336.
8. Doll, R., Hill, A. B. *Brit. med. Jour.* 1950, ii, 739.
9. Dungal, N. *Lancet*, 1950, ii, 245.
10. Pearl, R. *Science*, 1938, ii, 216.

In England Now

A Running Commentary by Peripatetic Correspondents

"THEY order this matter better in France." What it was that was better ordered Sterne does not tell us, but I think I have found an answer.

Large numbers of the French embellish my practice. I really mean embellish, for consultations with that race are strenuous, exciting, even explosive, but never dull. I count among my most valued patients an ancient wrinkled peasant woman, equipped with all the shrewdness and capacity for clear thought which springs so naturally from the soil of France.

She complained that things did not march' as they should over the last few years. A lack of energy, not much, mais quand même. A certain slowing of the tempo of life of the most mysterious. What could it be, one asked oneself?

At the end of the consultation I found myself somewhat embarrassed, and glad that I had to talk in French. I am less easily understood in that language, and I did not want to be understood too easily. A puzzled expression rested on her brow as I haltingly fished from the corners of my memory words sufficiently vague to suggest without saying outright that after four score years it is the nature of things to feel a little less energetic than in the past: that at times we might even, without alarm bien entendu, experience a passing weakness.

Weakness! That did it. By sheer luck I had the right word, a word which could partner the ailments of the young as well as of the old. Her face lit up, as only the face of a Frenchwoman can when an explanation strikes home and her mind is set at rest. "Oui," she said with great satisfaction, "C'est ça. C'est la grande faiblesse. Voilà!"

I felt in my own mind an answering echo to her satisfaction. Who would mind suffering from la grande faiblesse? I feel I could even die of it in the grand manner, calmly and with dignity. But to succumb wretchedly to its English counterpart—what would it be, senile debility?—perish the thought.

That is at least one of the things they order better in France. They ennoble the commonplace with a gracious dignity of expression mixed with a sense of the dramatic. I wish I had had to write a certificate for the old lady. No printed slip for her! A grand flourish with a goose-quill on the finest parchment—that alone would have been fitting.

* * *

The children—not mine unfortunately—found a fledgling thrush fallen from the nest. They fed it on worms which it engulfed greedily; but, as so often happens, the ungrateful bird died untimely, mysteriously and undiagnosed. The case did not come to autopsy, but a conference was held to consider in what respects therapy had been inadequate. "I know what we ought to have done," said Bridget. "We ought to have chewed the worms first." Next time she will, for she's a kind girl to birds, though perhaps less so to worms.

* * *

Having recently had occasion to inquire into the possibility of purchasing some electrical apparatus, we found ourselves led insensibly into a series of communications with an old-established French firm. Our latest receipt in this correspondence is a schedule entitled *Conditions de vente*, which appears to contain the nub or crux of the projected transaction. It is a complicated document, and after several pages concerned with such matters as *expédition*, *délai*, &c., we came at last to the vital factor of *prix*. This factor proved unexpectedly difficult to elucidate, being surrounded by a scientific smoke-screen of Gallic exuberance and plasticity. The section began forbiddingly:

"*Nos prix sont révisables suivant la formule*

$$P = P_o\left(0{,}10 + 0{,}80\frac{S}{S_o} + 0{,}10\frac{M}{M_o}\right)$$

où les différents paramètres sont définis ainsi :— . . ."

But we are made of stern stuff, undaunted by income-tax schedules and claims for mileage allowance; dragging to our bosom our invaluable New Little Larousse, we ploughed on. It appeared that P was the definitive price, P_o the estimated price, S the index of wages in the Electrical and related industries published (and rectified globally) by a mysterious body designated R.G.E. two months before the actual date of delivery, and S_o the index for the fortnight preceding the date of the estimate. M_o was the price of aluminium in sheets of 1 mm. (R.G.E.), and M the value on the last day of the first two-thirds of the actual delay in delivery. When we had got thus far our attention was distracted by a musical plash, and we observed with interest that a drop of sweat from our overheated brow had fallen on the paper. All we had wanted originally was a galvanometer, but we no longer felt the desire.

On the other hand, when we showed the document to one of our clinical colleagues who is still fortunate enough to have a few private patients he was at once interested, and he has produced a sliding scale of fees based on a similar principle. His final charge (F) is related to the estimate given to the patient (E) by the following equation:

$$F = E\left(0\cdot1 + 0\cdot5\frac{C}{C_o} + 0\cdot2\frac{P}{P_o} + 0\cdot2\frac{T}{T_o}\right)^n + \sqrt{D_c.D_w}$$

where C is the mean cost-of-living index in the period between the operation and the rendering of the account, and C_o the index figure at the time of arranging admission. P and P_o represent the corresponding figures for the cost of petrol, and T and T_o those for telephone rental. D_c and D_w represent physical depreciation of our colleague and his wife in units of earning and coping capacity respectively, and the exponential n has been added by a statistical friend who feels vaguely uneasy without it.

* * *

Readers of the *Britannica Book of the Year* for 1951[1] must prepare for a serious shock when they turn to the section headed "Words and Meanings, New." If they can support "depurged" for "one restored to acceptable political or other standing," and are able to picture their charlady as an "accommodater"—surely the gracious old word "obliger" should be retained?—they will still have to face a shocking debasement of the term "bogey." This noble description of a golfer's performance stands, in this country, for the perfect score for a hole; and a "birdie," of course, describes a hole done in one less than bogey, while an "eagle" is reserved for the rare feat of doing a hole in two under bogey. Now, it seems, our golfing colleagues in the United States have begun to apply the noun "bogey" to a hole done in one over par (par being the perfect score for the hole), while double-bogey is used for two strokes more than par: and what is worse, they also use these terms as verbs. At this corruption of long-accepted usage we can only shake grave heads.

* * *

On stopping in our local mountain hut the other week-end for sodden sandwiches and cold tea, we found the following entry neatly written in purple ink in the visitors' book:

"I hitch-hike from my home in Spa to Ostond, then in the steamer I came to Dover, then again I hitch-hike to Birmingham, Glasgow, Aberdeen, and Balmoral, where it was raining much. There as I standed in the downpour I saw your [illegible] Queen, who smiled and waved to me, yes to me, a poor [illegible] wet tramp, as she drive to the church, and I could [illegible] 'Good morning.' I am quite comeover. Now I am in this hut for two nights and I have no food and still it is raining [illegible] much, and I am off to Aviemore. God bless [illegible] this hut; God bless your beautiful Queen; God bless the whole British people."

The hut is situated in one of the remoter fastnesses of the Cairngorms, and is reached by a mountain path strewn with large boulders, liberally interspersed with bog and torrent. In these days of [illegible] pessimism, and complaint, we feel that our [illegible] visitor's exuberant good will in the face of [illegible] adversity should be something of an object lesson.

* * *

The Safe Food Campaign.—Notice in a [illegible] "All crockery used in this establishment is [illegible] each week."

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[1] London: Encyclopædia Britannica [illegible] £3 3s.

Letters to the Editor

THE PROSPECT OF GENERAL PRACTICE

SIR,—As a young general practitioner I find myself in complete disagreement with the conclusions of your correspondent (Aug. 16). At medical school my teachers did not deride general practitioners but named certain good ones and demonstrated their letters as examples of clinical judgment and observation. Some of those whom I knew personally excited my admiration and respect as much as my hospital chiefs did, so I entered general practice biased for, rather than against, it. After 5 years in it I would not change my job, and to find out why, I asked myself the questions which your correspondent answered with such crushing negatives.

1. Have I got conditions of work which allow me to exercise my technical skill and satisfy my intellectual thirst? Yes. In a moderate-sized partnership I do have time to examine my patients. I have no less equipment in my consulting-room than the specialist has in his; but, although I do not personally carry out barium meals, blood and chemical examinations, electrocardiographs, and so on, my interest in the result of these tests is no less and my satisfaction is as great if they prove me right. And my opportunities for follow-up are considerably greater: my patients give me no option but to follow them up, whereas the specialist often depends on me for further news of them.

2. Can I provide a happy family life for my children and bring them up in conditions which will let them be moderately civilised and well educated? Yes. Although I have to work harder than most men for a decent living, I do not need to put in the hours your correspondent suggests. My wife must answer telephones and doorbells on top of her domestic duties; but since she, I, or some other responsible person must always be in the house anyway for the children this is not quite the tie it seems. When one of my partners is on duty we can go out together, and local help is as willing to come to a doctor's house as to any other. Our children, it is true, must not scream and shout immediately outside the consulting-room door; but this is no great hardship for them. And since I did not find among my school and university contemporaries that doctors' sons were less civilised than other people's I do not worry on that score.

3. Does general practice allow me to work without thought of gain? No, but what occupation does? The well-educated member of any profession would surely spend more time in the theatre and the art gallery and less at his work if he were free from that stimulus. What could be more civilised for the salaried G.P. than to drop 1000 patients and devote the time gained to reading philosophy or playing the flute? Am I blackmailed by hostile circumstances? No. Legally the patient has the whip hand; but if he is thoughtless or stupid, or makes unnecessary demands, I no more hesitate to tell him so than my father did his private patients a generation ago. I lose no more patients in this way than I gain through my rivals taking the same line. The patient may report me to the executive council, but unless he has a genuine grievance he involves me in no more than an explanatory letter.

4. If my health falters my livelihood is endangered, but no more so than in any other job. The edicts of the Ministry of Health can surely seldom conflict with anybody's principles, and its regional medical officers do not spend their time searching our records for mistakes. As for the threat of my competitor getting a seat on the regional board, this would delight me because his administrative duties would leave him less time to compete against me without in any way increasing his attraction to my patients.

I do not wish to idealise general practice. It is hard work—it has its frustrations and annoyances, and it involves too much routine paper work—but it can be spiritually and intellectually satisfying and I believe in its future. It is important that good doctors should continue to be attracted to it; and for this reason articles like your correspondent's, which give a false picture, should be answered.

Newcastle upon Tyne. ANDREW SMITH.

SIR,—I would like to support Dr. Hanratty (Aug. 23) in his reply to your anonymous correspondent. General practice has always been just what the individual practitioner wished to make of it. This, for many of us, is its charm. In many ways this is more true now than ever before. Freed from the bar of money, a doctor can follow his cases as far as he wishes.

As for the "insults, stupidity, thoughtlessness, and unnecessary demands" of his patients, it is obvious that your correspondent has never thought of himself as the family doctor who is not only an adviser but a friend. Patients do not treat their doctors thus unless goaded by the unfriendly and unwilling attitude of the doctor. In my practice unnecessary calls are extremely rare; and night calls, apart from midwifery, very rare indeed.

There will be no research in general practice as long as the conception of research is one of a technical process requiring expensive apparatus. To my mind the general practitioner's research should be careful observation of the vast quantities of clinical and social material at his disposal. He should be able to call upon the services of a department of social medicine to help him to collect and analyse the material.

Possibly your correspondent will be surprised to hear that I not only chose general practice, but I enjoy it and would choose it again. Perhaps there are dissatisfied practitioners. If there are, I suggest they cease to look for outside causes of their dissatisfaction and apply the remedy from within themselves.

York. F. CHARLOTTE NAISH.

SIR,—Your correspondent certainly "went to town." The prospect is not so melodramatic, though full of poetic justice.

We have produced a breed of academic medicos, "lily-livered" when it comes to facing clinical medicine in the great unknown—outside the hospital ward, outpatient department, or examination halls. If you want general practice you must go and get it by proving your individual intrinsic value to the individual patient. The patient that seeks a doctor out is worth twenty dished up to him by official assignment or in a clinic: the relationship, a very personal and intimate one, starts propitiously in this personal approach.

There are still many openings for the man of courage and initiative combined with ability and a vocational calling. Let him put up his plate in a large residential or populous district, or where studied report bemoans the lack of a good doctor—a complaint I hear often. He will not have to wait very long before he is established if he gives good service.

The dissatisfied patient—and there are many more of them now than when I started in practice—is waiting for a G.P. whom he can approach on an equal footing, prepared to give time and interest to his case. He does not want, and certainly will not regard, as his G.P. the pen-pushing Civil Service drudge to whom he goes for certificates which could be as easily obtained at the post office counter, and with less waiting.

When I see a few well-qualified young men—and women—with courage and a vocational urge to treat and heal the sick putting up their plates and ready to deliver the goods I shall feel happier about the future, not only of medicine, but of the young Elizabethans.

London, W.1. W. PINNINGTON JENSON.

SIR,—Your correspondent paints a grim picture; but it is the work of a blindfold artist, for he confesses that he has not done any general practice.

Your correspondent's remarks were answered specifically by Dr. Hanratty. I would only add, first, that general practice offers great scope for research,[1] particularly into old age and its problems; and, secondly, that hospitals are, in my experience, only too pleased to allow the G.P. to have direct access to laboratory and X-ray departments. If this cuts down their out-patients and prevents unnecessary admissions, so much the better.

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[1] See Fry, J. *Brit. med. J.* Aug 2, 1952, p. 219.

Let us have criticism of general practice, but let it be first-hand. Sir, are you prepared to print an anonymous article by a G.P. on the Prospect of Academic Research?

London, W.11. L. MELVIN GREEN.

SIR,—It was with amazement that I read your correspondent's article. Not one word or thought of medicine as a vocation relieves this cry of woe. Surely he considered the attractions of other methods of earning a livelihood before he became disillusioned and entered his medical school to train as a doctor. Did he not realise that patients are ill during the night as well as during the day, and that office hours cannot be followed in medicine; or why else does he complain about the need to be available throughout the 24 hours?

A patient is a sick person—the same as any other of the writer's fellow men a day or a week ago, but now in pain or distress—*not a creature apart, full of* insults, stupidity, or wicked demands veiling his threat of legal action behind a whining plea for this and that. Now, as in the past, he is grateful for the care and attention given to him by his own doctor, and he is still the same person, "the victim of the often appalling mistakes," who appears tucked up in his hospital bed, and not a creature metamorphosed by the high technical skill of the consultant at the teaching hospital.

Let the writer analyse his training afresh. Does he wish to estimate each chemical abnormality, to have a radiograph for each râle and rhonchus, to record each extrasystole on shining paper—meanwhile what of the patients who lie in their homes while the scientifically trained doctor is cogitating over his tubes, his cardiographs, and radiographs. The patient will turn to the doctor who has learnt the art and science of diagnosis by observation and inspection, by bedside examination, and one who then can use his scientific background to call for tests from those working in laboratories.

The general practitioner has bowed to the seizure of his goodwill by the State, though he knows new and complicated problems have risen thereby—but he is still not salaried. We think that a salaried service will produce uniformity and loss of drive and ambition—abstract qualities that are difficult to formulate.

There are many outside general practice and on the threshold of medicine who do not know the anxieties and fears when one has the responsibility of a patient's life in one's hands—and the satisfied pleasure when that responsibility is discharged with credit. There are many who can only think of the team around the bed in the great teaching hospital, where the personal onus of care is not so heavily on one man, where the relatives are not watching each move and action, and where the patient's friends do not have to be met and spoken to each day.

No! General practice will still take many of the "good" doctors, and more will enter the ranks if others on the threshold stop crying when they see a little of the hardship and none of the rewards of this great vocation.

G.P.

SIR,—I read with mixed feelings of horror and indignation your correspondent's article. It is a complete travesty of the facts.

I have time, and am able, to investigate fully all patients needing it—X rays, full laboratory facilities, and hospital beds are at my disposal should I need them. I find, however, that I can do almost all medical investigation without hospital beds, reserving these for biopsies only; when a patient requires specialist treatment he usually attends the consultant with the investigations already completed.

If the practitioner is sympathetic and does a good job, prescribes for his patients what is good for them—not what they want—gives certificates where it is justifiable and refuses them otherwise (however much longer that may take) he will be respected by his patients; he will not be abused either literally or with thoughtlessness, and he will find peace and satisfaction in his work.

Surbiton, Surrey. DUNCAN MILNE.

SIR,—As a literary exercise The Prospect of General Practice would no doubt acquire high marks—but not from a general practitioner of any experience. Your correspondent has, it appears, spent his days so far in lofty academic circles. All he needs now is to spend a year or two in general practice which will be worth any amount of theorising on the subject. Research in general practice, one may remind him, will not come by sitting down and taking thought. It will have to come by patient waiting, and, as he correctly surmises, the duties of each day are sufficient in themselves.

General practice is only one division of medical practice, and those who follow it must be content to be G.P.S and nothing else. It is true that mistakes are made in general practice—some quite unforgivable—but one has only to read the daily papers to know of horrifying mistakes made in hospitals.

Your correspondent's gloomy views about bringing up his children, and about life in general practice, have no basis in fact. As one who has seen many years of it, I can safely say that general practice today is far more bearable than it was under the National Health Insurance. Patients are more considerate and are more prone to regard the doctor as a human being and not as an automaton. All the same it can be very exacting, and at times, even exhausting.

In conclusion I should like to assure your correspondent that, even though he and his like decide not to enter general practice, that particular division of medical labour will continue to carry out, satisfactorily in the main, the bulk of the medical work of the country as it always has done; and, taking it all in all, that work will compare favourably with anything that may be done in hospitals.

Brighton. G. L. DAVIES.

SIR,—As a final-year student, I find it alarming to have my intended branch of the profession denigrated by such remarks as "low professional standard and lack of opportunity for good work."

I have been privileged to accompany a G.P. on his rounds and attend his surgeries, and I was impressed by the modern techniques and remedies employed and by the care with which they were used. It was also interesting to observe the complete mutual confidence between the partners in the practice, which resulted in not ungenerous periods of leisure free from worry.

I fear, however, that your correspondent's pessimistic article will disuade some of those about to qualify from entering general practice.

Middlesex Hospital Medical School,
London, W.1. J. D. WIGDAHL.

SIR,—Through his specialist glasses your correspondent sees too darkly the prospect of general practice. There is no doubt that the emphasis since the introduction of the National Health Service on the development of the hospital and specialist services, and the almost complete neglect of the general-practitioner services, have reacted to the disadvantage of general practice.

Let us remember, however, that one of the most important reasons for the National Health Service Act, was the tottering state of our domiciliary services, which in many ways were showing signs of severe strain. When after July, 1948, great numbers of people who previously could not afford a doctor of their own very naturally took advantage of their new-found opportunity, the situation in many areas became almost chaotic. Far from seeing the new situation as a revelation of the inadequacy of pre-service conditions, those unsympathetically inclined put the blame on the new service.

Even as at present constituted, the National Health Service presents an opportunity for raising general practice to the level already reached by the hospital and specialist services. This lies, I believe, in the development of group practice from health centres, for which the Act makes statutory provision. Unfortunately, just as Lord Dawson's original recommendation for health centres, put forward in 1920, was pigeon-holed because of economic pressure, so today health centres, although described by the Minister who introduced the Act as the keystone of our domiciliary service, have again, ostensibly for the same reason, been held up except for a few already being built. These few are very substantial buildings; but it does not seem unreasonable to suggest, with our lack of experience of how health centres can best function, that more temporary prefabricated structures, designed for adaptation to changing needs, might have better served the purpose of what is really a pilot study.

Group practice in health centres involves the coöperation of doctors, nurses, social workers, technicians, and other ancillary staff. This calls for coördinated action by the regional hospital board, local health authority, and local executive council, which are the administrative bodies concerned. At present no statutory body coördinates the activities of these three; and it seems very necessary in the interests of an efficient domiciliary service that there should be set up some such coördinating committee, called perhaps an area health service council.

While in many respects the Working Party's report is disappointing, its recommendations will go some way to redress the balance between the specialist and general-practitioner services. It is much to be regretted that its contribution to the establishment of group practice is so lukewarm.

For many reasons general practice today is far from being as good as we were promised, and as it could be under the terms of the National Health Service Act. Nevertheless, after 28 years' experience in a mostly industrial practice, I can confidently assert that the high standards to which your correspondent quite rightly aspires are more nearly attainable today than before the introduction of the service four years ago.

Edinburgh. S. LIPETZ.

SIR,—The time has really come when correspondents to the medical journals on matters concerning the National Health Service should appreciate the true facts. The letters which appear from week to week, if read by any uninformed person, must cause serious damage to the medical profession. The following statements are often found:

That doctors are inundated with clerical work and are thus unable to give proper attention to their patients.

Most of us have less clerical work than we had in the days of private practice. Sending out bills and recording and collecting fees was an onerous task that no longer exists. The keeping of records is no more than any doctor had to do for all his patients in the old days. Prescriptions have always had to be written, even for private patients.

That we have lost the freedom to practise that we had in the days before the National Health Service.

We are now at liberty—and it is a great advantage—to call on patients as often as they need without any consideration of whether they can afford it or not. Patients can be expected to visit us, rather than that we should be expected to visit them at their own convenience.

That we have lost the freedom of prescribing what we consider patients need.

Never were we able, in the past, to prescribe drugs regardless of their cost. In the days of private practice any doctor should have borne in mind the cost to the patient of expensive drugs. Any good doctor would have considered whether the high cost of a certain drug was justified by its clinical action. The less conscientious doctor considered that what the chemist received he lost.

That we have lost the freedom to sell the goodwill of our practices.

Most of us borrowed the money to buy a practice in the days before the war, and it took us very many years to repay the cost of purchase. Now, with income-tax at a high rate, no young man can ever expect to repay the purchase price of a practice. The freedom now bestowed on the incoming partner and the intaking partner must be felt personally to be realised.

The financial side of medical practice under inflation should also be realised. Because the pound is worth only half what it was before the war, the fees in private practice should be increased to twice what they were then. The experience of most general practitioners must be that, far from being able to double their fees, they find that most patients feel that they need a decrease if they are to remain as private patients.

Petworth, Sussex. W. A. BALL.

LEAD PAINT: A HAZARD TO CHILDREN

SIR,—I had intended on my return to this country to inquire about the known incidence of lead poisoning in children and to ask my clinical friends to bear in mind that it might be occurring. I was, therefore, most interested in the article on this subject by Dr. Millichap and his colleagues in your issue of Aug. 23.

The city of Baltimore, Maryland, has a population of 950,000. During the period 1931–51 there have been in that city 293 cases of lead poisoning in children, of which 83 have been fatal. The age-distribution of the 293 cases, with deaths of the 83 in parentheses, was: under 1 year, 19 (8); 2 years, 167 (51); 3 years, 67 (15); 4 years, 21 (3); 5 years, 11 (2); over 5 years, 8 (4).

Cases are still occurring, despite the efforts of the health department to warn parents not to allow their children to chew painted toys or paintwork on window-sills. There were 34 cases in 1949, 31 in 1950, and 20 in the first six months of 1951. The peak period is July and August.

A recent city ordinance has prohibited the use, for indoor painting, of paint unless it is free from any lead pigment; and a free service for the examination of blood for punctate basophilia is provided by the city health department.

ALLEN DALEY
Recently Associate Health Officer,
Baltimore, Maryland.
London, W.14.

SIR,—Two children seen at this hospital in the past three months emphasise the plea made by Dr. Millichap and his colleagues for the recognition of the danger to young children in lead-containing paints. These cases also emphasise the need to consider the diagnosis of lead poisoning in children with vague cerebral symptoms, such as irritability and vomiting, and abnormal cerebrospinal fluid.

Both patients, aged 3 years and 16 months, presented with irritability and vomiting, and a diagnosis of tuberculous meningitis was considered. Pallor was, however, marked in the second child, and, taken in conjunction with the cerebrospinal fluid (C.S.F.) findings, suggested the diagnosis before more specific evidence was obtained. In both, the C.S.F. findings were typical of lead encephalopathy; lead lines were present in the bones; the punctate-basophil count was high (Lane's technique); and there was a high urinary-lead excretion. The first child is of special interest; for she was found to have a megaloblastic bone-marrow, and her case will be reported more fully in due course.

The source of lead in the first case is not yet definitely established, but the second child had ingested lead from the old and crumbling paintwork of an outside balcony. The lead content of the paint was 54% (calculated as the metal).

There is clearly a need for more safeguards against this danger than exist at present.

Whittington Hospital,
London, N.19.
M. B. MORRIS.

ACTION OF ANTIBIOTICS

SIR,—I consider it dangerous to let your interesting leading article of Aug. 23 pass without comment, especially in so far as penicillin action is concerned.

That penicillin affects the assimilation of glutamic acid is beyond doubt, but it is equally beyond doubt that death of the cell does not come about because it has been deprived of the vital preformed glutamic acid. Many penicillin-sensitive staphylococci will grow without added glutamic acid and a *Bacillus subtilis* has been described which is extremely sensitive to penicillin, even when growing on a medium composed of inorganic salts and glucose only. Thus, we can have both penicillin-sensitive and penicillin-resistant organisms which are nutritionally independent of preformed glutamic acid or of any other amino acid. Dr. E. F. Gale, who has done such excellent work on this subject, has wisely avoided jumping to the easy conclusions which you expound. In spite of the tremendous amount of work done in the last few years on the mode of action of antibiotics, we are far from understanding how any of them works.

Wright-Fleming Institute of
Microbiology, St. Mary's Hospital
Medical School, London, W.2.
DERRICK ROWLEY.

ATTENDANCE AT BOXING CONTESTS

SIR,—We are anxious to obtain the voluntary services of medical men to attend amateur boxing shows in London and the suburbs during the coming autumn and winter.

The shows usually take place in the evening, and the duties consist in examining the contestants (total time $^1/_2$–$^3/_4$ hour) and being available or on call for any serious injuries, which are usually very few. The only reward we can offer is a good boxing show and a convivial evening.

Medical officers will have the satisfaction of knowing that they are assisting to foster a high physical and moral standard in the health of the nation's youth.

Will doctors who are interested please write to me?

London Amateur Boxing Association,
69, Victoria Street, London, S.W.1.
J. L. BLONSTEIN
Hon. Medical Officer.

BLOOD-PRESSURE ESTIMATIONS IN CHILDREN

SIR,—Your explanation (Aug. 16) that you were referring to research conditions in your leading article on the treatment of bacterial meningitis disposes at once of two of my objections to your proposed scheme of blood-pressure estimations—namely, that child manometer cuffs are not generally available, and that the suggested procedure would prove appallingly time-consuming. But not, I think, of my third, and perhaps most important, objection—that in most cases even when a reading has been obtained its value is doubtful.

The Waterhouse-Friderichsen syndrome occurs predominantly in young children, often very young children. Though desperately ill they are not, unless in the terminal stages, inert; on the contrary they are restless and resistive. They struggle against the manometer cuff and have to be firmly held. Of what value are readings obtained under such restraint? And are we justified in provoking these patients to expend their diminishing reserves of strength for the sake of such equivocal findings? By all means let us have as many accurate blood-pressure estimations as we can in coöperative patients; I agree that they afford valuable confirmatory evidence in diagnosis. But diagnosis is not so difficult as suggested, and, with respect, has seldom to be made from other very severe forms of ordinary meningitis, for in fact there is little similarity between the two conditions. The crucial feature of the Waterhouse-Friderichsen syndrome is that signs of meningitis are either extremely slight or, more usually, absent, and the conditions usually suggested to the clinician are malignant purpura or pneumonia.

Perhaps I can make my position clearer if I say that in my view any patient who presents with collapse and a purpuric or ecchymotic (*not* petechial) rash, particularly if there is livid cyanosis and perhaps polypnœa, should have a lumbar puncture. If this reveals an opalescent or turbid fluid under increased pressure, cortisone and sulphonamides should be given without delay; for this is one of the most acute emergencies in medicine—one has seen a patient die within 12 hours of taking ill. The amount of cortisone required is relatively negligible. I agree that its value in this syndrome should be most carefully assessed; but I submit that this has already been shown to be considerable; and if we are to wait until correct blood-pressure estimations have been made, then I submit, Sir, that many lives will be lost that might otherwise be saved.

South Middlesex Hospital,
Isleworth.
G. E. BREEN.

CAROB FLOUR IN FUNCTIONAL VOMITING OF INFANTS

SIR,—Most babies who frequently vomit or regurgitate their food are just mild "posseters," but a few belong to the more serious and even alarming class of "habitual vomiters." These babies may reject their food any time within an hour of feeding. The trouble may start very soon after birth in either breast- or bottle-fed children. When an organic cause has been excluded, the diagnosis of "habitual vomiting" may reasonably be made. This is a functional disturbance of ingestion which includes cardio-œsophageal relaxation.[1] The problem of getting the baby to retain its food must then be tackled.

Most infants come to no harm from occasional or even quite regular vomiting, but the baby whose weight stays the same or actually falls is in danger, and undernourishment may lead to dehydration and atrophy. And in spite of this the infant is hungry, alert, and avid for food which it cannot hold.

The usual treatment is to thicken the food by adding, say, wheat flour or arrowroot to the milk formula or to the expressed breast-milk, thereby increasing the viscosity of the milk and helping to keep it in the stomach. Phenobarbitone may also be given before each feed. These measures usually work in the simpler cases. Fine-oatmeal gruel and pureed potato made with milk are sometimes used, or the consistence of the feed may be suitably altered by using powdered or condensed milks, extra fluid being given as water between feeds. Whatever method is used there is an important disadvantage—the formula is poorly balanced for the infant's nutritional needs, and growth may be affected.

It was with much relief that I heard of Professor Lelong's work in Paris on this problem. All degrees of persistent functional emesis in infants were treated with milk thickened by the addition of carob flour, a powder extracted from the seed of the Levantine carob tree. Information about this legume, *Ceratonia siliqua* (Linne), is given by Glanzmann.[2] This flour was prepared for Professor Lelong's trials by the Nestlé Company of Switzerland, and has proved indispensable. Its virtues are that it has no flavour, it thickens the milk without lessening its digestibility or changing its nutritive value, and it is completely inert and neutral. But it does alter the consistence of the feed so that it is rare for even a severe case not to respond satisfactorily.

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[1] Neuhauser, E. B. D., Berenberg, W. *Radiology*, 1947, 48, 480.

[2] Glanzmann, E. Einführung in die Kinderheilkunde. Vienna, 1949; p. 220.

0·5–2% (usually 1%) of the powder is added to each feed—i.e., one measure to 100 ml. (3 ounces) of cold breast, ordinary, or modified milk. Any sugar and water required is added to this mixture, and the whole is brought to the boil. When powdered or condensed (evaporated) milk is used, the powder is mixed with the necessary water, and the mixture brought to the boil for a moment before the milk is added with vigorous beating.

Carob flour is available on the Continent and is widely used in Switzerland, France, and Belgium. In this country the powder, which is marketed abroad under the trade name of 'Nestargel,' has received only one mention as far as I know; Evans and Mac Keith[3] say: "The addition of ½–1% of 'Poudre Épaississante Nestlé' Nestargel to the feed makes it so adhesive that the child cannot vomit it, but this preparation is as yet not generally obtainable."

The import of carob flour for sale in the United Kingdom is forbidden, and the flour which I have myself used was kindly supplied by the Nestlé Company. I have only been able to try it so far in nine cases, but all these have been severe enough to resist all routine measures. All nine babies were cured or remarkably improved in a very short time, all within two weeks and the majority within a week. The mothers were given the powder with instructions on its use, and they had no difficulty in preparing the feeds.

I have no doubt of the efficacy of carob flour in this condition. Its value deserves to be widely known, and the flour should be readily obtainable. I would go so far as to say that if there is no improvement after its use, the diagnosis of the cause of vomiting must be suspect. Before others can share my enthusiasm, the ban on the sale of carob flour in Britain must be lifted.

Dr. Helen Morley kindly provided me with several of the patients in my small series.

Duchess of York Hospital for Babies,
Manchester.
THEODORE JAMES.

NURSES IN THE MAKING

SIR,—Mr. Hodkinson's letter[4] has been followed by a leading article in your issue of Aug. 9.

My experience of a cadet scheme in this mental-deficiency hospital appears to run parallel to that of Mr. Hodkinson, even to the intention not to publicise it until more experience had been gained. The scheme has now been running for nearly 3 years, and results hitherto have been wholly satisfactory.

Two whole days a week are spent in school on "further education" with a teacher provided by the local authority. Three half-days a week are devoted, under the supervision of our nurse-training school, to subjects which will lead up to the preliminary State examination; and three half-days are spent in the various departments of the hospital. These young people are at no time regarded as nurses, and their status in the hospital is that of a student; association with all but the youngest patients is minimal, and regulations regarding the employment of young persons are strictly adhered to, although in view of the student status of the cadets these regulations rarely apply.

Mr. Hodkinson lists five advantages and five essential features. I have just looked up one of my earlier reports on our cadet scheme, and find that I came to the same conclusions, in almost the same order and the same words. If I had to select one outstanding element in the success of any cadet scheme, I would say that this is the "student" as opposed to the "employee" status of the cadet; and I would add that in this hospital we accept the "career" element in nursing, as opposed to the "vocation." All young people on application are medically examined and educationally and psychologically tested; and we believe that the young men or women who tell us that they wish to take up nursing because the career seems interesting, the money is good, and they wish some day to be a chief male nurse or matron, are better candidates than those who claim they have a call to do nursing. On inquiry this too often is found to mean that they have a call for nothing and that they are just drifting into nursing and will thus probably drift out again.

The cadet scheme in this hospital is practically our only source of student-nurse recruitment; it has saved the nurse-training school from extinction and the hospital from the closure of beds.

The raising of the minimum age for student nurses to 18 years is a blow to nurse recruitment, but not, I think, too serious a blow; it will dam but will not choke the stream.

Your statement that "there are good arguments for the view that whatever a girl does between leaving school and starting her nursing training, at least she should keep clear of hospitals" is a denial of the fact that some hospitals can lay themselves out to ensure that everything that can be done is done to provide for the proper mental, physical, and emotional maturation of the young male or female nursing cadet.

I believe that properly run cadet schemes, run on "further education" lines, are the answer to the nursing shortage. I also believe that badly run schemes are likely to cause much harm to nursing recruitment.

Prudhoe and Monkton Hospital,
Prudhoe-on-Tyne, Northumberland.
GEORGE MCCOULL.

INCISION FOR APPENDICECTOMY

SIR,—I was very interested in Mr. Young's account (Aug. 9) of his method of extending Battle's incision where pelvic or other disorders are unexpectedly encountered.

I have used in about a hundred cases a method which, for want of a better name, I call the "transverse retro-rectal approach," and which also may be extended if necessary.

An incision is made in the plane between the anterior superior spines of the ilium. Starting in the midline and extending to the right over the right rectus abdominis muscle, it may be made in the natural crease which often lies at this level. The rectus sheath is opened in the same direction as the skin incision; the rectus muscle is freed from its sheath posteriorly by stripping it with the index fingers, and the muscle is retracted medially. The posterior lamella of the rectus sheath with the closely adherent transversalis fascia and peritoneum is picked up above the level of the linea semicircularis and opened transversely: care must be taken not to include the gut, which is closely applied to the peritoneum here. The inferior epigastric artery, which has just entered the sheath across the linea semicircularis, is medial; it is usually adherent to the rectus muscle and is retracted with it.

If a pelvic or abdominal condition requiring a more extensive exposure be encountered the approach may be converted into a Pfannenstiel by extending the skin incision transversely to the left over the left rectus muscle, opening the left rectus sheath in the line of the skin incision, separating and retracting laterally the recti muscles, and extending the previous opening behind the right rectus transversely behind the left rectus. It is, of course, possible to extend the incision to the right by cutting through or separating the oblique and transversus muscles as in Weir's approach.

The advantages of the approach are that it is adequate, and the pelvic organs can be easily examined; and the incision can be extended without damage to nerves and, possibly, consequent hernia. Wound healing is earlier; sutures may be removed on the fifth day. The scar is thin, strong, and almost invisible. Keloid formation is rare—possibly because the incision lies in the natural

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3. Evans, P. R., Mac Keith, R. Infant Feeding and Feeding Difficulties. London, 1951.
4. Hodkinson, S. *Lancet*, 1952, i, 1113.

skin-tension lines of Langer. The scar does not tend to stretch, and as it is transverse and often in the crease line it is cosmetically satisfactory.

River Hospitals,
Joyce Green,
Dartford, Kent.

JOHN McDONALD.

HYPOGLYCÆMIA IN ROAD USERS

SIR,—Motor accidents have very rarely occurred because of hypoglycæmia in diabetics who are taking insulin. This condition may arise from several causes, such as omitting to eat the necessary carbohydrate at the usual time—i.e., at breakfast, in the middle of the morning, at the midday meal, at tea-time, or at the evening meal. If the carbohydrate is either omitted or delayed, a severe reaction may occur owing to unopposed overaction of the insulin. A hypoglycæmic attack may also be produced by taking unusual exercise shortly before the car is driven, or as a result of changing a wheel.

The medical advisory committee of the Diabetic Association therefore asks all doctors looking after diabetics taking insulin and driving motor-cars, or riding motor or pedal cycles, to make certain that their patients understand the possible causes of hypoglycæmic attacks and how they can be prevented by regular intake of carbohydrate at the usual meals, which should be taken punctually. Some extra carbohydrate should be eaten both before and after any unusual exercise. A supply of biscuits or 12 lumps of sugar or glucose should always be carried in the car or cycle in case a meal is unavoidably delayed, or unexpected exercise is necessary.

The committee especially hopes that, if a doctor knows that a patient sometimes does not recognise the symptoms of hypoglycæmia, he will advise his patient not to apply for a driving licence.

Diabetic Association,
152, Harley Street,
London, W.1.

R. D. LAWRENCE
Chairman,
Medical Advisory Committee.

FLUORINE INTAKE IN BRITAIN

SIR,—The decrease in the incidence and spread of dental caries in certain townships in the United States, resulting from the fluoridation of communal drinking-waters, has led to the suggestion that fluorine should be added to British public water-supplies at a concentration of one part per million which, together with the ingestion of fluorine in ordinary food, would put the total daily fluorine intake at about 2·20 mg.[1 2] Subsequently a basic ethical objection to such compusory mass medication was made on behalf of the League of British Housewives.[3]

Considerations of the real differences in nutrition and distribution of population between different countries appear to have been neglected by those responsible for the suggested fluoridation of water-supplies. Small amounts of fluorine occur naturally in many sources of British drinking-waters; but fluorine-containing ores, fluxes, and coals are now used industrially in this country in large quantities. Fluorine compounds are toxic when inspired or ingested; and, since they may be encountered in various ways in industrial processes, they present a definite hazard to the health of man and animals. Animal fluorosis is being increasingly noted by British farmers and veterinary officers, especially in the neighbourhood of iron and steel works and of coal-consuming electric power stations.

Animals can be moved from contaminated pasture, but human beings remain in a polluted atmosphere. The etching of window glass by hydrofluoric acid—an easily recognised sign of atmospheric pollution—is now seen in industrial homes; and in these contaminated regions, examination of the teeth of children and estimation of urinary fluorine in adults gives evidence of the absorption of fluorine in excess of that known to come from the local drinking-water.

In a healthy man a fluorine intake of up to 5 mg. daily can be eliminated, but above this level there is retention of fluorine in the body with cumulative effects in bone.[4] A recent investigation [5] has described the effects of chronic fluorosis on kidney structure and function in rats, with a view to demonstrating the existence of a fluorine hazard before such severe intoxication has resulted as to cause obvious skeletal lesions; the histological examination indicated that in the kidneys there was vascular, glomerular, and more obviously tubular, degeneration leading to interstitial fibrosis.

We do not know how high the actual intake of fluorine is at present in the various industrial regions of this country, and, until further inquiry is undertaken with regard to the fluorine hazards to which different neighbourhoods are now exposed, it seems most undesirable that fluorine should be added to public water-supplies in Britain.

Laboratory of Human Nutrition,
University of Oxford.

DAGMAR WILSON.

BONE REGENERATION

SIR,—Following your survey of this subject (Aug. 23) I should like to refer to recent work on bone grafts carried out in this department by Mr. John Hutchison.[6]

Bone autografts and homografts were implanted into bone, muscle, and the anterior chamber of the eye of rabbits, and their histological progress followed and compared from 10 to 180 days. Hutchison's findings are in many respects contrary to those recorded by Barth [7] and Reynolds and Oliver [8] to which you referred. Even at an early stage (10–21 days) there is a striking difference in the histological appearance of autografts and homografts. In the bone autograft, while the osteocytes, more particularly the centrally situated cells, die, the soft-tissue elements of the graft—periosteum, lining of Haversian canals, and endosteum—show active cellular proliferation and are responsible for the subsequent cellular repopulation of the graft which is complete after 40 days. The bony matrix retains its staining affinity, and by 42 days the picture is that of active living bone with no evidence of any dead bone, as implied in your article.

The autograft at 42 days therefore represents bone formed by the original cell elements of the graft and may well include much of the original bony matrix of the graft. As these cells constitute the essential living part of bone and are largely responsible for the new bone formation it is evident that the autografts survive. The period required for complete recovery varies according to the type of graft, and is naturally longer in dense cortical grafts. By contrast, sections of the bone homografts from 10 days onwards show typical dead bone with empty lacunæ and faintly stained opaque matrix —the classical sequestrum. There is, with an odd exception, no absorption of the dead homografts, which can be recovered 180 days after implantation.

Hutchison's findings correspond to those recently recorded in an experimental study by Ray et al.[9] Ham [10] has also noted the osteogenic activity of the surviving cells of bone autografts.

Both heterotopic bone autografts and homografts induced active osteogenesis by the connective tissue of the host from 10 to 42 days, which then ceased. In the case of homografts this new bone formed by the host tissue died after 42 days and was added to the graft

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1. Mackenzie, E. F. W. *Lancet*, 1952, i, 961.
2. *Ibid*, 1951, i, 1356.
3. Sykes, W. M. *Ibid*, 1952, i, 1112; *Ibid*, Aug. 2, 1952, p. 242.
4. McClure, F. J., Mitchell, H. H., Hamilton, T. S., Kinser, C. A. *J. industr. Hyg.* 1945, 27, 159.
5. Bond, A. M., Murray, M. M. *Brit. J. exp. Path.* 1952, 33, 168.
6. Hutchison, J. *Brit. J. Surg.* 1952, 39, 552.
7. Barth, A. *Arch. klin. Chir.* 1893, 46, 409.
8. Reynolds, F. C., Oliver, D. K. *J. Bone Jt Surg.* 1950, 32A, 283.
9. Ray, R. D., Degge, J., Gloyd, P., Mooney, G. *Ibid*, 1952, 34A, 638.
10. Ham, A. W. *Ibid*, p. 701.

sequestrum. Unlike Urist and McLean,[11] Hutchison found little evidence of host osteogenesis in intra-ocular transplants of bone autografts or homografts, and he concluded that this was due to the absence of marked tissue reaction. Ham is of the opinion that osteogenesis following implantation of bone grafts into muscle is entirely due to the surviving cells of the graft, and not to metaplasia of host connective-tissue cells. While this is not the generally accepted view, it would explain the death of the new bone formed around the implanted bone homograft.

Thus the behaviour of bone grafts in a general way resembles that of other tissue grafts—autografts survive and homografts die (except, of course, cornea and cartilage). The more critical initial test period before the bone autograft "takes" is to be expected because of the difficulty in vascularisation.

Department of Anatomy,
University of Glasgow. G. M. WYBURN.

FEEDING DISORDERS IN INFANTS

SIR,—In his comments (Aug. 16) on Sister Morrison's letter, Dr. Wood introduces a new theme—the advice given in the lay press—possibly because he happens to know that this is the medium for Sister Morrison's work.

She would not wish to reply about the success of her own work, but I think it should be known that mothers constantly write back that after they have followed her advice their babies are contented and progressing well. So far from being "baffled," the mothers are given a sense of reassurance and confidence.

Why should it be doubted that writers for the lay press have just as keen a sense of responsibility—and just the same range of opinion—as other members of their professions? And seeing their advice in type gives them the incentive, and the opportunity, to make it as clear as possible.

Nursery World,
154, Fleet Street,
London, E.C.4. MADELEINE POTTENGER.

BOOKS ON HOSPITALS

SIR,—I beg leave to supplement your correspondent's contribution (Aug. 23) on this subject with the titles of a few excellent publications he has omitted.

The functional evolution and the geographical distribution of early English hospitals is well described in *The Medieval Hospitals of England* by Mary Clay (1909), and in *Houses of Pity* by J. E. Hobson (1926). Two hundred years' history of Dublin's Rotunda Hospital has been recently recorded in two books which were reviewed in your columns.[12] In the same week the *British Medical Journal* published an interesting brief account[13] of the seven centuries' history of Europe's first mental hospital—the Bethlem Royal.

There are also two small books well worth reading which deal with the history and management of most of London's non-teaching hospitals. *The Metropolitan Asylums Board and its Work 1867–1930*, written by Sir Allan Powell, was published by the Board in 1930 and describes the vicissitudes of its 44 fever, mental, tuberculosis, children's, and special hospitals with 24,000 beds. *The L.C.C. Hospitals—a Retrospect* was published by the London County Council in 1949, and carries forward the history of 98 of London's "poor-law" and municipal hospitals with 72,000 beds from 1930 to 1948.

The Ministry of Health, which now controls most of the hospitals in England and Wales, has an unrivalled opportunity, which it should not miss, to produce the most up-to-date book on the hospital history of this country.

London, S.E.1. WILLIAM HARTSTON.

TREATMENT OF PULMONARY TUBERCULOSIS

SIR,—The symposium in your issue of Aug. 23 makes it clear that the treatment of pulmonary tuberculosis at Clare Hall Hospital is based on very sound principles.

There may be disagreement, however, with one of Dr. Macdonald's observations on the use of artificial pneumothorax. He says: "We hesitate to do a pneumothorax . . . of course . . . if there is too little disease." This hesitation would appear to originate in a wish to avoid serious complications, or possibly in a suspicion that the procedure might be unnecessary. But empyema, fistula, and inexpansible lung usually result from the use of pneumothorax treatment in unsuitable cases.[1] When the disease is minimal ("too little"), such complications need not ordinarily be expected. The observed prognosis of minimal pulmonary tuberculosis is not good, between 20% and 80% of cases showing progression during the first 2–3 years after diagnosis.[2–8] Early collapse therapy can improve the prognosis.[9–11] Therefore, neither of the presumed objections to the use of pneumothorax in minimal disease seems valid.

Many patients with minimal tuberculosis are now referred to the chest clinics from mass-radiography units. Adolescents and young adults form the majority of such cases. Progression of disease can be expected in a high percentage of these young people. Their supervision commonly consists in the inspection of serial radiographs taken at intervals of 3 to 6 months. But diffuse bronchogenic spread and cavitation during the intervening months is seen all too often. The advantage of early diagnosis is then lost. Any minimal disease which has shown the slightest tendency to progress whilst closely observed is probably one of "the positive criteria for inducing a pneumothorax" which your leading article seeks.

Poole Sanatorium, Nunthorpe,
nr. Middlesbrough. J. P. ANDERSON.

SIR,—The excellent article by Dr. Simmonds and his colleagues interested and instructed me. I was, however, pained to note the reference to "resection-minded Liverpool." I thought this bogy had been well and truly laid by Coope, but apparently it has to be done again.

There are in Liverpool a number of thoracic surgeons operating at various hospitals in coöperation with chest physicians. The number of different views on tuberculosis and its treatment is probably equal to the number of surgeons or the number of institutions concerned, whichever is the greater. F. R. Edwards and his associates, working at Aintree Hospital, have pushed the indications for resection much further than most people; but, as far as I am aware, they have never claimed that this is anything but a large-scale experiment. Other thoracic surgeons in Liverpool, in common with those in the rest of the country, will await the analysis of their cases and the 5-year follow-up figures with considerable interest, and possibly radical consequences to their future policy in treating pulmonary tuberculosis. Meanwhile, Liverpool remains a geographical area where all forms of treatment for pulmonary tuberculosis are practised, and each case is considered on its merits and the form of treatment is advised that is most likely to ensure success in the particular circumstances.

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11. Urist, M. R., McLean, F. C. *Ibid*, p. 443.
12. Curran, C. P. The Rotunda Hospital—Its Architects and Craftsmen. Dublin, 1946. Browne, O'D. T. D. The Rotunda Hospital, 1745–1945. Edinburgh, 1947. See *Lancet*, 1947, i, 916.
13. *Brit. med. J.* 1947, i, 935.

1. Mitchell, R. S. *Amer. Rev. Tuberc.* 1951, 64, 141.
2. Zacks, D. *Ibid*, 1939, 39, 683.
3. Simon, G. *Brit. J. Radiol.* 1943, 16, 217.
4. Brooks, W. D. W. *Lancet*, 1944, i, 745.
5. Bobrowitz, I. D., Hurst, A., Martin, M. *Amer. Rev. Tuberc.* 1947, 56, 110.
6. Tuberculosis in Young Adults: Prophit Tuberculosis Survey. London, 1948.
7. Chang, R. *Amer. Rev. Tuberc.* 1948, 58, 610.
8. Aspin, J. *Tubercle*, 1949, 30, 8.
9. Wingfield, R. C., Macpherson, A. M. G. *Brit. med. J.* 1936, i, 741.
10. Amberson, J. B. Cited in Prophit Tuberculosis Survey. London, 1938; p. 171.
11. Paine, A. L. *Amer. Rev. Tuberc.* 1951, 63, 644.

I myself find it increasingly embarrassing to have to explain to visitors and colleagues that I meet that I am in no immediate danger of forgetting how to do a thoracoplasty or an adhesion division. A general surgeon accused of being "cholecystectomy-minded" would rightly take this as a reflection on his professional judgment. The suggestion of being "anything-minded" implies that prejudice or obsession has taken the place of scientific judgment. May I please put it on record that this is not the case in Liverpool.

Liverpool. LESLIE J. TEMPLE.

MEGALOBLASTIC ANÆMIA OF PREGNANCY

SIR,—In your issue of Aug. 2 Dr. Israëls and Dr. Da Cunha emphasise the importance of early diagnosis in megaloblastic anæmia of pregnancy, as this disease is not at all rare and can be adequately treated. They state that folic acid remains the treatment of choice, because vitamin B_{12} has been found ineffective against this condition in temperate climates.

We have previously described[1] a case of megaloblastic anæmia in the puerperium reacting to vitamin B_{12}. In this case analysis of the gastric juice showed the presence of free HCl. This excluded the possibility of addisonian pernicious anæmia. Determination of the fat content of the fæces (total fat 50% of the dry weight) pointed to non-tropical sprue. We came to the conclusion that megaloblastic anæmia in pregnancy in the temperate zone may be classified as: (1) addisonian pernicious anæmia, (2) non-tropical sprue, and (3) true megaloblastic anæmia of pregnancy or puerperium.

Since then we have seen a patient of 23, primigravida. She was examined in November, 1950. Her hæmoglobin was then 12·5 g. per 100 ml. In April, 1951, she was admitted to hospital because of severe anæmia, which progressed while she was treated with iron.

The patient was 8 months pregnant. She complained of dyspnœa on exertion, headache, and œdema. She suffered from vomiting, which had improved during the last 2 or 3 weeks. Examination showed a systolic murmur. Liver and spleen were not palpable. The tongue was normal. No signs of polyneuritis or involvement of the central nervous system.

Investigations.—Hb 5·4 g. per 100 ml.; red blood-cells 1,200,000 per c.mm.; white blood-cells 10,000 per c.mm.; smear of peripheral blood showed 14 nucleated red cells (including some megaloblasts) per 100 white cells. Bone-marrow: hyperplastic, megaloblastic.

Fractional gastric analysis (free and total acidity in ml. of 0·1 *N* HCl per 100 ml.): (1) 0/27, (2) 0/5, (3) 0/7, (4) 0/12; after histamine (5) 6/6, (6) 14/30, (7) 28/45, (8) 34/48.

Serum-iron 370 µg. per 100 ml.; blood-bilirubin 0·6 mg. per 100 ml.

Fæces over a 3-day period on a Schmidt's diet: total weight 110 g.; dry weight 30·5% of total weight; total fat 29% of the dry weight.

Glucose-tolerance curve: fasting, 79 mg. per 100 ml., 30 min. 174 mg., 60 min. 149 mg., 90 min. 73 mg., 120 min. 65 mg., 150 min. 74 mg.

Treatment.—She was given 400 ml. of blood, which raised her Hb to 6·2 g. per 100 ml., her red-cell count to 1,500,000 per c.mm., and the hæmatocrit volume to 22·1%. Treatment with vitamin B_{12} was started on April 18; 15 µg. daily was given by injection for three days. On the third day she felt better, and the subjective improvement continued. It was accompanied by a reticulocyte crisis of 17·3% on the ninth day. On May 2 her Hb was 9·07 g. per 100 ml., red cells 2,180,000, and hæmatocrit volume 30%. Vitamin B_{12} was again given (15 µg. every other day) until May 13, when she was delivered of a healthy child.

Blood examination on Jan. 18, 1952, showed Hb 12·8 g. per 100 ml., and red cells 4,710,000 per c.mm.

In this case the normal fat content of the fæces and the normal glucose-tolerance curve excluded the possibility of non-tropical sprue, while the presence of free HCl after histamine is strongly against the diagnosis of addisonian pernicious anæmia.

At the University of Utrecht medical clinic Verloop[2] observed the effectiveness of vitamin B_{12} in similar patients. In the Netherlands at least, there are two groups of megaloblastic anæmia of pregnancy: the first is caused by a deficiency of vitamin B_{12}; and the second by a lack of folic acid. This differentiation is, of course, of practical importance because of the danger of neurological lesions in patients with vitamin-B_{12} deficiency who are given folic acid.

University of Groningen,
Holland. H. O. NIEWEG.

ACHALASIA *v.* CARDIOSPASM

SIR,—Hurst is dead: otherwise he would have replied to your peripatetic correspondent's attack (Aug. 16). Hurst gave up many of the concepts and therapies mentioned long before his death. "The absent acid-barrier in pernicious anæmia" was forgotten in 1928, although I well remember in 1930 Castle, who attended one of Hurst's combined rounds, saying with obvious sincerity that if Hurst had not emphasised the absence of acid and published his supposedly cured case of Addisonian anæmia, he (Castle) would never have thought of doing his experiment of predigesting a steak in a healthy stomach and transferring it to a patient with Addisonian anæmia.

Though Hurst gave up his views about catarrhal jaundice, somewhat obstinately, he never gave up the concept of achalasia. When I do a rectal examination in a patient, if he has a fistula, a fissure, or a thrombosed pile, the sphincter sometimes goes into spasm and this I call anal spasm. In people with a healthy lower gut, the finger usually slips in easily—i.e., there is complete "chalasia." Hurst constantly pointed out that when the mercury tube (I cannot remember his miscalling it a "bougie") passed into the stomach as the sphincter relaxed, the tube was not gripped as it would be in cardiospasm. It was this observation which made him ask Sir Cooper Perry "for a single word to express 'absence of relaxation.'"

This observation I confirmed this morning when I visited a patient who in the past twenty years has passed her tube over 3000 times. This woman of 53 kindly passed her tube while I waited in the next room, and I was able forthwith to show that there was no gripping, or, as she said: "When the tube passes the obstruction, which is rather difficult, there is no difficulty in withdrawing it." She, however, usually keeps it down for five minutes, and she has discovered that this suffices for two to three days of easy swallowing. She has also discovered that it helps to have had a light meal.

Your peripatetic correspondent says that Douthwaite congratulates Avery Jones on excluding "the inept word from his new book." But Avery Jones has not done so. Two of his authors, both surgeons, write thus:

Ronald Belsey (p. 156) says in the differential diagnosis of hiatus hernia from "Achalasia of the cardia. Dilatation of the œsophagus is rare in hiatus hernia, even with stenosis and usual in achalasia. The symptoms are different and the response to octyl nitrite is diagnostic of achalasia"; and Geoffrey Wooller (pp. 179–199) gives achalasia as a synonym for cardiospasm but uses the word cardiospasm "in the belief that spasm of the cardia exists in the majority of patients." although he admits: "The cause of cardiospasm is unknown. Psychogenic trauma is an important factor in initiating its onset."

I am grateful to your peripatetic correspondent for making me do a little research, and rather than try to decry Hurst's work and his disciples as he does I would like to suggest that we get more information on two unsettled points.

Firstly, several people doubt Geoffrey Rake's work,[3] confirmed by E. A. Gallinaro,[4] that achalasia is caused by degeneration of Auerbach's plexus and think this is the effect rather than the cause. Surely it is possible to examine Auerbach's plexus in patients dying from other forms of prolonged obstruction to settle this point, which has been in doubt for twenty-five years.

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[1] Nieweg, H. O., van Buchem, F. S. P., Stenfert Kroese, W. F. *Acta med. scand.* 1952, 142, 45.

[2] Verloop, M. C. Personal communication.

[3] *Guy's Hosp. Rep.* 1926, 76, 145; *Ibid*, 1927, 77, 141.

[4] *Rass. Neurol. veg.* 1947, 4, 464.

Secondly, believing as I do that achalasia is curable by Hurst's mercury tube, the passage of which I admit is unpleasant to many people and well-nigh impossible for children, can we get some idea how often it must be passed ? Psychology plays its part, and I remember how forcefully that was impressed on me in 1924 when as a ward clerk I sat at John Ryle's feet.

> An outpatient, a boy of some eighteen years, on being asked how his achalasia was, said he was much better, had gained in weight, could swallow well, &c. Ryle, not realising that the boy had not finished, pointed out to us how Dr. Hurst had invented this tube and what great advantage the boy had received. Thereupon the boy said he had really come up to say that he had not passed the tube for some weeks when, at a religious meeting, he had received the laying-on of hands. John Ryle immediately said that was the type of discipline so good for us.

Unfortunately I cannot tell the end of the story, but G. Wooller in Avery Jones's book *Modern Trends in Gastroenterology* records instances of "cardiospasm" occurring after psychological trauma, and I am sure there are other "cures" such as the one recorded above. Until we know this we cannot really judge the value of surgical treatment ; we should also know more about the asymptomatic patients—one of whom I know, besides being the headmaster of a public school, is also a distinguished athlete. I feel that Hurst if he were alive would be the standard-bearer of surgeons who operate successfully on this condition ; but he lived in the age of "cardioplasty, œsophagoplasty and œsophagogastrostomy" which, as Wooller says, "are killing operations" ; and even though Hurst persuaded surgeons to operate, they approached the cardia abdominally, and so had no real successes.

If I have written in a partisan manner it is because, as John Ryle said in the introduction to Hurst's autobiography : "To know Hurst and his enthusiasms, his generosity, his courage and his foibles, was an education in itself. All who worked with him regarded him with admiration and affection." Nevertheless medicine demands the most rigid disciplines and so, casting aside personal considerations, I say my strongest conviction is that the commonest cause of "idiopathic" enlargement and dilatation of the œsophagus is failure of the cardiac sphincter to relax, and this syndrome merits the word "achalasia."

Rugby. R. E. SMITH.

CHLOROPHYLL AS DEODORANT

SIR,—The phrase "as dark as the inside of a cow" is traditional, and it is probable that our own insides are about equally dark though this does not have the authority of tradition. Photosynthesis, as the name implies, depends on light, and it is only after illumination that chlorophyll-containing systems are able to bring about the reaction between carbon dioxide and water that releases oxygen. Your suggestion (Aug. 23) that the alleged deodorising action of chlorophyll could be due to oxygen formation seems therefore a little improbable. Furthermore this action has not yet been brought about by isolated chlorophyll but only by fairly fresh chloroplast preparations.

But an explanation of the phenomenon might well be postponed until it is certain that there is a phenomenon to explain. Can no-one produce a statistically significant number of "second-best friends" on whom a proper experiment could be tried ?

Rothamsted Experimental Station,
Harpenden, Herts.
N. W. PIRIE.

SIR,—In your leading article you reproduce from the *News Chronicle* of July 30 a couplet to the effect that goats, in spite of the fact that they feed all day long on chlorophyll, tend to be odorous. Whilst we are not disputing this fact, we would remark that only water-soluble derivatives have been used as deodorants. Chlorophyll, as found in nature, is not water-soluble and it has to be specially processed in order to render it so. All the claims concerning the deodorant properties of chlorophyll have been based on this water-soluble variety.

Ashe Laboratories Ltd.,
Leatherhead.
L. DEADMAN
Chief chemist.

FUNCTIONAL DISORDERS OF THE SMALL INTESTINE

SIR,—With the increasing advocacy of the operation of partial gastrectomy in this country, functional disorders of the small intestine seem likely to become of importance, and it is good to see Dr. Morton Gill and Dr. Falle drawing attention to them in their article (Aug. 23).

In some people partial gastrectomy appears to uncover a latent tendency to a small-gut motility disturbance; in others the functional disorder undoubtedly precedes the formation of a peptic ulcer and is present before gastrectomy. In these unfortunates disastrous results are inevitable ; it behoves us to make sure before recommending operation that the motor function of the small gut is stable, especially if the patient is a woman.

Harrogate. A. J. GLAZEBROOK.

Obituary

JOHN GEOFFREY CUTTS

M.R.C.S.

Dr. Geoffrey Cutts, medical officer to the Northwood, Pinner and District Hospital, died in London on Aug. 18, from poliomyelitis, at the age of 37.

He was educated at Oakham in Rutlandshire, and at St. Mary's Hospital, where he qualified in 1940. After holding house-appointments elsewhere, he returned to St. Mary's as resident anæsthetist in 1942, and the following year he was appointed house-surgeon to the surgical unit at Harefield Chest Hospital. In 1944 he joined the Royal Navy, and he served as E.N.T. specialist in H.M. Hospital Ship *Tjitjilengka* in the Far East. At the end of the war he joined an old-established firm of general practitioners in Hatch End, and was soon appointed to the staff of Northwood Hospital.

W. R. writes : "Northwood Hospital is one of those centres where general practitioners work together as a happy team and, thanks to his early training in anæsthetics and E.N.T. work, Cutts proved himself a most accomplished specialist in both those departments. Not a man to be hurried, he showed dignity and a steady approach to his work. A little shy, slightly stubborn, he never jumped to hasty conclusions or reached a decision without careful thought. The best time to see him was at a difficult obstetric case. It is there that patience may be a supreme gift, and Geoffrey Cutts possessed it more than most of us. In the last few years of difficulty and transition he acted as secretary to the medical staff with conspicuous success. Good general practitioners are not born every day, and we have lost one of the best of them at a tragically early age."

Dr. Cutts leaves a widow and two young children.

Births, Marriages, and Deaths

BIRTHS

GOLD.—On Aug. 28, at South Hill Farm, Eastcote, Pinner, to Betty wife of Dr. Stephen Gold—a son.

HARDMAN.—On Aug. 28, at the Churchill Hospital, Oxford, to Philippa (née Woolf), wife of Dr. Maurice Hardman—a son.

WOLFE.—On Aug. 30, at *University College Hospital*, London, W.C.1, to Lesley (née Fox), wife of Mr. H. R. I. Wolfe, M.S., F.R.C.S.—a son.

DEATHS

HUNNARD.—On Aug. 30, at Dulwich Wood Avenue, London, S.E.19, Arthur Hunnard, M.B. Lond., aged 81.

HUNTER.—On Aug. 27, Charles Stewart Hunter, L.R.C.P.E., D.P.H., F.R.S.E., of 12, Beemead Avenue, Streatham, S.W.16, late of Darvel and Carnoustie.

STEPHENSON.—On Aug. 26, at West Haddon, William Arthur Stephenson, M.R.C.S., aged 84.

Notes and News

CAPITAL EXPENDITURE ON HOSPITALS

In calling on hospital authorities to submit capital estimates for 1953–54, the Ministry of Health announces (R.H.B. [52] 97) adjustment of the previous formula, particularly to help those regions where the need seems to be greatest. Boards are to submit estimates, within their allocations, which are to be in gross figures of which boards will be authorised to spend 80% during the year. The additional percentage has been included to allow greater flexibility within the programme. The following are the allocations to regional boards in 1953–54:

Region	*£000*
Newcastle upon Tyne	526
Leeds	475
Sheffield	721
East Anglia	248
North-west Metropolitan	600
North-east Metropolitan	468
South-east Metropolitan	499
South-west Metropolitan	787
Oxford	235
South Western	429
Birmingham	715
Manchester	681
Liverpool	325
Welsh	478

To boards of governors the allocation will be in the range of £40,000–80,000 for undergraduate teaching hospitals and of £10,000–35,000 for postgraduate teaching hospitals.

Boards are to assume that the allocation for 1954–55 will not be greater than that in 1953–54. The Ministry draws attention to the urgent need to increase the provision for mentally ill and mentally defective patients. It also suggests that boards, in planning their capital programme, should have particular regard for works which may bring about some decrease in maintenance costs. The Ministry will continue to make special provision from a central reserve for certain large schemes that are now being carried out.

SENIOR REGISTRARS IN THE NORTH-WEST METROPOLITAN REGION

According to the Ministry of Health's revised allocation, this region is to have substantially fewer senior registrars than at present. The regional hospital board has accordingly been considering how they can most fairly cut their coat to fit their cloth. They have decided to give notice to all the senior registrars now under contract with them, to take effect on March 31, 1953. Before that date the reduced number of posts will be readvertised and all the present senior registrars will be free to apply for them.

The board also proposes to appoint a number of "assistant physicians" and "assistant surgeons."

> The holder of one of these posts will have the status of consultant and be on the consultant salary scale, but he will be attached to a particular firm. He will have his own beds but the general scope of his responsibility will be outlined by the head of the firm. The appointment will be on a whole-time basis for five years with the option of transferring to a part-time appointment for the maximum number of sessions at the end of that period.

The senior administrative officer assured the board that he had received from the chairman of the Joint Committee of Consultants and Specialists and the Royal Colleges a verbal assurance that these proposals were acceptable to them.

The board has agreed to a proposal made by the board of governors of St. Mary's Hospital for an interchange of senior registrars, between selected regional hospitals and St. Mary's Hospital. For the present it is suggested that six senior registrars in medicine and six senior registrars in surgery should spend two years of their appointments at St. Mary's Hospital and two years in regional hospitals. The following regional hospitals have been asked to take part in the scheme: Paddington Hospital, Ashford Hospital, and West Middlesex Hospital.

Royal College of Obstetricians and Gynæcologists

Prof. Miles H. Phillips is to deliver the William Meredith Fletcher Shaw lecture at 1, Wimpole Street, London, W.1, at 2.45 P.M. on Friday, Sept. 26. He will speak on Percivall Willughby's *Observations* in Midwifery.

Institute of Laryngology and Otology

On Friday, Sept. 12, at 5 P.M., at the institute, 330, Gray's Inn Road, W.C.1, Dr. Norton Canfield, of Yale University, will open a discussion on the Analysis of Clinical Hearing Records.

Royal Institute of Public Health and Hygiene

On Wednesday, Oct. 15, at 4.30 P.M., Dr. W. D. M. Paton will deliver the Bengue lecture at the institute, 28, Portland Place, London, W.1. He is to speak on the Uses of the Methonium Compounds.

Postgraduate Courses for General Practitioners at Cambridge

During 1952–53 a series of one-day symposia for general practitioners *will be held* on Saturdays at Addenbrooke's Hospital, Cambridge. Each symposium will consist of three to five lectures or lecture-discussions and demonstrations of clinical cases or modern methods. The following programme has been arranged: nervous diseases (Oct. 25); obstetrics and gynæcology (Nov. 22); surgical diagnosis and minor surgery (Dec. 20); radiotherapy (Jan. 24); dermatology (Feb. 28); orthopædics and fractures (March 28); cardiovascular diseases (April 25); common fevers (May 30); pædiatrics (June 27); diseases of the ear, nose and throat (July 25): diseases of the eye. Further information may be obtained from the secretary of the Medical School, University of Cambridge.

British Postgraduate Medical Federation

On Tuesday, Oct. 7, at 4.45 P.M., at the Senate House of the University of London, Malet Street, W.C.1, Prof. J. Z. Young, F.R.S., is to give the opening lecture of the 1952–53 course on the Scientific Basis of Medicine. He is to speak on the Influence of Language on Medicine.

King's College Hospital, London

Dr. F. M. R. Walshe, F.R.S., will deliver the opening address of the session at the medical school, Denmark Hill, S.E.5, on Friday, Oct. 3, at 3 P.M. The annual dinner of past and present students will be held at the Savoy Hotel, W.C.2, on Saturday, Oct. 4, at 7.45 P.M.

University College Hospital, London

On Tuesday, Oct. 7, Sir Wilson Jameson will deliver the opening address of the session at the medical school, University Street, W.C.1, at 2.50 P.M. A course of postgraduate demonstrations for old students of the hospital will be given at the hospital on Oct. 30 and 31. Dr. F. M. R. Walshe, F.R.S., will take the chair at the annual dinner, which is being held at the Savoy Hotel at 8 P.M. on Oct. 31.

Barclay Prize

The late Dr. A. E. Barclay bequeathed £1000 to the *British Journal of Radiology*. The council of the journal has decided to use this bequest to offer a Barclay prize. The prize will normally be awarded annually to the author of the best account of original work in diagnostic or experimental radiology.

> The first award will be made in 1953, and candidates should inform the e[illegible] essay, with a brief indication of [illegible] han Sept. 30, 1952. The closing [illegible] 31, 1952. Further particulars [illegible] etary, 32, Welbeck Street, London, W.1.

Prescriptions in July

The Ministry of Health announces that in England and Wales during July the number of prescriptions declared to be submitted was 15,326,000, which was a decrease of 5·5% on the total for July, 1951. The number of forms declared to be submitted was 9,127,000 (decrease 11·6%); and the ratio of prescriptions to forms was 1·68 (1·57 in July, 1951). This year prescriptions for July were 909,000 more than in June. In 1951, July prescriptions were less than in June (as is usual); the difference was about 833,000.

Remuneration of General Practitioners

For the quarter ending Sept. 30, 1952, practitioners are to receive remuneration at the same rate as under the old arrangements together with a provisional supplement, proportional to the first amount, from the money made available by the Danckwerts award (E.C.O. 68/52). It is proposed to apply the same method of payment to the quarters ending Dec. 31, 1952, and March 31, 1953. The sum which has been paid into the central pool as a result of the Danckwerts award is at present provisional. It will be finally determined after March 31, 1953, and any necessary adjustments to the amounts already paid to executive councils will be made then.

As an interim measure the drug capitation fee is to be increased from 6*s.* 6*d.* per annum to 9*s.* 9*d.* with effect from April 1, 1952.

Congress on Rheology

The second International Congress on Rheology will be held at Oxford from July 26 to 31, 1953, under the presidency of Sir Geoffrey Taylor, F.R.S. Further particulars may be had from Mr. G. W. Scott Blair, D.SC., the University, Reading.

London College of Osteopathy

A postgraduate course for registered medical practitioners to be held at the college will begin in October. Further particulars may be had from the secretary of the college, 25, Dorset Square, London, N.W.1.

Pakistan Medical Association

Pakistani doctors in this country have formed a United Kingdom branch of this society. The following office-bearers have been elected: president, Dr. S. D. Jouhar; secretary and treasurer, Dr. M. Shafi (19, Bernard Street, London, W.C.1); committee members, Dr. T. H. Moghul, Dr. A. M. Akram, Dr. K. Y. Ansari, Dr. Saif-ud-Din Ahmad, and Dr. Mohd Abdul Rashid.

International Congress for Microbiology

The sixth International Congress for Microbiology will be held in Rome from Sept. 6 to 12, 1953, under the presidency of Dr. V. Puntoni. Further particulars may be had from the secretariat of the congress, Istituto d'Igiene (G. Sanarelli), Città Universitaria, Rome.

Course on Rehabilitation in Scandinavia

A group-training course on the Rehabilitation of the Adult Disabled is to be held in Sweden, Finland, and Denmark from Sept. 8 to Nov. 8. It has been organised by Dr. Harold Balme under the auspices of the United Nations, the World Health Organisation, and the International Labour Organisation.

Control of Medical Man-power

Mr. A. Lawrence Abel has replaced Mr. J. B. Oldham as a representative of the Royal College of Surgeons on the Central Medical Recruitment Committee for England and Wales; and Sir William Marshall has replaced Mr. Thomas Hunter as a representative of the Scottish Executive Councils' Association on the Scottish Central Medical Recruitment Committee.

Orphans' Pensions and Children's Allowances

In view of the increase in the family allowance rate to 8*s.* a week, the Minister of National Insurance has made regulations (1952 S.I. no. 1559. H.M. Stationery Office. 3*d.*) adjusting benefits for children payable under the old Contributory Pensions Acts. People receiving an orphan's pension or child's allowance and having at least two children in the family should inquire from the local national insurance office whether they are eligible for an increase. The regulations do not affect orphans for whom a guardian's allowance or industrial death benefit is in payment.

Unusual Foods for Human Consumption

The Nutrition Society is holding a conference on this subject at Bedford College, London, N.W.1, on Saturday, Oct. 18, at 10.15 A.M. The following papers are to be read: Seaweeds and their Value in Food-Stuffs (W. A. P. Black); Mushrooms and Toadstools (J. Ramsbottom); Insects as Food (W. S. Bristowe); Indigenous Foods of Central America (F. Aylward); Diet of Canadian Indians and Esquimeaux (H. M. Sinclair); Food of Australian Aborigines (G. H. Bourne); Protein in the Diet of the Isoko tribe of the Niger Delta (B. M. Nicol). Further particulars may be had from the programmes secretary, Mr. R. J. L. Allen, Monkhouse & Glasscock Ltd., Snowsfields, London, S.E.1.

Present Problems in Nutrition Research

The International Union of Nutrition Sciences is holding a symposium on this subject at Basle from Oct. 1 to 4. The speakers will include: Dr. J. Trémolières (Paris), Prof. A. I. Virtanen (Helsinki), Dr. D. P. Cuthbertson (Aberdeen), Prof. E. Crasemann (Zürich), Prof. E. J. Bigwood (Brussels), Prof. K. Lang (Mainz), Prof. K. Bernhard (Basle), Prof. K. Thomas (Göttingen), Prof. O. Högl (Berne), Prof. E. Abramson (Tomteboda, Sweden), Mr. S. J. Folley, D SC., F.R.S. (Reading), Prof. A. B. L. Beznák (Birmingham), Mr. L. J. Harris, D.SC. (Cambridge), Prof. H. Dam (Copenhagen), Prof. H. D. Cremer (Mainz), Prof. V. Demole (Lausanne), Dr. W. R. Aykroyd (F.A.O., Rome), Prof. A. G. van Veen (F.A.O., Rome). Further information may be had from the secretariat, c/o *Experientia*, Verlag Birkhäuser A.G., Basle, Elisabethenstrasse, 15, Switzerland.

Medical Mycologists

The committee on medical and veterinary mycopathology of the International Association of Microbiologists has compiled an international address list of medical mycologists. Copies (1*s.*) may be had from the Commonwealth Mycological Institute, Kew, Surrey.

No. 2 (Br.) General Hospital

The sixth reunion dinner of this hospital will be held at Simpson's Restaurant, Strand, London, W.C.2, on Saturday, Oct. 4. Tickets may be had from Dr. J. H. Easton, 25, Biddenham Turn, Bedford.

Graduated Beakers for Injectable Fluids

A new British Standard has been published (B.S. 1847:1952) for graduated beakers for injectable fluids (for hospital use). This specifies graduated heat-resistant glass beakers of 50 ml., 100 ml., and 300 ml. capacity. Copies of the standard (price 2*s.*) may be obtained from the British Standards Institution, Sales Branch, 24, Victoria Street, London, S.W.1.

King Edward's Hospital Fund are now issuing a second edition of their series of catering circulars. The following are available: Use of the Meat Ration, Care of Catering Equipment, Layout and Design, Sources of Waste in Catering, and Rations and Rationing. The circulars are issued free to hospitals, and copies can also be obtained (1*s.* post free) from the offices of the Fund, 10, Old Jewry, London, E.C.2.

During September Dr. Earl R. Loew, professor of physiology in Boston University School of Medicine, is acting as guest professor in the department of pharmacology and therapeutics, St. Andrews University Medical School, Dundee.

Prof. Robert [illegible] mas Anderson, and Dr. W. C. Cockburn are [illegible] ing September, under the [illegible] of the World [illegible] conduct refresher courses in the control of [illegible] at the main medical centres there.

The headquarters of the Ministry of National Insurance are now at 10, John Adam Street, London, W.C.2 (Telephone: Whitehall 9066).

Appointments

BARBER, J. M., M.D. Belf., M.R.C.P.: consultant physician, Ards Hospital, Newtownards and Bangor Hospital, Bangor.

BATES, J. L., M.B. Lond., M.R.C.P., D.P.M., D.C.H.: asst. psychiatrist (S.H.M.O.), Borocourt Institute for Mental Defectives, near Reading.

BULSTRODE, J. C., M.R.C.S., D.M.R.: consultant radiologist, Princess Elizabeth Hospital, Guernsey.

DE FONSEKA, C. P., M.B. Ceylon, F.R.C.S.: surgical registrar, Bath group of hospitals.

EDGCUMBE, J. O. P., M.A., M.D. Camb.: consultant pathologist, Exeter clinical area.

EDWARDS, C. H., M.R.C.P.: clinical asst. (part-time), department for nervous diseases, St. Mary's Hospital, London.

FITZMAURICE, W. J., M.B. Birm.: appointed factory doctor, Alcester district, Warwickshire.

GUILD, Euphemia, M.B. Edin., D.P.H.: asst. school M.O., Huddersfield.

JONES, H. M., M.B. Lond., F.R.C.S., D.L.O.: part-time consultant in otolaryngology, Royal Eye and Ear Hospital, Bradford.

MAITLAND, D. R., M.B. Edin., F.R.C.P.E., D.D.R.: consultant radiologist, radiological department, Royal Infirmary, Edinburgh.

MULHALL, P., M.B. Dubl.: asst. che [illegible] and [illegible] ors Radnorshire area, with clinical [illegible] Sanatorium and the Adelina Patti [illegible]

SINCLAIR, W. W., M.B [illegible]

STEWART, I. S., M.D. I [illegible] the Bingley, Keig [illegible] at the Hospital, [illegible] Grassington.

ZALESKI, WITOLD, M.B. Polish School of Medicine, Edin.: asst. psychiatrist (S.H.M.O.), Pewsey Hospital for Mental Defectives.

University College Hospital, London:

GREAVES, D. P., M.B. Sheff., F.R.C.S., D.O.M.S.: consultant ophthalmic surgeon.

KINGDOM, L. G., M.B. Camb., F.R.C.S.: consultant E.N.T. surgeon.

POND, D. A., M.D. Camb., M.R.C.P., D.P.M.: consultant physician, department of psychological medicine.

East Anglian Regional Hospital Board:

JUBY, H. B., M.B. Lond, D.L.O.: E.N.T. registrar, Norfolk and Norwich Hospital.

SUTTON, P. H., M.D., B.SC. Lond., M.R.C.P.: consultant chest physician, Norwich area chest clinic.

WORKMAN, J. M., B.M. Oxfd: senior registrar in chest medicine, Ipswich area chest clinic.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

PROGRESS IN THE TREATMENT OF BREAST CANCER*

D. W. SMITHERS
M.D. Camb., F.R.C.P., D.M.R.
PROFESSOR OF RADIOTHERAPY IN THE UNIVERSITY OF LONDON AT THE ROYAL CANCER HOSPITAL

I HAVE chosen the subject of Progress in the Treatment of Breast Cancer for several reasons, chiefly because it was this disease which prompted the foundation of this lecture, but also because it provides a good illustration of the theme, within the general title laid down, which I think most requires discussion at the present time. This theme is the need for a return from the "universal cause and cure" attitude, which has inspired so much experimental cancer research and has widely infected the medical profession, to the clinical view of the human problem which it really is. We are in danger of becoming bemused by a wealth of disconnected and impressive scientific detail into believing that the research-worker is nearer to the problem than the doctor, when the reverse is the case.

The clinical view, however, needs to be revitalised so that advancement in knowledge may find a practical expression helpful in prevention and treatment. The oversimplified clinical view which has so long been the basis of our treatment methods has led us into a far too rigid and largely false division of cancer patients into those in whom we must make as rapid and as drastic an attempt at cure as possible, and those whom, because we regard the situation as hopeless, we abandon either to a half-hearted attempt at palliation or to the quacks who provide the encouragement we fail to give.

On Progress

Halsted looking back in 1897 concluded that up to that time no woman with breast cancer had ever been cured. There are those today who think that not only was he right then but that there has been little fundamental change in the situation since his time. They wave aside our survival-rates, the evidence which their predecessors in scepticism had demanded from us, point to our failure to make a drastic reduction in the general breast-cancer death-rate, assure us that there are no grounds for our fond belief that the earlier we give our treatment the greater the chance of cure, and assert that those patients whom we so carefully pick out to treat would live as long if we did nothing. These people are not clinicians, not theirs the daily decision of what to do for Mrs. Jones who has arrived with a frightened husband, an anxious daughter, and a lump in the breast. They are pathologists, hygienists, biometricians, and statisticians, the pyrrhonists of medicine whose facts are not regularly warmed by compassion. It is most important that we listen because we may learn. They will at least keep us from complacency, though those of us who regularly deal with cancer patients are not lightly to be accused of this failing. We may, however, comfort ourselves with the assurance that their figures do not contain the whole of truth and that they are in some danger of coming to know the significance of everything and the value of nothing.

If we are to allow ourselves to speak of progress we must take a realisatic view of the past, examine the basis for our present beliefs and practice, and plan the future so as to promote the best interests of our patients and not those of surgery, radiotherapy, chemotherapy, or even the Registrar-General's annual report.

RELIEF OF SUFFERING

In looking back over the past for signs of progress I would put first relief of suffering. This is not something we can arrange on a table or fit into a chart. Surgery removes the anxiety of the presence of a lump in the breast, and, as judgment has improved, has continued to prevent the discomfort of ulceration while steadily reducing the incidence of local recurrence. We cannot compute a figure to express the value of hope supplied or of relief from the worry, pain, and distress which would have gone with the steady local advance of a tumour. We cannot put these benefits into a survival-rate for patients who develop distant metastases and live no longer than they would have done untreated. Surgery, looking back over the years, has solid cause to congratulate itself on the relief of suffering it has achieved for patients with breast cancer.

Radiotherapy in its comparatively short life has already established a claim to be considered the most valuable means of palliation at our disposal for patients with malignant disease. It assays one of the most difficult tasks in medicine. It is confronted daily by human tragedy which makes incessant demands for cheerful reassurance or gradual enlightenment—demands that tax our humanity, understanding, and ingenuity to the full. It requires an acquaintance with a wide field of clinical medicine and the ability to work closely, harmoniously, and often most unselfishly, with many different surgeons. The safety of the patients and of the workers in these departments, as well as the efficient conduct of treatment, cannot be assured without a high degree of technical proficiency in a complicated branch of applied science. The degree of progress in the relief of suffering of patients with breast cancer for which it has been responsible can be appreciated at once if we consider how we should now get along without it in those hospitals where hundreds of these patients present themselves for our help each year.

Surgical castration was used before X rays were discovered; ovarian irradiation has been employed for thirty years; and hormone treatment has for the past fourteen years come to join surgery and radiotherapy in the treatment of breast cancer patients. After all this time we are still uncertain about their future possibilities. We can, however, see relief obtained quite dramatically at times which was not obtainable before, and is still not obtainable by any other means. Great interest is aroused by the chance to influence disseminated tumours either directly or by alterations in the environment in which they grow. The possibility of learning more about the control of growth and of adding to the efficiency of our tumour treatment methods that hormone therapy has provided is a spur and a challenge.

All this I regard as good evidence of progress.

LONGER SURVIVAL

I have taken relief of suffering first because it seems to me to be one of the chief duties of medicine; but we like to think that we save life and persist in judging our efforts by the sometimes dubious criterion of survival. The only continuous record of survival of all new patients with breast cancer attending one hospital since the introduction of serious attempts at treatment that I know of is that of the Massachusetts General Hospital (Taylor 1949). This remarkable record is almost complete from 1894 to 1940 (fig. 1). If we place these results in a time relationship with those obtained in other hospitals where all new patients seen, whether treated or not, have been included, we can see that it is a fair representation of the state of affairs in such centres

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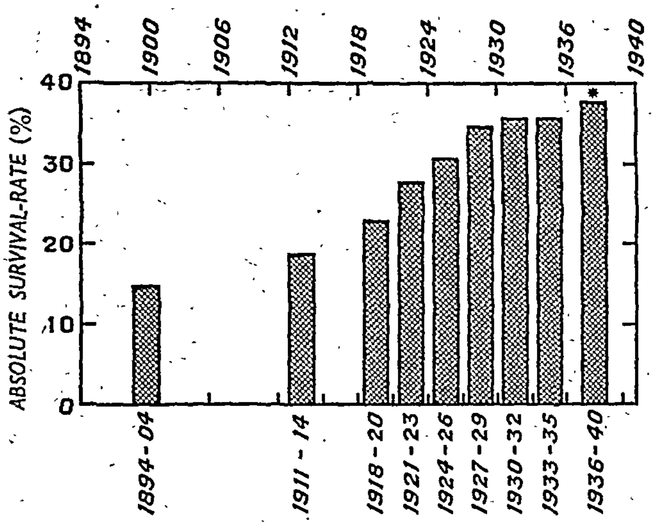
* The First Dorothy Platt memorial lecture, given at King's College Hospital Medical School on July 1, 1952. This lecture was established by the late Mr. J. B. Hunter, to whom Miss Dorothy Platt gave a donation to be used for the advancement of the knowledge of cancer.



*The figure of 38% for 1936–40 is based on the assumption of an operability-rate of 75% for those years, it having varied from 71% to 80% during the preceding 40 years and the total new cases seen for 1936–40 not being in the text.

Fig. 1—Results of treatment in patients with cancer of the breast attending the Massachusetts General Hospital from 1894 to 1940, calculated from the "total primary cases."

(fig. 2). What it shows is that the survival-rates of all patients with breast cancer seen in certain hospitals which report their entire material, in several countries, has markedly improved. It does not show that such an improvement has been general and it does not show that the improvement has been due to the treatment given. These survival-rates are obtainable from only a few centres, and they are the ones, as shown by their interest in recording and by the knowledge of their results which they have had to guide them, in which improvement in treatment is likely to have occurred, but also, because of their reputation, to which an increasing proportion of earlier cases is likely to have been referred. It does show that in such centres the chance that a patient attending with breast cancer will survive five years has probably been more than doubled in the last thirty years.

This improvement could be due to a number of things. It could be due to a change in the selection of patients attending the hospitals which record their results; it could be due to a change in the type of tumours developing, with a swing towards a less malignant character; it could be due to an improvement in speed of diagnosis and in time of starting treatment; it could be due to an improvement in diagnosis resulting in the inclusion of more less-malignant tumours in the total recorded by adding some which had previously either been missed or regarded as non-malignant; it could be due either to improvement in the methods of treatment themselves or to a better selection of treatment method for each individual patient; lastly, it could be due to some combination of these factors.

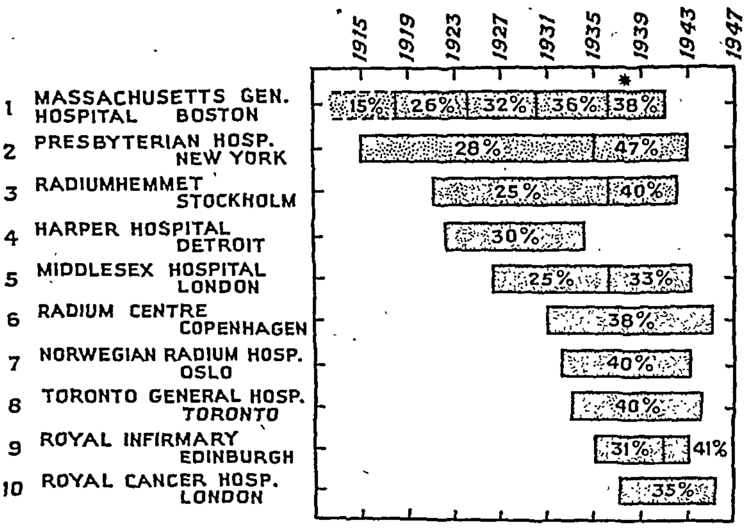
Change in Malignancy of Tumours

It would be difficult to prove or disprove that the character of breast cancer has changed with the years, tending to become less malignant. Histological grading does give an indication of malignancy, but if we were to try to assess such a trend by comparing the proportions of cases in each histological grade from time to time we should be confused by differences in grading methods and skill and, even more important, by differences in the proportions of tumours graded. Since accurate grading is not possible with small pieces of tumour it can only be done on operable patients whose tumours are heavily weighted towards the more differentiated. Since grading is an arbitrary division into sections of a continuous spectrum of degree of differentiation, usually arranged to have a large central group with smaller groups on either side, it is not easy to observe any gradual change merely by listing from time to time the proportion found in each.

The degree of clinical advancement of the disease at the time the patients are first seen is in part a reflection of the malignancy of the tumours concerned, and the fact that the operability-rate at the Massachusetts General Hospital has not changed in [illegible] years suggests that there has been no marked trend towards a diminution in malignancy. An improvement in stage distribution has occurred, however, in some other centres, notably Radiumhemmet, corresponding with their improvement in results, and it is debatable how far such trends may be due to earlier diagnosis, better selection, or alteration in character of the tumours. There does not seem to be any real evidence on which we would be justified at present in making the assumption that the character of breast cancer is changing.

Improved Diagnosis

Improved diagnosis may have resulted in the inclusion of some patients omitted altogether in the past, or some tumours previously regarded as non-malignant. If so, there may have been a change, not in the nature of the disease, but in the selection of an increased proportion of more favourable cases in the groups reported. Certain benign lesions of the breast may simulate cancer—e.g., ad[illegible] fat necrosis, tuberculous mastitis, the b[illegible] named granular cell "myoblastoma," and plasma-cell mastitis—and some circumscribed carcinomas may be mistaken for be[illegible] tumours or cysts. On balance improved diagnosis should tend to detect and so [illegible]



*On the assumption that the operability-rate has not changed and that the total number of new patients seen during this period was 527.

Fig. 2—Variation of absolute survival-rate with date of treatment in patients with cancer of the breast.

(1) Taylor 1949. (2) Haagensen and Stout 1942, Haagensen 1949. (3) Berven 1949, Nohrman 1949. (4) Evans and Leucutia 1939. (5) Truscott 1947, Windeyer 1949. (6) Kaae and Nielsen 1951. (7) Engelstad 1948. (8) Richards 1948. (9) McWhirter 1948, 1949. (10) Smithers et al. 1952.

ore non-malignant tumours which might have been cluded in the past, than discover and so include alignant tumours which might have been omitted.

An important influence here might be a real change of pinion about a group of tumours formerly regarded s benign and now thought of as malignant. I know f no such general swing of opinion in breast cancer, hough there are considerable differences in interpretaon between pathologists, particularly with regard to the ividing line between duct papillomas and duct carciomas. There does not seem to be good evidence that nproved methods of diagnosis have increased the roportion of the less malignant tumours in the patients ecorded as having breast cancer though it would be ifficult to show that this were not so.

eduction of Delay in Starting Treatment

Those who are most persistent in telling us that there s no evidence of improvement in survival due to treatment also maintain that early diagnosis makes no difference to the prognosis. This is not so. Prognosis robably depends more on the type of tumour that a atient develops than on any other factor since this so rgely determines the degree of advancement of the isease by the time the patient starts treatment (see able). Patients with slow growing breast tumours may resent themselves at hospitals for the first time having oticed a lump for many months and still survive for any years after treatment. A group of patients with ng histories will in fact contain a high proportion with e less malignant tumours, since if they had developed ore malignant ones at the same time and had had no eatment they would have been dead. With the more alignant tumours early treatment is of great importnce. Many will have metastasised before the patient first seen but the sharp deterioration which occurs survival time with histories of three months or more an indication of the importance of speed in this group.

Unfortunately there is not much real evidence of any cline in the period of delay which occurs between ticing the first symptom and starting treatment. gures giving the change in average delay do not give clear picture of the important issue, since it is only ring the first two or possibly three months that delay of much importance. Quite a few patients with a od prognosis and histories of two, three, or more ars may well produce a misleadingly high figure for the erage delay.

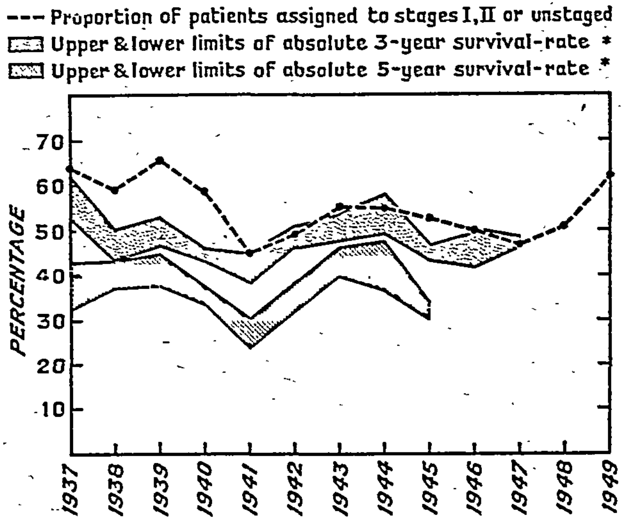
anges in Selection of Patients

The selection of patients attending the hospitals ere complete records are kept and where results are blished may well account for the differences in survivales between them. To see if it may not have accounted the improvement in results over the years within one hospital we need evidence that this improvement has not merely followed a change in stage distribution. We have just seen that there has been no change in operability-rate at the Massachusetts General Hospital in fifty years. At other centres the position is different; at Radiumhemmet for instance the proportion of early cases increased from 50% to over 70% for the periods 1921–35 and 1936–41. In my own hospital there has been no steady change in the stage distribution, but since 1937 there have been fluctuations from year to year. A decline in the percentage of early cases during the first war years was clearly reflected in a corresponding fall in survival-rate (fig. 3). Definitions of staging and of operability are sadly lacking in uniformity, and comparisons are most difficult. It is clear, however, that the results obtained are closely dependent on the material treated and that alteration in this alone may well account for much of the change in survival-rate which, when it moves in the right direction, we attribute to our therapeutic skill.

IVIVAL OF PATIENTS WITH OPERABLE BREAST CANCER CCORDING TO AXILLARY LYMPH-NODE INVOLVEMENT AND RADE OF MALIGNANCY OF TUMOUR

sed on 482 patients seen at the Royal Cancer Hospital, 7–1950 for whom the necessary details were recorded. Graded by Dr. M. Thangavelu.)

ade	Lymph-nodes not involved		Lymph-nodes involved		Proportion of patients with lymph-nodes involved
	(No. of patients)	% surviving: 5 years 10 years	(No. of patients)	% surviving: 5 years 10 years	
I	(45) ..	90·6 68·0	(37) ..	77·8 29·5	45%
I	(96) ..	74·4 57·6	(224) ..	34·0 14·9	70%
I	(12) ..	28·2 28·2	(68) ..	6·2 0·0	85%



*According to whether untraced patients are regarded as alive or dead.

Fig. 3—Results of treatment of patients with cancer of the breast at the Royal Cancer Hospital set in relation to variation in proportion of patients in early stages.

A DOWNWARD TREND

There are a number of reasons why there has been no great fall in the general mortality-rate from breast cancer. It is not in itself an argument against treatment having improved in the better centres, since they deal with only a small proportion of the total and since no more than a gradual and limited improvement can be expected with existing methods. There are also difficulties with death certification since the tendency to record death as due to breast cancer in any patient who has once had the disease is so strong. Until 1940 in fact, the Registrar-General's office often changed the recorded cause of death to cancer when this was mentioned as a subsidiary cause by a doctor who had himself attributed the death to something else. It is going to be difficult to judge the effect of treatment by changes in mortality-rates if we are never going to let a patient who has once had breast cancer die of anything else. With all these difficulties, however, if a correction is made both for the growth of the population and its increasingly adverse age composition a slight downward trend in mortality-rate for England and Wales appears.

Survival without Treatment

Accurate data on the duration of life in patients with untreated breast cancer would be most valuable. The published work agrees in suggesting that the average time from first symptom to death is about three years.

Probably many variables may influence the expansile auricular pulsation. Elkin et al.[2] suggest that the following factors are relevant: left auricular size, flexibility and elastic stretch of the auricular wall, rate of auricular diastolic filling from the pulmonary veins, presence of mural thrombus, irregular rhythm, transmitted thrust from a vigorous right auricular expansion in tricuspid incompetence, and the systolic contracting impulse of a hypertrophied right ventricle. Of their 29 patients with mitral stenosis who showed this radiological sign 14 had no systolic murmur and only 8 were thought on clinical evidence to have mitral incompetence. All 29 patients underwent valvotomy; and in 5 of the 14 without systolic murmurs mitral incompetence was proved at operation by a palpable regurgitant jet on the surgeon's finger. This finding was evidently related closely to the blood-pressure level recorded at the time of operation—an interesting observation that deserves further attention. Elkin et al. noted that the regurgitant stream was stronger when the blood-pressure was higher, and its absence in some cases, with a valve not necessarily fully competent, could be explained by diminished ventricular strength at the time.

The anomaly in mitral stenosis of systolic auricular expansion, seen radiographically, unaccompanied by a systolic murmur has been carefully studied by Froment et al.[3] who believe that "auricular retropulsion" contributes to this paradox. Six patients with a calcified valve were observed fluoroscopically; each was in sinus rhythm, and their left auricles were only moderately dilated. In ventricular systole the mitral valve moved—contrary to the physiological direction—towards the auricle. It thus seemed probable that in certain "mitral" hearts, particularly perhaps those in which the principal mass was formed by a turgid auricle containing $^1/_2$–1 litre of blood, the physiological movement of the auriculoventricular septum was reversed, with the ventricle firmly anchored at its base. It is, then, this recoil of the auriculoventricular septum, moving piston-like inside a cavity obstructed by the narrowed mitral valve, that may give the impression of systolic expansion, whether or not a ventriculo-auricular reflux is superadded. Retropulsion with apparent systolic auricular expansion, Froment et al. conclude, is essentially, if not exclusively, a sign of mitral endocarditis with auricular stasis, and is not strictly indicative of mitral insufficiency; in prognosis it may have some value.

After a lapse of many years mitral incompetence once more becomes a fashionable diagnosis. Many views were expressed recently at the European Congress of Cardiology held in London, but there was general agreement that the pendulum of diagnosis is swinging back to the stethoscope. It is perhaps disappointing that no constantly reliable information has come from the many detailed studies employing cardiac catheterisation. Pulmonary capillary pressure curves often give a characteristic pattern, with fusion of the A, C, and V waves, and angiocardiograms show a lingering opacification of the left auricle, but no dependable clinical correlation can always be proved by these methods. The same criticism applies to electrokymography and also to the measurement of œsophageal pressures at the auricular level. Auscultation is on the whole the most informative single diagnostic approach.

In some patients with mitral disease, whose symptoms have justified cardiotomy, the surgeon has been surprised to find predominant valvular incompetence, rather than stenosis, when clinical indications have favoured the latter. Surgical relief seems to be equally necessary in such cases. The technical possibility of correcting the defect is discussed in this issue by Mr. Andrew Logan and Dr. Richard Turner. They successfully treated 15 patients by threading a pericardial strip through the wall of the left ventricle to provide a sling for the valve. The resulting improvement was not spectacular, and the authors are cautious not to overestimate the possibilities of this operation. Until we know more about the complicated mechanics of the mitral valve cusps, both in health and in disease, plastic surgery cannot have a standard place in treatment. Many valves, for example, are rigidly calcified, and in these cases mitral incompetence is commoner. There is an increasing danger that our enthusiasm for surgery in the treatment of mitral disease will divert attention from the prognostic importance of old myocardial damage, both auricular and ventricular, caused by the initial rheumatic inflammation.

RETAINED PLACENTA

Burton-Brown's radiographic study[1] of placental separation has shown that after normal delivery of the infant the uterus must contract further if the placenta is to be separated. Separation is usually, but not always, accompanied by retroplacental hæmorrhage. Alvarez and Caldeyro-Barcia[2] have observed the pressure changes in the ligated umbilical-cord vessels and found that normally contractions recur at the rate of 4 per 10 minutes and that the average time for physiological separation is 6 minutes.

In different hands management of the third stage of labour varies from cautious non-interference, except in the presence of hæmorrhage, to the administration of oxytocics during completion of the second stage in order to hasten separation of the placenta and minimise blood loss. Stern[3] interferes in the third stage only for hæmorrhage; and then he gives ergometrine and gently expresses the placenta, or removes this manually if necessary. When the third stage is prolonged without hæmorrhage, he does not interfere at all. Of 17,002 patients delivered at his hospital in 1947–51, only 395 (2·32%) had a third stage lasting over one hour; and of these 144 (0·85%) had no bleeding in this stage. In 13 patients the third stage lasted for more than twelve hours. There were no maternal deaths. Stern concludes that the danger of serious postpartum hæmorrhage after the first hour or two of the third stage is very slight; thus expression should not be attempted, since the danger of retention of the placenta is less than the risk of manual removal.

Hammond[4] accepts the evidence that the use of ergometrine before the third stage lowers the incidence of postpartum hæmorrhage, and believes that the risk of contraction ring with this drug has been exaggerated. On the other hand, he asserts that abnormal retention of the placenta, as reflected in the proportion of cases where manual removal is needed, may be increased: the reported rates with ergometrine are four to six times as high as the admirably low figure of 0·26% for manual removal in the Guy's Hospital series described by Hammond.

All agree that meddlesome manipulation of the fundus of the uterus is liable to disturb the third stage. The Credé manœuvre is perhaps in undeserved disrepute because it is sometimes practised without regard to Credé's directions that contraction of the upper segment and expression of the placenta into the birth canal should be secured before expulsion is attempted.

Furthermore, with manual removal, there is a definite risk of shock and infection, especially great in the debilitated and in patients with heart and lung disease.

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[2] Elkin, M., Sosman, M. C., Harken, D. E., Dexter, L. *New Engl. J. Med.* 1952, 246, 958.

[3] Froment, R., Gonin, A., Gallavardin, L. *Arch. Mal. Cœur*, 1950, 43, 678.

[1] Burton-Brown, J. *J. Obstet. Gynæc.* 1949, 56, 847.

[2] Alvarez, H., Caldeyro-Barcia, R. *Proc. R. Soc. Med.* 1952, 45, 540.

[3] Stern, D. M. *Medicus, Karachi*, 1952, 3, 183.

[4] Hammond, G. T. *J. Obstet. Gynæc.* 1952, 59, 493.

Thus accounts of the routine use of ergometrine before separation of the placenta in large series of cases will be awaited with keen interest.

THE NEW MARTINDALE

It will be surprising if pharmacists and physicians all over the world do not feel their hearts strangely warmed by the sight of the 23rd edition of Martindale's *Extra Pharmacopœia*, volume I of which has just been published. Here indeed is one of the old familiar figures, clad in decent blue buckram, and embellished (though with restraint) by gold lettering. But he is fatter—more than four times fatter—than the poor creature born some seventy years ago; and this is partly because he has just made a meal of his even more aged competitor, Squire's *Companion to the British Pharmacopœia*.

Martindale is a book full of surprises, so that some readers may find themselves wishing that they had been introduced to it while they were students, when a thousand and one minor queries, too heterogeneous to take to any one of their teachers, went unanswered. Where else could they so conveniently obtain information on say 'Amesec,' anti-rust solution, and Wahoo bark (prescribable on form E.C.10)? And how else could they confirm that the doctor who declared his faith in Basham's mixture was really serious, even if misguided about its therapeutic merits?

Armed with Martindale, the medical practitioner can hope to contend with the increasing spate of proprietary preparations; and he will be delighted to find that the latest compound tablet is nothing more than two or three of his old *B.P.* friends in fancy dress. The materia medica of the *Extra Pharmacopœia*, running to more than 1000 pages, is derived not only from British publications but also from American and Continental sources. The admirable practice of interspersing the mass of pharmaceutical facts with therapeutic comment is preserved in this edition, and about 4000 original papers have been briefly abstracted for this purpose. On this subject, however, the editors sound a note of warning: "Since the *Extra Pharmacopœia* is a reference book on materia medica and not a textbook of therapeutics no attempt is made to offer authoritative assessments of the value of medicinal agents where this is the subject of controversy. The aim throughout is to give an unbiased presentation of the published work." This carefully worded statement goes far towards disarming criticism. Perhaps it also indicates a measure of uneasiness among the editors, who may occasionally wonder whether their zeal to serve both pharmacists and doctors invariably gives the best results. They would be the first to admit that the medical references represent a selection touching merely the fringe of a vast subject, and that undue importance may occasionally be attached to a publication simply because it is a recent one. If this is so, it may well be asked whether the book would not gain in value by the adoption of more exacting standards in the choice of references to illustrate the use of drugs.

Statements are made here and there which might be interpreted as guidance to the doctor when in fact the information is merely of historical interest. For example: "Garlic has expectorant, antiseptic, diaphoretic, and diuretic properties, and has been used as the syrup in the treatment of chronic bronchitis, phthisis, and other pulmonary conditions." But perhaps the argument in favour of developing a more critical therapeutic approach is most apparent in the therapeutic index. Admittedly this is only an index, and the reader must turn to the appropriate pages to see if any statements are made about the relative merits of the drugs listed. But could not this index be printed in such a way as to focus attention on the drugs which have been shown to be effective, and to minimise the importance of drugs which are now known to be useless or unreliable? For example, among a score of alleged remedies for travel-sickness should not hyoscine and dextrose be printed in bold type? Surely the mention of cerium oxalate merely confuses the issue. Again, under typhoid fever, we find chloramphenicol given the same prominence as anti-typhoid serum and sulphurous acid. The reference to sulphurous acid says: "It is seldom used internally but has been employed, freely diluted, in cholera, and has been given in typhoid in 20 to 30 m. doses . . . every two or three hours." If this serves any purpose at all, it is merely to make us understand why Osler became a therapeutic nihilist. These curious remnants are scattered through the text, and they seem out of place by the side of the admirable special sections on such subjects as antibiotics, antisera, blood-transfusion, and dangerous-drugs legislation.

If there is a good deal of chaff there is also—thanks to the exertions of the pure chemist and the pharmaceutical chemist—a great deal of wheat; and it would be difficult to imagine a pleasanter way of surveying the harvest than to browse through the *Extra Pharmacopœia*. Martindale is in fact unique; and all pharmacists and physicians will wish to have this extremely valuable book which has become indispensable in their work. Many members of the two professions will also wish to pay tribute to the editors who have worked with exemplary skill and tenacity to make this volume worthy of its numerous predecessors.

CHROMOBACTERIAL INFECTIONS

The chromobacteria are gram-negative, motile, nonsporing, and aerobic bacilli which produce various pigments in culture. They are usually considered to be non-pathogenic saprophytes. Their occurrence in association with human lesions was rarely recorded in the pre-antibiotic era, but the evidence suggests that such infections may be seen more often as a consequence of modern chemotherapy. In 1951 Wheat et al.[1] reported 11 cases of urinary tract infection caused by *Chr. prodigiosum* (*Serratia marcescens*); 2 of these patients also had septicæmia, and 1 of them died of endocarditis. Some form of mechanical interference with the urinary tract, such as catheterisation, cystoscopy, or a surgical operation, preceded the infection in every case; and though the source of the organisms was not determined, it seemed likely that they had been introduced in this way. The infecting organism invariably had a high resistance to penicillin, streptomycin, chloramphenicol, aureomycin, and terramycin, and the authors felt that the use of antibiotics, which eliminated all the organisms commonly responsible for urinary infections, had prepared the way for invasion by the chromobacteria.

Recently another fatal septicæmia caused by *Chr. prodigiosum* was reported by Patterson et al.[2] This case differed from those reported by Wheat et al. in two important ways. First, the septicæmia developed as a complication in a patient acutely ill with severe and repeated hæmorrhages from a penetrating peptic ulcer; the urinary tract remained sterile throughout. Secondly, the strain of *Chr. prodigiosum* isolated from the bloodstream was highly sensitive in vitro to streptomycin and neomycin, and partly sensitive to chloramphenicol, aureomycin, and terramycin. The septicæmia apparently began after 17 days of penicillin therapy, though a positive blood-culture was not obtained until the 29th day, when combined penicillin and aureomycin was being given. Thereafter various combinations of drugs were tried: aureomycin was given for 2 days, aureomycin and streptomycin for 4 days, streptomycin and chloramphenicol for 6 days, streptomycin alone for 1 day, streptomycin and intravenous aureomycin for

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1. Wheat, R. P., Zuckerman, A., Rantz, L. A. *Arch. intern. Med.* 1951, 88, 461.
2. Patterson, R. H., Banister, G. B., Knight, V. *Ibid*, 1952, 90, 79.

6 days, and finally neomycin for 1 day; but the infection resisted all treatment, and when the patient died the blood-culture was still positive and there were signs of bronchopneumonia. Post-mortem examination was not possible; so little is known of any complicating lesions, such as abscesses or endocarditis, which might have diminished the response to chemotherapy. It is, however, surprising that in this patient the septicæmia was apparently unaltered in any way by any of the antibiotics given, even though the organism was at least partially sensitive to them all. As the antibiotics were often given in pairs, it is possible that antagonism between them, of the type reported by Jawetz and Gunnison,[3] reduced the effectiveness of streptomycin, to which the organism was most sensitive in vitro.

Reports of monilial infections complicating treatment with antibiotics are becoming more frequent,[4,5] and it may well be that the chromobacteria too will assume an importance hitherto unsuspected. Although many "local" types of infection with these organisms, in the urinary tract for instance, may heal spontaneously, clearly the results of systemic invasion are likely to be grave—a fact that must be accepted as another warning of the dangers of the indiscriminate use of antibiotics.

TUBERCULOSIS AND THE NURSE

As hosts to infective organisms we are far from cordial, and have a number of well-recognised gambits for making them not feel at home. Our relations with the tubercle bacillus, however, are ambiguous; for, though we cannot be said to like the fellow, we are less adroit than usual in getting rid of him. As Dr. F. A. H. Simmonds remarks, in a capable handbook[6] designed for the use of hospitals (and especially for medical superintendents, matrons, nurse teachers, and home sisters), though tuberculosis causes much ill health, so that time and effort must be spent in preventing it, it nevertheless affects most people only slightly. If we had means of detecting in advance those with poor resistance we should be saved a great deal of trouble; as it is, we must make do with the facts we have. We know, for instance, that nearly all of us encounter and get infected by the tubercle bacillus, not once in a lifetime but probably many times; and that a successful outcome turns on various factors—on inborn resistance, the increased immunity which follows a successfully resisted primary lesion, age, sex, race, and nutrition. It may also turn on the frequency of infection and the size of the dose; but here informed opinion is divided. Family contacts, especially children, of patients with active pulmonary tuberculosis are certainly more apt to develop the disease than otherwise comparable people; and they are almost bound to inhale tubercle bacilli more often, and in larger numbers, than other family groups. But the family with a tuberculous parent is often short of money, which may mean that the children are poorly nourished; and moreover they may have inherited a poor resistance to the disease. Again there is good reason to believe, Dr. Simmonds says, that the arrangement of the bronchial tree and the ciliary mechanism prevent large droplets from entering the lung; only small particles are likely to penetrate to the smaller bronchi, and even then only occasional particles are likely to get through. So even when an infectious patient coughs carelessly, only droplets carrying a small number of bacilli, or even a single bacillus, will ever be able to reach the pulmonary alveoli of a bystander, and then but rarely. Moreover, even a patient with advanced tuberculosis, when he coughs, expels only a few droplets carrying heavy infection: many contain none. In theory, indeed, it should be almost impossible to get oneself infected with tuberculosis by contact with an open case. On the other hand, we know it can happen.

The question of reinfection is equally confusing: for while some authorities hold that repeated reinfections are particularly dangerous, causing most pulmonary tuberculosis after the primary infection, others think that repeated small doses of reinfection may actually benefit the recipient by raising his immunity. Others, again, say that reinfection is impossible, and that tuberculosis arising after the primary focus has healed must always be due to the outbreak of latent infection.

All these factors and opinions must be taken into account when a programme is planned for the protection of nurses, medical students, almoners, physiotherapists, radiographers, laboratory technicians, ward-maids, young porters, and anyone else in the susceptible age-groups liable to encounter tuberculous infection in hospital. Dr. Simmonds recalls that the risk of infection may be greater in general hospitals, from unsuspected cases, than it is in sanatoria where precautions against infection are enforced; and his recommendations for the protection of staff apply equally to either kind of institution.

He insists that the nursing staff chosen should be healthy to start with, and kept healthy by proper care. The general clinical examination, on admission, should be supplemented by an estimation of hæmoglobin, by measuring the erythrocyte-sedimentation rate (to establish the normal rate for the individual), and by tuberculin tests, X-ray examination, and some psychological assessment of personality, not necessarily by means of tests. Periodical re-examinations should be made as a routine, so that they do not arouse alarm; and these should include weight records, and chest radiography at intervals of 3–6 months, especially in those still negative to tuberculin tests. Such negative reactors should not be put into wards or departments where tuberculosis is likely to be met. In his detailed instructions for applying tuberculin tests he lays stress on what should be accepted as a positive reading and what should not—an important point, since readings of the same results by different individuals often show considerable variety. Negative reactors, in his opinion, should always be given the opportunity of B.C.G. vaccination; for even if a nurse manages to avoid tuberculous patients during her student training she is unlikely to do so throughout her career. But the essence of prevention lies less, perhaps, in artificially produced immunity than in keeping the nurses's own defences in first-class trim—that is in keeping her well nourished, fit, and happy. Dr. Simmonds speaks tellingly of the value of good meals and plenty of them, eaten in congenial surroundings. Agreeable quarters, clubs and recreations, transport to town, and reasonable hours of duty are amenities which every hospital should provide, in order to safeguard the health—in some cases the lives—of its nurses.

ELECTRONIC STERILISATION

BIOLOGICAL and other preparations are apt to be damaged by thermal or chemical treatment; and thus sterilisation by high-velocity electrons is now attracting research-workers' attention. At a meeting recently convened by the Department of Scientific and Industrial Research it emerged that this method of sterilisation, *though likely to prove expensive, offers* great advantages: and in the U.S.A. it has already been shown to sterilise sutures and surgical dressings, blood-plasma, penicillin, cosmetics, and vaccines.

Electron accelerators with an effective anode voltage of the order of 2–3 million volts have been used. Such energies are not great enough to induce radioactivity in irradiated products. In general they kill large organisms more readily than small. At the Massachusetts Institute of Technology the sterilisation doses proved to be as follows: insects 100,000 units, vegetative bacteria 500,000 units, moulds and yeasts 1 million nits, and bacterial spores 2 million units; viruses and nzymes required 5–10 million units.

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[3] Jawetz, E., Gunnison, J. B. *Antibiotics*, 1952, 2, 243.
[4] Taylor, H., Rundle, J. A. *Lancet*, 1952, i, 1236.
[5] Wolff, F. W. *Ibid*, p. 1236.
[6] The Protection of the Nurse Against Tuberculosis. London: National Association for the Prevention of Tuberculosis, 1952. Pp. 90. 10s. 6d.

The cost of an electron generator capable of sterilising ton of product per hour would be £140,000, though the unning cost would be only 1½d. per lb. This high apital cost has stimulated interest in other sources of electrons, such as γ rays from by-products of the Atomic Energy Project; and it is estimated that a Co^{60} source costing £2000 would sterilise 7 lb. of product per day at a cost of 1s. per lb.

COSMETICS AND THE SKIN

"Hypoallergic" cosmetics are much advertised in the United States; so perhaps cosmetic dermatitis is commoner there than in this country. Possibly cosmetics are used more freely in America; or they may contain a greater number of potentially sensitising substances; or a larger proportion of the people who use them may have a relatively lower threshold for sensitisation. But even in this country, cosmetics, jewellery, and clothing are common enough irritants, for they come third after occupational hazards and plants as a cause of dermatitis. Moynahan[1] says that permanent-waving reagents give most trouble, but Garnier and Marshall[2] believe that the hair dye, *p*-phenylenediamine, and similar compounds are most often responsible. Lipsticks and nail varnish come next, while face creams and powders are rare offenders, though occasionally they contain perfumes or orris or rice powder which may produce a dermatitis.

Permanent-waving compounds and depilatories are primary irritants, attacking the keratin chemically and breaking down disulphide linkages. The keratin of the skin cannot be expected to escape when the keratin of the hair is thus attacked. Oxidation dyes of the "para" type are also primary irritants, and so are alkalis used for various purposes. Most of the other substances act as sensitising agents.

Dermatitis from *p*-phenylenediamine may occur after the first or after any subsequent application. A negative patch test, although a guide, does not exclude all risk: a trivial scratch may be the focus from which the exuding dermatitis starts, and no amount of warning on the package can eliminate the risk of dermatitis from an abrasion received after the hair has been dyed. *p*-Phenylenediamine can cause such a severe dermatitis that its use should be strongly discouraged, or even abandoned, like that of the highly toxic metallic dyes of the past. In the permanent-waving process keratin disulphide linkages are broken down and re-formed, but, if the process is overdone, it may become irreversible. Dermatitis may arise from heat or from the chemicals used. If the hair is bleached soon afterwards or, worse still, dyed, waved, and then (when the result proves unpopular) decolorised again, the long-suffering linkages may collapse and the hair break.

Lipstick dermatitis may be caused by sensitisation to one of the ingredients or to the development of light-sensitivity from the photodynamic substance, eosin. Only a few individuals are susceptible to eosin, and not all forms of eosin are equally harmful, so that relief may be obtained by changing to a lipstick containing another form of eosin or to one in which a non-eosinic dye is used. If there is eczematous sensitisation to some constituent, patch-testing may reveal the cause. One firm in the United States offers to supply doctors with patch-testing outfits of the constituents of its products. It has to be remembered that toothpastes may also cause cheilitis, or even an eczematous dermatitis.[3]

Nail varnish, when it causes trouble, usually does so where the hands come into habitual contact with the skin—e.g., on the eyelids, ears, and neck, and around the anogenital region. The hands themselves are rarely affected. Cuticle remover, another primary irritant, may affect the same sites as nail varnish, or it may be a cause of paronychia. It may also be responsible for brittleness and flaking of the nails, but the chief cause of this is the excessive degreasing and dehydrating action of modern detergents.

There are many interesting side-lines to the study of cosmetic dermatology; for example, dermatitis has been attributed to the use of nail lacquer as a coating for costume jewellery.[4] Nickel or chromium plating is most likely to be responsible when watch-straps, ear-clips, or other metallic articles are involved. Eczematous reactions of the nail bed have been reported from "under-coats" containing synthetic resins and rubbers, and experimental work suggests that such substances can pass directly through the nail plate,[5] [6] causing discoloration, subungual hæmorrhages, loosening of the nail, and paronychia. Eau-de-cologne applied behind the ears may cause the peculiar linear Berlocque pigmentary dermatitis, and in creams it is sometimes responsible for hyperpigmentation of the face. Other perfumes may be the cause of sensitisation dermatitis. It is as well to advise patients that the more expensive cosmetics are not necessarily the least likely to cause sensitisation, particularly where perfumes are concerned, for the most exotic preparations have had their victims. Cosmetic dermatitis is not confined to its users; Plotz[7] has described a dermatitis in infants caused by contact with their mothers' lacquered hair.

Among clothing, reactions are sometimes caused by dyed furs (the "para" group again), other dyed materials, nickel-plated fittings, and rubber articles such as dress protectors. Rubber sponges used for applying cosmetics, or for general purposes, have given trouble,[8] and so have the rubber fillers of eyelash curlers.[9] With rubber, it is the accelerators, activators, or anti-oxidants, usually synthetic organic compounds, that are responsible. One of them (an anti-oxidant—the monobenzyl ether of hydroquinone) may also cause depigmentation of the skin.[10] Synthetic plastic and adhesive materials used in the manufacture of hats and shoes can also cause dermatitis.

Hypersensitivity to cosmetics may be specific, and a true allergic phenomenon. Why then do individuals acquire hypersensitivity to cosmetics which they have used for years with impunity? Occasionally this may be due to some change in the composition of the cosmetic, but clinical experience suggests that it is often caused by a change in the health of the user. States of autonomic overexcitability seem to run parallel with an all-round increase of skin sensitivity. This clinical belief has recently been given some scientific backing by the demonstration of increased sensitivity of the skin of guineapigs to contact irritants applied after a period of interference with the animals' sleep.[11]

Dr. A. E. Gow, physician to St. Bartholomew's Hospital, London, died on Sept. 19. Dr. Gow was honorary physician to the household of the Duchess of Kent.

Sir Geoffrey Vickers, v.c., has been appointed a member of the Medical Research Council by the Privy Council. The following have also been appointed members after consultation with the M.R.C. and with the president of the Royal Society: Prof. G. R. Cameron, f.r.s., Prof. A. J. Lewis, and Sir James Spence.

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Special Articles

THE OCCUPATIONAL ADAPTATION OF HIGH-GRADE MENTAL DEFECTIVES

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Mental-deficiency Hospitals

In England and Wales there are just over 105,000 mental defectives under statutory care. The Ministry of Health (1950) gave the number in institutions in January, 1949, as 54,887; the rest were [illegible] or statutory supervision. Of those in [illegible] were children under the age of 16; the remaining 47,000 were adults.

Every patient is *classified* according to the grade of his defect, but no figures are given by the Ministry, or by the Board of Control, as to the number of idiots, imbeciles, and feeble-minded persons in institutions. Nor is it easy to arrive at an estimate of the numbers in each grade.

From figures published by Penrose (1949) based on his Colchester survey, and from information given later in this paper, one of us (Tizard 1951) has calculated that about 54% of adult patients are above imbecile grade in intelligence. If *Penrose's data are representative, two-thirds of the feeble-minded or dull patients in institutions are young persons between 16 and 29 years of age; while only 3% of adults in* institutions are more than 45 years of age and above imbecile grade in intelligence.

Thus it seems probable that over half the adult cases in institutions are high-grade patients; and of these a large proportion must be regarded as young, trainable adults and adolescents who may eventually be discharged from the provisions of the Mental Deficiency Acts.

EXISTING TRAINING METHODS

The occupational potentialities of high-grade and low-grade patients are very different. Low-grade patients need, and are given, occupational therapy. High-grade patients on the other hand, need occupational training, and are today employed either on work which is of direct use to the hospital, or on skilled or semi-skilled trades under the *direction of craftsmen. For this work they* receive small sums in pocket-money. Patients on daily or resident licence usually work on farms or as general labourers, or go to small firms as errand boys, to public houses, to laundries, to hospitals as domestics, or to private employers as servants. These patients receive larger sums as pocket-money, and usually have the rest of their money, except for that deducted for board and lodging, banked for them. They are able to draw on their bank account for clothes, holidays, presents, and so on, with the permission of the hospital authorities. In 1946 there were 5571 patients on licence from institutions in England and Wales; and an average of about 900 patients is discharged annually.

During the last few years the number of patients on daily and resident licence has increased considerably. Training schemes in institutions have, on the other hand, changed little. Numbers of patients work as labourers in mental-deficiency hospitals, and this training probably stands them in good stead if they later work as labourers *in the community. Large numbers of high-grade patients* can, however, still be found working at the occupations *described by Bickmore* (1913): carpentry, bookbinding, envelope-making, box-making, brush-making, basket-making, raffia work, mat-making, tin-smithing, tailoring, upholstering and mattress-making, printing, needlework, painting, building, wood-chopping and bundling, and shoe-repairing. The titles of some of these occupations *give little idea of the character of the work performed;* and the teaching methods of the trainers, and the equipment used in the workshops, are often extremely old-fashioned. Only in the protected *environment* of a hospital could these uneconomical and out-moded methods *continue.*

The following specific criticisms of much of the *occupational training may be made:*

1. *Most of the training is designed to give the patients* something to do rather than to employ them on work of value to the community. In times of severe and chronic unemployment, when very few defectives can be sent on licence to the community, and when public policy deems it expedient for institutions not to compete in any sense with private employers, this is readily understandable. In times of full employment *and general shortages a different attitude to the training of defectives seems advisable.*
2. The work done in institution workshops bears almost no relation to the types of job which defectives do when on licence. A mere handful of those who are trained so laboriously on the skilled and semi-skilled operations learn to perform them competently enough to be able to obtain work as artisans in the community. The bulk of defectives are employed only on less skilled work.
3. The equipment used in institution workshops is almost without exception obsolete as far as industry is concerned. Much work which is done commercially by machine is done by hand, or for the most part by the most primitive of machines. Little is done to speed up production to the tempo required to keep a job in the community, and the defectives get no experience in handling machines, and so becoming accustomed to them. Consequently output remains low, and even though labour is free the selling costs are often higher than commercial selling costs, which are reduced by the economies of large-scale buying and by efficient machine production. This factor of economic cost is obscured in the annual reports of some institutions which give "turnover figures" but not a profit-and-loss balance-sheet of workshop expenses.
4. Little contact is made with commercial firms which might be induced to take numbers of defectives who have already received some training into their own factories. Thus, in many hospitals, a potential stepping-stone to life in the community is not made use of.
5. The work is too often carried out in an atmosphere devoid of incentives. Neither the report of the Mental Deficiency Committee (Wood Report 1929), nor *Bickmore* (1913) mention monetary rewards—*assuming apparently that* praise and blame from an instructor are sufficient for defectives. But the absence of monetary rewards in some hospitals makes the problem of providing incentives a *difficult one*, and also prevents patients from learning the value of money. Unless those who will probably be sent on licence in the future *are given more money to spend while they are in institutions, they are unlikely to learn from their own mistakes how money* can be wasted, and what money can buy.
6. *The supervision of patients on daily service* or resident licence is often inadequate. [illegible] *no social worker, and few* [illegible] *hospitals nurses do the necessary work, but in any case few hospitals have more than one or two people who are responsible* for placing and follow-up. For adequate supervision a much greater number is needed.

COST OF PRESENT METHODS

The economic cost to the community of the present methods of employing *defectives has been critically examined by Gibbens (1948).* He analyses the statistics of the Surrey County Council for *1938 and concludes that* some 67% of institutional defectives are apparently regarded as being employable in the full sense. The London County Council statistics, also analysed by Gibbens, suggest that about 43% of patients are fully employable. From these two figures he concludes that fully 40-50% of adult institutional patients are employable.

Other work on the employability of defectives, which *we have reviewed elsewhere (Tizard and O'Connor 1950),* emphasises that the number of defectives capable of *satisfactory social and occupational* adjustment in the community has often been seriously underestimated.

Economic conditions have been largely responsible for this; but under conditions of full employment there is still a considerable lag in the sending of patients to licence.

The number of patients rehabilitated today could be greatly increased if ways could be found of lessening the high incidence of occupational maladjustment among defectives sent on licence to the community. The extent of this maladjustment is indicated by the large numbers of licences revoked each year in most hospitals for mental defectives. One of its consequences is that many physician-superintendents are reluctant to send patients on licence because of the probabilities of failure, with its resulting economic, social, and personal costs. Unfortunately, however, keeping patients in institutions also entails economic, social, and personal costs, which are no less real because they are not counted or measured.

SIZE OF INSTITUTIONS

Difficulties in training high-grade patients are increased by the fact that most institutional defectives are housed in huge "colonies" of 500–2000 or more beds. In 1946, according to an analysis one of us (Tizard 1952) made of information published by the Board of Control (1931, 1946a and b), more than two-thirds of all defective patients were in institutions of more than 500 beds, while nearly half were in institutions containing more than 1000 beds. Though the need for smaller units has long been recognised, in 1946 only 13 institutions had hostel accommodation for patients. The comprehensive colony is believed to be the most economical method of housing institutional patients. Thus the Wood Report (1929) argues that in comprehensive colonies high-grade patients can be employed on maintenance and essential services, so saving the cost of paid staff. Nevertheless separate hostels for high-grade patients appear to be psychologically desirable; and, as the figures given below indicate, patients in them could contribute substantially to their keep. On balance, classified institutions might be both more economical as well as more in keeping with current psychiatric opinion than comprehensive ones.

Employability of High-grade Defectives

The widely recognised shortcomings of the mental-deficiency services, which have been sketched above, formed a starting-point for the research which has been carried out during the last three years, under the direction of Prof. Aubrey Lewis. The purpose of the research has been to study the conditions under which institutional high-grade defectives can best be employed, both inside and outside institutions. This has meant some study of the competence of high-grade patients, and an investigation into behaviour problems. Experimental workshops have been set up in Darenth Park, in collaboration with Dr. J. K. Collier Laing, the physician-superintendent, and his staff. Darenth Park is a hospital in the South-East Metropolitan Region which includes among its patients several hundred high-grade, adult defectives. Here patients have been trained for jobs to which they might later be sent from the hospital to perform in normal industrial conditions. Some consideration has been given to problems of supervision and incentives in the training workshops. The bulk of the research has been carried out with male patients.

We group our results under four main headings: psychometric studies of high-grade male defectives and prediction of occupational success; workshop investigations; success of workshop patients on daily licence; and factors influencing the success and failure of other patients on daily licence.

PSYCHOMETRIC STUDIES

In 1949 a psychometric study was made of 104 cases.

The sample consisted of all those male patients admitted consecutively to Darenth Park over the preceding three years who were feeble-minded, not grossly handicapped physically, still living and working inside the institution at the time of testing, and between 16 and 45 years of age. They were given a battery of intelligence, psychomotor, and personality tests, and with the help of Dr. J. M. Crawford we also rated them for instability and anxiety.

In 1950 a second sample of 100 patients was given the most promising of the tests in the 1949 battery, together with additional tests included for research purposes. In the second sample half were fresh cases; the remainder had already been tested in our first study. It was possible with this combination of data to check Beta weights and obtain test reliabilities.

Results can conveniently be discussed under the headings of intelligence tests, other cognitive and motor tests, and objective tests of personality.

Intelligence Tests

Perhaps the most significant finding was the high average intelligence quotient (I.Q.) and the wide range of scores obtained by patients on standardised tests of intelligence. Combining results with the Progressive Matrices test, obtained by us at Darenth and another hospital, and by Stickland (1952) at a third hospital, we find the mean I.Q. of 360 adult patients to be 75·61 (S.D. 10·01). Stickland reports no significant difference between the scores of males and females, so it seems likely that these figures are representative for both sexes.

A suggestion sometimes made that the Matrices test is unreliable for defectives has not been confirmed by our experience of retests after long periods.

Other Cognitive and Motor Tests

Inadequate standardisation of these tests makes it difficult to compare our findings with those of other investigators working with normal adults. Since they have been fully discussed elsewhere (Tizard 1950) the technical difficulties of interpreting results are omitted. One finding from Darenth Park should, however, be mentioned. The median reading-age of 100 patients tested on the Schonell mechanical reading scale, which has been very soundly standardised on Army recruits, (Ministry of Education 1950) was 8·6 years; and the range of reading ability was wide, being as follows:

Score (to nearest year) ..	14	13	12	11	10	9	8	7	6	5 or less
No. of cases..	2	3	5	12	16	14	16	8	4	20

100

The correlation between reading-age and verbal intelligence, as measured on the Bellevue verbal scale, was only 0·427. This finding suggests, first, that many patients in hospitals for mental defectives are educationally retarded—that is, they are more backward educationally than they are in intelligence, and hence might profit by further schooling—and secondly, that a very considerable proportion of them are capable of reading simple material, and that adequate provision of suitable books and other reading matter is desirable. Some hospitals would like to do more to teach patients but have difficulty in obtaining the necessary funds to appoint teachers.

Objective Personality Tests

It has been held that one aspect of neurotic personality is the poor work-history of the neurotic; and an attempt was made to test this hypothesis with a defective population. We also studied the relative value, for predicting success at work, of tests assessing neurosis, the diagnosis of a psychiatrist, and a quantified history of behaviour. Success was measured in terms of the number of failures of a particular boy to hold jobs. A full analysis of results is given elsewhere (O'Connor 1951a and b, 1952). The main findings confirmed the view that the outlook for success at work was best measured, not by cognitive or intelligence tests, but by tests of personality traits. This conclusion was reached by separate analyses of the results with both the first and second samples. Further studies, of which details may be had on request, made it clear that the use of tests for predicting whether or not a patient should be given a trial on daily licence is of doubtful value; and, in view of this, all patients (other than those who are manifestly unable to work in the community) should be given opportunities for daily licence from time to time, as is already done in some hospitals. The important problems of occupational psychiatry among the mentally handicapped are not problems of selection, or even of vocational guidance as the term is usually used today: rather they are problems of training patients, if necessary in a sheltered environment, and of providing adequate supervision and assistance in the community. Occupational training in the wide sense of the word must include the training and habilitation of those unstable patients who constitute the chief sources of trouble both to their families and to the community. One such training scheme has been described by Laing (1951).

WORKSHOP INVESTIGATIONS

In January, 1950, the Darenth and Stone Hospital Management Committee set up a first, and subsequently a second and third, experimental workshop. These were to serve two purposes: (1) to learn whether it is possible to train defectives to do such routine repetitive work as is done by normal workers in industry, and whether their training in institution workshops contributed to their success; and (2) to determine the optimum conditions of employment.

Suitable work of a routine repetitive nature, paid for at trade-union piece-rates, was obtained from two firms willing to subcontract work to Darenth Park. The firms were approached through the Ministry of Labour.

One firm sends plastic for hand trimming, and one sends cardboard for folding and processing. Initially small quantities of this unskilled work were sent, but after a few weeks the firms sent much larger quantities. At present 140 patients are employed in the shops.

The experimental shops are controlled by hospital nurses. For each boy daily and weekly records of output are kept, and the boy is paid according to what he earns. All money received from the firm is credited to the patients, and at first they were allowed to receive in cash half of what they earned, up to a maximum of about £1. The rest was banked for them, and they were encouraged to save as much as possible to buy clothes, presents for relatives, and pay for holidays and outings and so on.

During 1951, however, this system was modified by the hospital authorities for administrative reasons, and the incentive bonuses were scaled down.

The average wage is now 6*s*. 8*d*. a week, the range being 2*s*. 6*d*. to 15*s*. with 2*s*. 6*d*. bonus for the best boys in each shop. Outings are still arranged and boys who begin work on licence are fitted out with clothes, half the cost of which is met directly out of their earnings. The number of lower-grade patients has also been increased; so the original function of the shops as training centres has been modified.

Between the beginning of May and the end of July, 1950 (i.e., before the system was modified), the average weekly wage of 24 boys employed was just over 27*s*. The shops as a whole earned £1250 during the first eight months, and £2750 in just over a year. During 1951, £3000 was earned by the shops as a whole. The patients work a $35^1/_2$-hour week to fit in with hospital requirements.

An experiment was designed to determine the effects of different types of supervision on the behaviour of patients in the shops.

Three groups of 12 patients each, matched for previous productivity, served as subjects. The mean I.Q. of the patients taking part in the experiment was 68·00 (S.D. 9·57 points) on the *Bellevue verbal scale*. The mean age was 19·45 years (S.D. 4·41 years). Three types of supervision—strict, friendly, and laissez-faire—were carried out by three nurses who acted as supervisors during the investigation. The experiment ran for 12 weeks and was divided into three periods of 4 weeks each, so that each supervisor served in each of the three shops, changing his type of supervision in each. Behaviour and output during the experiment were recorded quantitatively for each boy, and the results analysed by analysis of variance (Tizard 1952).

Two findings may be mentioned:

1. Significant differences between the behaviour of groups under the three kinds of supervision were noted. Laissez-faire supervision gave rise to considerable aggression, which was not found in groups under strict or friendly supervision, either in or out of the workshops.

2. The experience obtained suggested ways in which nurses might be more efficiently trained to undertake supervision. Both practical training, such as is given to teachers in training, and formal discussions of what to do in handling patients (on lines adapted by the Hawthorne investigators) seem desirable.

SUCCESS ON DAILY LICENCE

During 1950 and 1951 a total of 194 patients were employed in the workshops, of whom 60 were tried on licence. Some of the patients went from the workshops to work at one of the firms subcontracting work (Kolster-Brandes of Sidcup). Others went to other work for which they had had no special training. In December, 1951, their distribution was as follows:

From workshops to daily licence and succeeded on their first trial	[illegible]
From workshops to daily licence and succeeded after being unsuccessfully placed	5
Tried unsuccessfully on daily licence	15
Dismissed or removed from workshops (not tried on daily licence)	[illegible]
From workshops to resident licence with their parents ..	[illegible]
In workshops but not tried on licence	[illegible]
Total	194

The table shows the success and failure of patients tried on licence at Kolster-Brandes (K.B.) and at other types of employment. Though the numbers are not large, there is a significant difference between the success of boys placed with K.B. as compared with that of boys placed elsewhere. This is believed to be due not only to the training received but also to the type of supervision given at a large firm where patients are under the charge of an exceptionally capable and understanding supervisor. We are unable to determine the extent to which each of these factors contributed to the boys' success on licence, but there is no doubt about the success itself. The boys seem to benefit both by working alongside normal employees and by remaining in company with others whom they know.

OTHER PATIENTS ON DAILY LICENCE

In addition to the boys who went to a factory from the hospital workshops, many were employed directly, without training, as building labourers. Apart from physical disability three main causes for failure can be seen from an analysis of the job records. These are lack of motivation, failure due to initial lack of adjustment to the job, and finally emotional instability amounting to neurosis.

Examples of apparent changes in motivation were first seen in the workshop, when boys who had been working at a slow tempo speeded up almost overnight. Similar changes were reported from supervisors on the jobs to which the boys were sent. A major and remediable cause of failure was initial maladjustment. This was particularly noticed among the boys working on the building site. On this job supervision generally

SUCCESSES AND FAILURES AS BETWEEN K.B. AND OTHER FORMS OF DAILY LICENCE (EXCLUDING 2 BOYS TRIED BOTH AT K.B. AND IN OTHER FORMS OF EMPLOYMENT)

—	Daily licence			
	Successes	Failures	Total	Percentage failure
K.B. ..	27	6	33	18
Other ..	14	11	25	44
Total ..	41	17	58	

$\chi^2 = 4{\cdot}58$. $p < {\cdot}05$.

was not good; gangers under pressure to complete contracted work showing little patience with boys who had never attempted heavy work under competitive conditions. In the first month 34% of defectives left as compared with 21% of normal labourers; but over the first six months the percentages were nearly the same—51% for the defectives and 58% for other workers. Emotional instability or neurotic tendency was responsible for some failures. Failures of this latter kind were usually for disciplinary reasons and the boys were often of above average intelligence for the group. Histories usually supported test findings and psychiatrists' opinions of the instability of these boys.

Emotionally unstable boys are in a minority; and we feel that much failure can be avoided, either by suitable supervision, or by adequate motivation and wise guidance. Such a policy at Darenth Park has given the following results:

In April, 1949, 65 of a total of 1015 male patients were on daily licence, but by March, 1951, 161 of the 1087 male patients were working outside the hospital on licence—an increase from 5·4 to 14·8% in two years, without an appreciable increase in the incidence of failure. During 1951 patients on licence earned £30,000 and paid £16,500 to the Treasury for their board and lodging. No comparable increase has occurred in the country as a whole.

Summary

Some 55,000 mental defectives, of whom about 47,000 are adults, are in mental-deficiency hospitals or institutions in England and Wales. Half of these are feebleminded.

The training of these people is often not related to work which they might be called upon to perform when sent on licence, because, with very few exceptions, institutional policy has not been to return defectives to the community, but to segregate them. Hence training tends to be misdirected from this point of view, incentives are unreal and ineffective, and training costs are unnecessarily high.

In our view large institutions are unsatisfactory as places for training.

High-grade defectives trained for and employed on simple repetitive work can, and do, succeed in many cases, when well supervised and adjusted to strange surroundings. Few fail, and of those who do many can be rehabilitated when attention is given to their problems.

Psychometric cross-sectional studies and a longitudinal workshop experiment are reported. With high-grade adolescent defectives with a mean I.Q. of 70–75, tests of neurotic tendency better predict success at work than do tests of intelligence. In general, however, with prediction at its present level, no practical use can be made of these findings; selection for jobs in a period of full employment should be as liberal as medical opinion and social safety will allow.

Training and supervision are apparently more important than considerations of basic "psychological" quality, whether of abilities or personality traits. The main problem of occupational psychology is not selection, but training, motivation, and supervision.

Our thanks are due to Dr. J. K. Collier Laing, physician-superintendent of Darenth Park, for the facilities which he and his committee have generously placed at our disposal, and for his interest in the work.

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SUPPLY OF NURSES

SPEAKING at Plymouth last week, Mr. Iain Macleod, the Minister of Health, said that during the four years since the inception of the National Health Service the total nursing and midwifery staff in hospitals had increased by about 25,000 full-time and 9000 part-time, and over 30,000 additional hospital beds had been opened, while the number of student nurses (51,648 at the end of June) was the highest yet recorded. While this progress gave some cause for satisfaction, three considerations must be kept in mind.

> "First, there are still some fields, notably our mental hospitals and mental-deficiency institutions, in which there is a really grave shortage of nurses. Secondly, the pressure of work in many of our acute wards is tending to increase because of the introduction of complex new techniques and the earlier discharge of patients. Thirdly—and this is perhaps the most fundamental consideration—we cannot expect the numbers in the profession to continue increasing indefinitely: not only is the total number of young women now considerably smaller than just before the war because of the low birth-rate in the '30s, but the number of competing professions open to them is tending all the time to increase."

It was essential, the Minister said, to make the best use of all the nurses. Among ways of doing this were the effective use of the preventive health services, including the health visitor and home nurse, and a reduction of the incidence of wastage during nurse-training. About 20,000 student nurses were admitted to training schools each year, yet the annual output of trained nurses was only about 9000–10,000. It was hoped that the Hospital Job Analysis conducted by the Nuffield Provincial Hospitals Trust, the report of which was expected soon, would give useful guidance towards making a better planned use of trained nurses and ancillaries.

> "When there is, as here, a strict upper limit to the number of people with particular qualifications, it is merely elementary common sense to make sure that they are employed only on work calling for that qualification and that other work is devolved to less highly qualified staff. It also becomes a public duty to make sure that the number of qualified people employed is the minimum needed for the work to be done. In other words, that there is neither waste nor extravagance."

Mr. Macleod also referred to the three-year gap from 15 to 18—the minimum school-leaving age and the minimum age at which training as a nurse can now begin. No problem arose if the girl was able to remain at school until the age of 18, but the total numbers required by the profession were such that they could not all be recruited from that source; and the problem was how to maintain an interest in nursing among a sufficient number of those girls who have to leave school and take a job at 15 or 16. After speaking of "pre-nursing courses," cadet schemes, and the certificate of the National Nursery Examination Board, he pointed out that the girl who takes another job is by no means irrevocably lost to nursing: a survey by the Nursing Recruitment Centre showed that no fewer than 34·8% of the candidates accepted as student nurses during a three-month period had come from other work, while a further 10·5% had come from nursery work or training.

> "I am very conscious," he added, "that the problems of the teaching hospitals in this field of nursing recruitment are a good deal simpler than those of the ordinary hospitals, and the ordinary hospitals are after all the great majority. We must watch carefully to see that we do not lose the ground we have gained."

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INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

In 1947 the Royal College of Physicians arranged an International Congress of Physicians which was held in London. This gave rise to the formation of the International Society of Internal Medicine, which had its first congress in Paris in 1950. The second congress met in London last week, from Sept. 15 to 18, under the patronage of Her Majesty THE QUEEN and the presidency of Sir RUSSELL BRAIN, P.R.C.P. At the opening session the guests were welcomed by Mr. IAIN MACLEOD, the Minister of Health, and a Government reception was held on the same evening at Church-House, Westminster. On the next night there was a reception at the Royal College of Physicians, and on Sept. 17 the congress dinner took place at the Mansion House.

Speaking at the dinner, Lord MORAN said that no visit to London was complete unless the visitor dined with the Lord Mayor. In England we revered tradition, and when tradition was lost in time the reverence was touched with affection. The City of London was old yet ever young, and it was not without significance that the present Lord Mayor, Sir Leslie Boyce, was born and bred in Australia. Responding, the LORD MAYOR claimed that London was still going strong, even if once in a thousand years it had to send to the other end of the world to find a Lord Mayor. On the assumption that internal medicine was something out of a bottle, he had been apprehensive lest the congress members would convert his Egyptian Hall into a giant dispensary; but he was reassured on learning that the business of the congress consisted in symposia, defined by the dictionary as drinking parties. He hoped that the delegates would take back the greetings of the citizens of London to the civic heads of the cities whence they came. Prof. A. GIGON, of Basle, proposing the toast of Internal Medicine, considered several possible new specific names for the genus *Homo*, and (adopting that of Bergson) concluded that London showed him both *sapiens* and *ridens*. Medicine, and the organisation of medical congresses, needed both the mosaics of team-work and the obelisks of individuality, and he thanked those whose long labours had combined to create the *jardin d'amitié* of the past few days—including particularly Lady Brain and Sir Harold Boldero. *Vivat, floreat, crescat* Internal Medicine! Sir RUSSELL BRAIN, in his reply, paid tribute to the two assistant secretaries, Dr. Alastair Hunter and Dr. J. F. Stokes, and their chief Sir Harold Boldero: "as a centre of coördination he far surpasses the cerebellum." The physician of today must always be anxious as to whether he has left out any of those investigations that may be crucial in diagnosis. Was there, then, any hope of internal medicine becoming simpler? He believed not. As more facts accumulated, there must be far more relations between them. Only ignorance was simple. Now that knowledge could no longer be brought into one mind, we must bring minds together. Having reached (according to biologists) the limit of evolution of the human brain, we must evolve in another direction—beyond *Homo sapiens* to another stage. For this he suggested the name *Homo consultans* (a term which expressed the highest activity of the human mind). Man must somehow become wise enough to develop in every sphere of life the art and technique of consultation.

The scientific sessions, held at Friends House, took the form of four symposia, with subsequent discussions.

THE SPRUE SYNDROME

The first scientific meeting of the congress was held under the chairmanship of Dr. NANNA SVARTZ (Stockholm).

STEATORRHŒA OR IDIOPATHIC FATTY DIARRHŒA

Dr. C. D. DE LANGEN (Utrecht) spoke of his clinical experience with tropical sprue in Batavia. He laid stress on the need to look on sprue as a disease that affected the whole man and not merely as a disturbance of digestion. Steatorrhœa of varying duration and severity might be associated with many conditions—with Graves's disease, Addison's disease, cardiac failure, Whipple's disease, or even the smoking of a Havana cigar. One of the most constant features of the disease was meteorism, and he did not believe that this was caused by an abnormal degree of gas formation due to fermentation processes in the small intestine; on the contrary, he attributed it to defective absorption of gas, this defect being caused by a disorder of circulation. In Dr. de Langen's opinion, the only people who developed sprue were those with an unstable peripheral circulation, and the circulatory disturbance was the basis of the general absorption defect. He denied that conditions in the capillary bed were entirely controlled by hydrostatic and osmotic pressure, and pointed out that every part of the body, including the intestinal wall, had a capillary system with special characteristics: conditions in the capillary bed varied not only from tissue to tissue but also from moment to moment in the same tissue. He agreed with many of Verzár's observations, but thought they could be interpreted better in terms of circulatory defects than in terms of a disturbance of phosphorylation. The assumption of a circulatory defect also explained the absence of morphological changes in the intestinal wall. Substances such as folic acid and strychnine, which improved absorption, did so by virtue of their effect on the circulation. Metabolites were taken up not only by the villi but also by the capillaries of the intestinal wall. Thus absorption became a diphasic process analogous to the diphasic excretion process of the kidney. Normally, the comparatively long fatty-acid molecules would "bounce" up and down on the outside of the capillary wall and would find it easy to penetrate head-on when the circulation was active and the "pores" were dilated. They would find their penetration inhibited by a defective circulation and thus their absorption would be impaired.

BLOOD CHANGES AND VITAMIN DEFICIENCY

Dr. A. L. FROEHLICH (Antwerp) began by discussing the blood levels of the minerals in idiopathic steatorrhœa. The values for both sodium and chloride were diminished, especially if there was much fluid loss. The potassium level usually remained unchanged but might drop occasionally with the disappearance of œdema. As deoxycortone administration did not improve these biochemical findings, they were not due to cortical deficiency of the adrenal. A drop in the calcium level with the appearance of tetany was common. This Dr. Froehlich attributed rather to a primary absorption defect than to the formation of calcium soaps, for it responded rapidly to injections of vitamin D. The serum-protein level was also reduced, mainly through reduction of the albumin fraction; the reason for this was either the abnormal use of amino-acids for energy purposes or, possibly, defective synthesis in the liver. The level rose with cortisone therapy. Total lipids were reduced. The free-cholesterol level remained normal, as did the neutral fat, whereas the esterified cholesterol was reduced. A similar picture occurred in malnutrition and pernicious anæmia. Dr. Froehlich thought that vitamin B_{12} might be necessary for cholesterol and phospholipid formation in the liver, for there was a rapid rise in the levels with the administration of this vitamin in cases of pernicious anæmia.

He went on to discuss the results of feeding experiments. The blood-sugar did not respond in the usual way to the ingestion of glucose. The curve remained flat, and in due course even hypoglycæmia might develop. Although he agreed with Frazer's theory of a mechanical bsorption defect, he did not regard it as a sufficient xplanation of the phenomenon of hypoglycæmia. An bnormal avidity for glucose by the liver in idiopathic teatorrhœa might be the basis for this reaction. Reviewng the different opinions about the response of blood-fat o a fat meal, he associated himself with those workers who found an absence of the normal postprandial hyperipæmia, mainly due to the absence of an increase of neutral fat. As far as the bile was concerned he found n absence of choline and bile salts in steatorrhœa, which he tentatively put down to liver failure. He disagreed with Ingelfinger and Moss's hypothesis of defective acetylcholine synthesis in the intestinal wall. These authors found no response to neostigmine injections in cases that showed a radiological "deficiency-pattern" of the small intestine, but found a prompt response after the administration of acetyl β-methylcholine. Dr. Froehlich, on the other hand, found in such cases that neostigmine markedly increased segmentation. Deficiency of vitamin B was a common finding, mainly in the tropical variety of the disease, and these changes could be satisfactorily explained by Frazer's competition theory. The macrocytic anæmia might be due either to a lack of intrinsic factor or to the poor absorption of the extrinsic one. Deficiency of the fat-soluble vitamins was common—mainly of vitamin D with associated osteoporosis and tetany. Hypoprothrombinæmia was not an unusual finding, though gross hæmorrhages were rare. Dr. Froehlich described one case of abnormal pigment formation in smooth muscle, very similar to the findings in experimental vitamin-E deficiency.

He believed in the essential difference between idiopathic steatorrhœa and tropical sprue. A third syndrome—the bile-lack syndrome—might have to be separated from the others.

ÆTIOLOGY OF IDIOPATHIC STEATORRHŒA AND RELATED CONDITIONS

Prof. A. C. **FRAZER** (Birmingham) then outlined his conception of the sprue syndrome. Neither the liver nor the adrenal could be looked upon as the organ primarily responsible for idiopathic steatorrhœa, for neither with gross liver damage nor in Addison's disease did anything resembling sprue syndrome occur. The primary fault lay in the intestine.

Fat-balance studies and experiments with the intraduodenal administration of glucose and even urea had shown that the absorption not only of fat, but also of substances which depend for their absorption on different mechanisms, was defective. The ubiquitous nature of the defect suggested that the cause was purely mechanical. Radiological studies had confirmed this opinion. The "deficiency pattern" which was a constant feature of idiopathic steatorrhœa could be reproduced in the normal individual by the administration of various mucigenic substances. The admixture of increasing quantities of mucus to an ordinary barium suspension in vitro would produce an increasing degree of flocculation. If non-flocculable barium was used for the radiography of the small intestine, the "deficiency pattern" would disappear. These facts suggested that the "deficiency pattern" was not due to incoördination of the intestinal musculature caused by vitamin deficiency, but to flocculation of the barium by excessive mucus. When non-flocculable barium was used, the radiological appearance of the small intestine was that of a dilated gut with reduced motility. Frazer regarded this reduced motility—probably involving the villi—and the barrier created by excessive mucus secretion as two important factors depressing and delaying absorption from the small intestine.

Wheat-flour played an important part in the pathogenesis of cœliac disease, for such children were cured if it was removed from the diet. On such a diet they differed from normal children only in so far as their abnormal sensitivity to wheat-flour remained. They would deteriorate again if wheat-flour was once more incorporated in the diet. The mechanism appeared not to be an allergic one. Intestinal motility was depressed and not stimulated; there was no eosinophilia; and skin tests with wheat-flour were negative. It could be shown that the agenising process was not responsible, for substitution of non-agenised for agenised flour did not affect the results. It was the gluten portion which was the essential factor. This was not a mucigenic stimulus, but interfered with intestinal motility. Frazer therefore believed that in cœliac disease depressed motility played a more important part than excessive mucus formation.

Delayed absorption led to the following secondary effects: in the first place the caloric intake and the intake of essential nutrients might be reduced and cause emaciation, especially if further aggravated by a deficient appetite. Secondly, owing to the prolonged presence of a rich medium in the small intestine, there was an extension of bacterial growth into regions which were normally almost sterile. This change in the intestinal flora caused fermentation of carbohydrates, with the production of short-chain fatty acids which stimulated mucus secretion. Frazer, however, agreed with de Langen that this was probably not the only cause of meteorism. Abnormal bacterial acitivity might lead to the formation of amines that could affect gastro-intestinal motility and possibly have an effect on the vessels of the small intestine.

The degree and extension of bacterial growth would determine the degree and severity of the disease. If it was slight, a mild "pre-sprue" condition would be created; with further extension a vicious circle was set up and there would be an overt sprue syndrome.

Primary precipitating causes of the disease were mucigenic stimuli. Infection, infestation, and the ingestion of rancid fats probably played important parts.

EFFECT OF CORTICOSTEROIDS

Dr. **CHESTER JONES** (Boston) started his communication by objecting to the term "idiopathic steatorrhœa," because, he said, this seemed to imply that the only feature of the disease was a disturbance of fat absorption. Absorption of many other substances was also defective, and he therefore preferred the non-committal term "sprue syndrome." The tropical variety responded so readily to liver extract, folic acid, and vitamin B_{12} that it was regarded by many as a deficiency disease. Dr. Chester Jones suspected that the two diseases had a common denominator, but did not regard their identity as proved.

He went on to discuss clinical, biochemical, and therapeutic findings in a series of 9 cases of non-tropical sprue from his own clinic. All showed marked clinical, radiological, hæmatological, and biochemical changes. The biochemical changes included depressed glucose and vitamin-A tolerance tests. The latter test and the presence of steatorrhœa he regarded as the most constant features of the disease. All cases had responded poorly to the usual form of therapy, and, after a control period, treatment with cortisone or A.C.T.H. was started. (Dr. Chester Jones made it clear that it was the well-known effect of these substances on cellular activity that had induced him to start this treatment, and that it should not be regarded as a form of replacement therapy.) All patients showed marked improvement after a latent period of a few days. There was a feeling of well-being, the stools diminished in number, and meteorism disappeared. Fat-balance studies revealed a reduction in the percentage of dietary fat excreted: the response of the chylomicron count after a fatty meal improved, and so did the glucose-tolerance curve. The serum-protein level rose. Hæmoglobin values responded slowly, and the vitamin-A tolerance showed little change. With cessation of therapy patients deteriorated again. One patient did not respond to the original course of treatment, but improved when the dose was raised.

Dr. Chester Jones thought that the essential feature of the disease was a general absorption defect due to a "disturbance in intestinal mucosal cell dynamics."

DISCUSSION

Dr. F. Bulic reported on an epidemic of steatorrhœa in the Yugoslav army during the late war. The men were on a deficient diet which consisted mainly of meat and small amounts of cornflour. Many developed a frothy diarrhœa, and the clinical appearance resembled the dry form of the famine syndrome. The addition of tinned food to the diet did not lead to improvement. The epidemic, however, was cut short when the company was moved to a different district, where fresh fruit and vegetables were available.

Dr. H. A. Salvesen (Oslo) discussed the incidence of low blood-pressure in idiopathic steatorrhœa. Hypertension, he said, did not occur, and there was a tendency to hypotension. No correlation between the blood-pressure findings and the presence of anæmia or electrolyte changes could be established. The cause was not known, but Dr. Salvesen assumed that it was due to the lack of absorption of a pressor factor, possibly caused by defective fat absorption. Hepatitis with jaundice also reduced the blood-pressure, and tying of the common bile-duct in Goldberger dogs prevented experimental hypertension, possibly owing to liver damage. The responsible factor was assumed to be of lipoid nature.

Dr. A. Vaz Serra (Portugal) spoke of the poor results of treatment along orthodox lines and advocated intensive study of such possible ætiological factors as food and infection.

Dr. W. T. Cooke (Birmingham) discussed the correlation of various constituents of the fæces in steatorrhœa. He had found a significant correlation between total solids and fat, but not between water content and fat. A significant correlation existed between fæcal water content and sodium and in some patients also between water and potassium.

Prof. C. Jiménez-Diaz (Madrid) stressed the importance of the active secretion of fat into the intestinal lumen, as opposed to the defective absorption of dietary fat. He gave details of such excretion into isolated intestinal loops in dogs. Calorimetric studies revealed a correlation between fæcal fat content and total caloric excretion.

Dr. R. H. Girdwood (Edinburgh) made some interesting observations on the fate of the antimegaloblastic principles. Both in tropical sprue and idiopathic steatorrhœa he had found poor absorption of folic acid, and he therefore favoured parenteral as well as oral medication. One of his patients did not respond to prolonged and intensive folic acid treatment, but improved rapidly when he had penicillin injections in addition. After oral medication the citrovorum factor appeared as such in the blood and urine of patients suffering from pernicious anæmia. In cases of steatorrhœa with normal hydrochloric acid it was broken down and appeared as folic acid.

Dr. D. Adlersberg (New York) expressed his bewilderment at the multiplicity of theories about the pathogenesis of the sprue syndrome. He reported the response of a number of cases, previously resistant to treatment, to the administration of cortisone, A.C.T.H., and Compound F. It was necessary to start with an adequate dose, to avoid reducing this too soon, and to carry on with maintenance treatment indefinitely. He regarded intestinal obstruction as a not infrequent fatal termination of the disease.

Prof. E. Martin (Geneva) discussed the different manifestations of sprue and the need to elucidate the reasons for these differences.

Prof. C. Holten (Denmark) described a case of steatorrhœa and tetany due to a non-malignant growth involving the mesentery.

Most speakers seemed to agree that the absorptive defect is a general one which makes it unlikely that interference with such specific processes as the phosphorylation mechanism is concerned. The ubiquitous nature of the defect, and the absence of morphological changes, suggest a mechanical cause. Excessive mucus secretion, depressed motility, and depressed circulation were put forward as possible explanations. It was generally assumed that the intestine itself was at fault. Vitamin deficiencies were on the whole looked upon as of a secondary nature. An adrenal defect does not seem to be a primary cause, and treatment with corticosteroids is not to be regarded as replacement therapy.

The most important advances on the therapeutic side appear to be the withholding of wheat-flour from the *diet of children with cœliac disease,*[1] and treatment with A.C.T.H. or corticosteroids in adults with severe and otherwise intractable steatorrhœa.

DISTURBANCES OF FLUID AND ELECTROLYTE BALANCE

First Session

The proceedings were opened formally by Prof. Gigon, president of the International Society of Internal Medicine.

HOMŒOSTATIC MECHANISMS

Prof. J. G. G. Borst (Amsterdam) said that many years' study of the kidney had convinced him that it was endowed with intelligence; but it was also a member of a team—in fact of several teams. Most changes in body-fluids could be interpreted in terms of three types of natural diuresis which he had previously described.[2] These three types were water diuresis, saline diuresis, and the diurnal rhythm of water and salt excretion; each type of polyuria had a corresponding type of oliguria. But for the second mechanism (saline diuresis) it would be highly dangerous for normal people to eat soup, and in fact we should all have to go on a low-salt diet. This second mechanism was predominantly affected when cardiac output was reduced, whether as a result of cardiac disease or of diminution in blood volume. When the second mechanism of oliguria was operating, it dominated the first mechanism, so that the body was no longer normally responsive to changes in plasma-electrolyte concentration. For example, in cardiac or nephrotic œdema, the plasma-salt concentration might be low without stimulating a water diuresis. Conversely, in dehydration salt might be retained although the salt content of the plasma was already high. In such patients, protein breakdown caused an osmotic diuresis, and the high urine volume might be misinterpreted as a sign that adequate water was being given.

For a long time he had thought that the only meaning of the third mechanism (diurnal rhythm) was to make the study of renal function more difficult; but it was in fact useful in avoiding nocturia and also in preventing salt and water retention during the day, which might give us œdema of the legs in the upright posture. In healthy people, diurnal rhythm was the dominant cause of change in salt and water excretion, so that at night salt and water excretion were low, although in terms of the second mechanism one might expect them to be high because of the increased venous return on lying down. Quite moderate circulatory insufficiency ht alter this, with reversal of the urine diurnal thm, and excretion of salt and water mainly through night. In patients treated with adrenocorticotropic mone (A.C.T.H.) or cortisone, the diurnal rhythm of and water excretion was less evident, and they readily eloped nocturia. In Dr. Borst's view, concomitant nges in salt and water excretion could be independent changes in glomerular filtration, and there was no dence that the tubular response to changes in cardiac tput was controlled by the adrenal cortex: in fact, tients with Addison's disease behaved as normals in s respect.

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[1] See *Lancet*, 1952, i, 836, 857.

[2] Borst, J. G. G., de Vries, L. A. *Ibid*, 1950, ii, 1.

RÔLE OF THE ADRENAL CORTEX

Dr. F. T. G. **Prunty** (London) emphasised that nsfers of water and electrolytes from one phase of dy-fluid to another might be as important as changes excretion. Although the relation between water and ctrolyte controlled the "long-term state" of the ganism, it was necessary to study the separate effects the adrenal cortex on water and on salt excretion.

Patients with Addison's disease did not give a normal sponse to water ingestion, even when they were aintained with deoxycortone. Also they tended to crete excess of water during the night. Normal water uresis could be restored by giving 100 mg. of cortisone ily. It had been postulated that cortisone acted by activating posterior pituitary hormone; but the sponse of a patient with Addison's disease to pitressin d been unaffected by cortisone. Patients with hypotuitarism likewise had impaired water diuresis, and them both A.C.T.H. and cortisone corrected this normality.

There was great individual variation in the effect of .T.H. on sodium and chloride excretion. Some patients owed only a transient retention of these ions, with er a negative balance in spite of continued hormone ministration. Others had prolonged retention, with nical œdema requiring the use of mercurial diuretics. a patient with Addison's disease, cortisone was effective by comparison with deoxycortone, and even emed to antagonise the salt-retaining effect of deoxyrtone. It was possible that there was a natural adrenal rmone predominantly concerned with electrolyte metalism, in view of the demonstration by Tait et al.[3] that rtisone could not account for any significant part of e salt-retaining action of adrenal cortical extract. ere was a good deal of detailed evidence that adrenal rtical hormones promoted a shift of fluid from cells extracellular fluid; this expansion of extracellular lume might affect renal excretion of salt and water dependently of any direct hormone action on the bule cells.

RENAL FAILURE

Prof. **Robert Platt** (Manchester) discussed the rious expedients whereby kidneys whose excretory nction had largely been destroyed by disease continued preserve the water and salt content of the body. In st cases of advanced renal disease, until the last few ys of life, there was neither œdema nor dehydration, d the plasma concentration of sodium and potassium s within normal limits. He and his colleagues had alysed the renal function of rats which had had about ree-quarters of their kidney substance excised. The cretion of urea, creatinine, sodium, potassium, and ter in these animals was strikingly similar to that seen human renal failure; and it might be concluded that e essential disability in human renal failure was merical insufficiency of nephrons, and not a distortion the function of those nephrons which remained. In man renal failure, the blood-urea often remained at an evated but constant level for considerable periods, and such circumstances the daily output of urea must be normal. This meant that each of the surviving nephrons must be excreting perhaps five times the amount of urea which a nephron in a normal kidney would be excreting; in other words, there must be a continuous osmotic diuresis. This could account for the polyuria of renal failure, and also for the diminished reabsorption of sodium. There must be diminished reabsorption of sodium, for the filtered load of sodium would be reduced in proportion to the filtration-rate, whereas the excretion of sodium was within normal limits. The excretion of potassium in the urine sometimes exceeded the calculated amount of potassium filtered by the glomeruli, showing secretion of potassium by the tubules; and there was sometimes evidence that the tubules were secreting water, or at least a hypotonic fluid. This was easier to demonstrate in renal failure, because of the low glomerular filtration of water and other substances; but there was no reason to suppose it did not happen in the normal kidney. Study of the performance of the failing kidney suggested that the patient's interests could be best served by allowing him a liberal intake of salt and water, but restricting protein to 30–40 g. daily.

DIABETIC COMA

Dr. **René S. Mach** (Geneva) said that the amount of water and electrolyte lost through the kidney in diabetic coma could be assessed either by stopping insulin in a patient during a balance experiment, or by observing the amounts retained during recovery from natural coma. Large amounts of sodium and chloride were lost; this came mostly from the extracellular fluid, but some might come from the bones. In acidosis intracellular sodium was often decreased, and it was not known whether some of the sodium lost in diabetic coma came from the cells. Potassium was also lost in large amount, mainly from the intracellular compartment; the potassium lost could not be accounted for by protein breakdown. Water was also lost—mainly through the kidneys but to some extent also by hyperventilation and by vomiting. The plasma levels of sodium and chloride might be normal, but were more commonly reduced owing to glucose infusions. Usually the plasma level of potassium was not reduced at first, but fell during treatment. Several factors were concerned in the expansion of extracellular fluid, the increased urinary loss of potassium during saline infusion, and the entry of potassium into the cells during glycogen synthesis. The loss of water and electrolytes in the urine was evident before there was significant acidosis, and was then related to the increasing glycosuria. The onset of acidosis increased the loss of sodium and potassium. Keto-acids were excreted in combination with base; also, acidosis lowered the valency of cellular organic anions, and so made base available for excretion.

Clinically, the loss of extracellular electrolyte and water led to reduced blood volume, with peripheral vascular collapse and renal ischæmia. During recovery, the fall in serum-potassium might cause muscle paralysis, gasping respiration, and myocardial failure. Hypertonic glucose solutions were contra-indicated in treating diabetic coma, for they aggravated the osmotic diuresis and so the loss of water and electrolytes.

DISCUSSION

Dr. G. **Sala** (Italy) described studies he had made on the effect of cortisone on water diuresis in patients with Addison's disease. He had found some increase in the glomerular filtration-rate. Dr. E. **Coelho** (Lisbon) discussed the plasma-potassium in Addison's disease. He had found that the serum-potassium level might bear little relation to the total body content of potassium, and he showed electrocardiograms which illustrated the effect of changes in potassium metabolism on the heart. Dr. E. **Azérad** (France) had shown that in normal

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Tait, J. F., Simpson, S. A., Grundy, H. M. *Ibid*, 1952, i, 122.

subjects about 80% of the filtered potassium was reabsorbed.

Dr. L. WISLICKI (Jerusalem) had observed that nicotinamide caused a notable suppression of urine flow even after diuresis had been induced. This antidiuresis still occurred in hypophysectomised animals and so was presumably independent of the antidiuretic hormone mechanism. Although there was some drop in blood-pressure, the antidiuresis lasted for some hours after the blood-pressure had returned to normal. Examination of the kidneys showed hydropic degeneration of the tubule cells, and he concluded that nicotinamide had a direct toxic action on tubular function.

Second Session

Sir HAROLD HIMSWORTH, who took the chair at the second session, cautiously disclaimed any special knowledge of the subject other than by way of intellectual inheritance from his predecessor in the chair of medicine at University College, Sidney Ringer. Ringer's laboratory assistant had used tap water instead of distilled water in preparing perfusion solutions, and the impact of this chance on Ringer's prepared mind had really paved the way for the present expert discussion.

UNDERNUTRITION

Prof. R. A. MCCANCE, F.R.S., and Miss E. M. WIDDOWSON, D.SC. (Cambridge) described some of the ways in which the composition of the body was affected by undernutrition. Some of these had long been familiar, such as the decrease in fat and the small size of the heart, liver, and muscles. Improved methods of analysis, and the breakdown of body composition into fat, water, and "lean body mass" had helped to define the changes. Their own studies had shown that the proportion of the body occupied by extracellular fluid was always increased in undernutrition. None of the explanations for this increase in extracellular fluid was entirely adequate. They believed that replacement of body space previously occupied by fat and cellular tissue was an important cause of the increase in extracellular fluid. A lowered concentration of plasma-proteins and a high-salt intake would aggravate œdema. Although an increase in extracellular fluid was constant, clinical œdema might be absent in undernutrition—a fact appreciated by Dürer, who had drawn "Hunger" as an emaciated horseman without œdema.

Dr. McCance and Dr. Widdowson had analysed more closely the small size of the liver in undernutrition. By estimation of the ribonuclease content of the liver and of the individual liver cell, the number of liver cells could be computed; and it appeared that in undernutrition the liver cells were individually shrunken—a finding which had been anticipated qualitatively by the histologists of the last century.

CELLULAR HYPERHYDRATION

Dr. J. HAMBURGER (Paris) discussed a syndrome of cellular hyperhydration which was becoming recognised as a result of increasing awareness of the distinction between extracellular and cellular fluid. The syndrome could be produced experimentally either by reducing the extracellular osmotic pressure by water infusion, or by exposing the cells to a variety of toxic agents, including cyanide, histamine, carbon dioxide, and acids. A combination of experimental studies with clinical observations had led him to delineate a clinical picture whose chief features were nausea and anorexia, weakness, headache, cramps, and convulsions. There was oliguria and some nitrogen retention. Laboratory investigation showed an increased difference between estimates of total body-water and extracellular fluid. There was an increase in mean corpuscular volume, and a fall in the effective osmotic pressure of plasma. It was important to recognise the syndrome clinically, for the patient might otherwise be treated with water or glucose solution, whereas it responded well to hypertonic saline. Cellular overhydration might sometimes coexist with extracellular overhydration, in which case further salt should not be given; in such cases he had seen good results from hypertonic intestinal perfusion, which removed water from the cells without adding salt to the body.

BASE-BINDING BY SERUM-PROTEIN

Dr. O. J. BROCH (Oslo) discussed hyponatræmia and the base-binding effect of serum-proteins. A low serum-sodium was not uncommon in cachectic states, especially with fever, and giving salt might not raise the serum-sodium level. He had observed patients in whom the total base content of the serum was low but the determined anions (HCO_3 and Cl) were normal, so that there was an "acid surplus" of as much as 21 m.eq. per litre in one patient with hepatic cirrhosis. He attributed this to a diminution in the base-binding capacity of serum-protein. Conversely, it was possible in patients with liver cirrhosis to increase the total base of serum without increasing the anion content; this pointed to an increase in the base-binding by protein. Experimental work in the distribution of electrolytes between serum and extracellular fluid had supported the view that the serum-proteins could bind different amounts of base under different conditions; in this way they could considerably influence osmotic regulation within the body. *When hyponatræmia was due to change in the base-binding power of serum-protein, there was no disturbance of water equilibrium, and no indication therefore for giving salt in treatment.*

RESPONSE TO INJURY

Mr. A. W. WILKINSON (Edinburgh) reviewed the disturbances in body-fluids which were likely to be met with in surgical patients. Any injury, even a surgical operation, was followed by profound metabolic changes, with marked alteration in the urinary output of nitrogen, water, and electrolytes. There was evidence that the adrenal cortex was concerned in these changes, which represented a normal response to injury, and could not readily be modified. In most cases the body could withstand these metabolic distortions without parenteral therapy other than blood-transfusion; but losses of body-fluids might lead to rapid depletion of water and electrolytes, and necessitate parenteral replacement therapy.

Some patients, notably those with œsophageal or pyloric obstruction, were already partly starved and depleted of potassium. Adequate preoperative treatment was needed in some patients to promote wound healing. Although fistulæ only rarely complicated upper abdominal surgery, they were important when they occurred, because large amounts of water and electrolytes were lost but it was not always possible to collect and measure the discharges. In the presence of inflammation, sodium was retained by the kidneys, and might produce distortion in the internal distribution of body-fluid. Alkalosis and acidosis were less important clinically than changes in sodium and potassium distribution. Other surgical conditions which demanded close attention to body-fluid balance were ileostomy, peritonitis, and intestinal obstruction.

DISCUSSION

Dr. D. A. K. BLACK (Manchester) suggested that, since clinical syndromes of electrolyte depletion usually involved several electrolytes, the effects on other electrolytes of induced depletions of one electrolyte required further study. As an example, he showed that induced potassium depletion led to sodium retention if sodium was available in the diet. There was expansion of extracellular fluid, and this might be a small-scale replica of the expansion found in undernutrition. Clinically, there was some evidence that sodium retention and alkalosis might be advantageous in mitigating the effects of potassium loss.

In patients with pyloric stenosis Dr. A. Svanborg (Stockholm) had encountered alkalosis, which was associated with low serum-potassium, and responded to potassium but not to sodium salts.

Dr. M. Soriano-Jiménez (Madrid) had found high titres of antidiuretic substances in the urine of patients with œdema and ascites of hepatic or renal origin. Dr. A. Gajdos (France), using the antipyrin method, had found little difference in the water content of the body of normal subjects and of patients with liver disease. Dr. Ask-Upmark (Norway) had seen osteomalacia follow gastric resection in several patients; he had reported this some years ago, but had not seen other reports of its occurrence.

THE NEUROTROPIC VIRUSES

Sir Russell Brain, who presided at the session on this subject, said that poliomyelitis either had become commoner or was being recognised more often. The study of it had increased in complexity and now attracted attention widely.

POLIOMYELITIS AND COXSACKIE GROUP

Dr. John Paul (Yale), in opening the discussion, said that man himself was the principal source of infection with the poliomyelitis virus. Insects such as flies and cockroaches could harbour virus, but these were not essential agents for spread. The new method of tissue culture devised by J. F. Enders, of Boston, had made some investigations possible in the test-tube, and the era of experimental infection of monkeys, which had held back research because of expense, was perhaps over. The identification of strains had become easier. The Lansing strain, the first to be named, was outnumbered by the much more common Brunhilde strain; the Leon strain was comparatively rare. Immunological tests had shown that myelitis was unusual in systemic infection with the virus. Children withstood this better than adults, in whom the onset was more insidious, two distinct bouts of fever were less common, the illness was longer, pain in the limbs and back was more pronounced, and the prognosis was more serious. At present 25% of those attacked were over 15 years of age. Provoking influences, such as trauma, stress, surgical operations, and immunisations, affected the host; and environmental influences—particularly climate and season—affected the virus. The greatest change in the natural history of the disease was, however, associated with hygiene. In crowded cities, where the standard of living was low, children were born with a high titre of antibodies: this titre rapidly fell but during childhood rose so that by the age of 15 most children had immunity. A high antibody titre was not the same as a high level of immunity, but it did show "footprints of past infections." In these overcrowded communities anterior poliomyelitis remained an endemic disease of young children—i.e., infantile paralysis. The North Alaskan Eskimo showed a completely different picture. In children there was hardly any evidence of immunity; and when the disease occurred it was in epidemic form, attacking adults as well as children. Between these extremes there was every graduation.

Dr. Paul believed that poliomyelitis was not a respiratory infection, but that the usual portal of entry was the mouth. Why warm weather favoured the spread was unknown. Prevention was the hope. To rid the world of the virus was probably impossible; and to be free of endemicity, like Eskimos, carried severe risks. Immunisation was in its infancy; there was no adequate vaccine, and certainly none specific to each of the three strains, though repeated tissue culture might alter the property. Courage would be needed to test on a large scale a vaccine which would ultimately have to be assessed on man. Gamma-globulin given to exposed individuals was another possibility; but results with it were not yet known.

Dr. H. von Magnus (Copenhagen) described the diseases caused by Coxsackie viruses; these viruses were now recognisable by the fact that in suckling mice they gave rise to myositis, pancreatitis, &c. The presence of virus and positive immunological tests had to be interpreted most carefully because double infection was common. Paralysis in a patient with a positive culture of Coxsackie (C) virus who later developed immunological evidence of infection was probably never due to C virus but to a poliomyelitis virus which was a co-traveller. The 16 strains of C virus caused a medley of illnesses, of which herpangina, epidemic myalgia, and short-lived fever were the commonest. Herpangina usually manifested itself with headache, pyrexia, and a sore throat caused by a vesicular enanthem in the tonsillar region. In both herpangina and Bornholm disease infection with Coxsackie virus was constantly present. Possibly some of the "P.U.O.s" now known to be caused by a similar virus would later be recognised as distinct clinical entities. Because of multiplicity of types of C virus, routine laboratory investigation was impossible.

Dr. W. Ritchie Russell (Oxford) said that the acute case of poliomyelitis made exacting demands on doctors and nurses. Continuity of treatment, preferably in a large general hospital or in a special hospital, was desirable provided patients could be nursed so as to prevent spread of infection. The latent period between infection and manifestation of possible paralytic symptoms needed the most careful supervision. Sedation was desirable, although the best sedative was undetermined. The simplest tests, such as asking a child to kiss his knee three times a day, were desirable; and children should be protected against exhaustive muscle testing in the prodromal period. Even transfer to hospital carried a risk. In cases where disturbed respiratory function was suspected, passive breathing in a respirator possibly had advantages. Early diagnosis would be more important if a host-cell interference drug was discovered; and mobile teams might be necessary. Treatment by physiotherapy was important. There was no room for timid gentleness after the acute stage; fatigue of muscle then had no deleterious effect, and movements to prevent spasm were beneficial. Instruments for accurate measurement of muscle recovery were useful. Pharyngeal microphones overcame some of the difficulties of noisy respirators. Bulbar cases were best nursed out of respirators, so that they could have postural drainage.

DISCUSSION

Dr. W. N. Pickles (Aysgarth) showed an interesting chart of five cases of Bell's palsy occurring at the same times as herpes zoster and chickenpox. These were the only cases of Bell's palsy in his practice in 20 years.

Prof. C. H. Stuart-Harris (Sheffield) described an epidemic of herpangina in four children aged 3 to 13. Fæces in dilution of 1 in 10 million yielded C virus.

Dr. O. Thordarsen said that Bornholm disease had been present in Iceland since 1847. It had caused outbreaks each year since 1928. In 1947, out of 57,000 people in Reykjavik 225 were attacked; and C virus was present in a high percentage of random samples.

Dr. L. Condorelli said that in Italy infection with Coxsackie virus caused few signs of fever but principally neurological symptoms—sometimes encephalitic and sometimes, apoplectic—and at other times lumbar tenderness. Despite very high counts in the cerebrospinal fluid recovery was usually complete in 14 days.

Dr. R. E. SMITH (Rugby) said that just as anterior poliomyelitis was more severe in the adult, so also was posterior poliomyelitis or herpes zoster. Reports on treatment with vitamin B suggested that the ageing posterior-born cells could be supported in their combat with the virus. Two clinical types were recognisable, one of which was associated with chickenpox.

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ANTIBIOTICS IN MAN

At the concluding session, with Sir LIONEL WHITBY in the chair, Sir ALEXANDER FLEMING, F.R.S., discussed antibiotics in general terms, with more special reference to the factors to be taken into account in selecting the right drug or combination of drugs in the treatment of any infection. All the antibiotics, he said, were to some extent selective in their action: though some might be effective against a wider range of micro-organisms than others, yet none were inhibitory to all bacteria. Consequently in antibiotic therapy there were two main problems. First it was necessary to use an antibiotic effective against the infecting microbe. This necessitated a considerable amount of laboratory control, not only for identification of the organism but also for determination of its sensitivity in vitro to the various antibiotics. Secondly, the physician must ensure that the antibiotic reached the organisms in the body in a concentration high enough to destroy them. This problem, Sir Alexander said, was often neglected. It was necessary to think further than the mere introduction of an antibiotic into the blood-stream, for this was often insufficient to allow penetration into an abscess cavity or across the blood-brain and other barriers.

He then turned to the question of combinations of antibiotics in therapy. Such combinations might be considerably more effective than the simple summation of the individual actions of the drugs alone, though it appeared from the work of Jawetz and his colleagues that in many cases the addition of one antibiotic to another might cause a diminution of the activity of both. To illustrate the complexities of the subject, the example was quoted of an organism which was sensitive to penicillin in vitro. The addition of aureomycin caused a lessened response to penicillin, the two drugs being antagonistic to each other. When, however, the same organism was made artificially resistant to penicillin, the addition of aureomycin caused an increased response, the two drugs now acting synergistically.

Finally, Sir Alexander mentioned the subject of nomenclature. By definition, one of the fundamental features of an antibiotic, he said, was its production by a living organism. But 'Chloromycetin' was now produced solely by synthetic means. Should this substance, therefore, be cast out of the antibiotic fold and listed merely as a chemotherapeutic agent, like arsphenamine, the sulphonamides, or isonicotinic acid hydrazide? One might drop the term antibiotic and call all these substances chemotherapeutic agents, but on the whole he felt it would be better to continue the present practice of calling a substance an antiobiotic if it was originally produced by a living organism.

DOSES AND COMPLICATIONS

Dr. F. MAGRASSI (Naples) devoted his talk to various aspects of the posology of penicillin, streptomycin, aureomycin, and chloramphenicol, and to the complications which can arise from the use of these substances. In the earliest days of penicillin therapy, he said, there was thought to be an exact correspondence between the antibacterial power of the antibiotic in vitro and its activity in vivo, and participation by the defensive mechanisms of the body was held to be insignificant. Today this conception had lost most of its value, not only for penicillin but also for streptomycin, aureomycin, and chloramphenicol. Though in many cases one found a correspondence between the sensitivity of an infecting organism in vitro and its response to an antibiotic in vivo, there were cases in which antibiotics were clinically effective even though the organism appeared resistant in vitro. Similarly, in some instances the organism might be highly sensitive in vitro to an antibiotic which had negligible value clinically. Many of these latter results could be explained by the failure of the antibiotic to reach the organism in sufficient concentration by the route employed.

The complications sometimes associated with antibiotic therapy might arise through various mechanisms. Direct toxicity varied considerably with different antibiotics. The toxicity of penicillin was so low that it could be regarded as practically non-existent, whereas that of streptomycin was considerable. Complications arising from hypersensitivity to antibiotics were numerous: they were similar to allergic reactions to other drugs and affected commonly the nervous, cutaneous, and digestive systems. In this category of complications Dr. Magrassi discussed the blood dyscrasias following chloramphenicol. There was, he said, no evidence of direct toxicity of the drug on the bone-marrow, and it seemed likely that the disorders were allergic manifestations in patients hypersensitive to the antibiotic.

Another important group of complications of antibiotic therapy were those resulting from the action of the drugs on the bacterial flora of the body. The organisms causing the infection for which an antibiotic was being administered might become resistant to the drug and necessitate a revision of treatment. Alternatively, elimination of the infecting organisms might be followed by overgrowth of other bacteria or fungi resistant to the antibiotic. These might cause extension of the disease if their pathogenic propensities were sufficient. Finally, the possibility of disturbances in the synthesis or utilisation of vitamins and other substances by interference with the normal intestinal bacterial ecology must be taken into account in the management of antibiotic therapy.

EFFECTIVE CONCENTRATIONS

Prof. ALAN KEKWICK (London) said that the standard doses of the drugs were, in the main, designed to produce bacteriostatic or bactericidal concentrations in the blood, but such levels did not necessarily reflect an equivalent therapeutic effectiveness in other tissues. Knowledge of the distribution of antibiotics throughout many of the tissues in man was still largely incomplete, though a good deal of information was available regarding the concentrations attainable in many body-fluids and cavities. Penetration through the blood-brain barrier—notoriously poor for penicillin, even after large doses—continued to give cause for concern. Hardly any terramycin reached the cerebrospinal fluid from the blood, while the level of streptomycin was only a fifth to a tenth of that in the plasma. Aureomycin concentrations of about half that in the plasma might be attained only after a delay of several days. Chloramphenicol, however, penetrated with the greatest facility, giving levels up to three-quarters the plasma level in a very short time. Ease of penetration of these five antibiotics into body cavities followed a similar pattern to that of the cerebrospinal fluid. In the pleura the concentrations of penicillin, streptomycin, and terramycin that might be attained were about half to a quarter of the plasma levels. Aureomycin penetrated better, but only after considerable delay, while chloramphenicol rapidly gave high concentrations. Similar penetrative powers were observed for the pericardial sac and the peritoneal cavity, concentrations in the latter being somewhat higher than those in the pleural cavities. In the nasal sinuses and the aqueous and vitreous of the eye the levels of each antibiotic attainable were considerably lower than those elsewhere.

All five substances were excreted by the kidney. About 75% of the penicillin or terramycin administered might be recovered in biologically active form from the urine, while about 50% of streptomycin was recoverable. Both aureomycin and chloramphenicol were largely destroyed in the body, and only 15% of the former and 10% of the latter were excreted in the urine in a form active against bacteria.

Penicillin and streptomycin had the advantage over the other three antibiotics that they were largely nonirritant and could be introduced in quite large doses into the subarachnoid space, from which some absorption into the blood-stream occurred, giving levels about 10% of those in the cerebrospinal fluid. There was very little absorption from the pleural and peritoneal cavities, especially when these were inflamed.

The amount of each antibiotic absorbed after oral administration varied considerably. About 20% of penicillin was absorbed by this route, the remainder being destroyed by bacteria in the large intestine. Streptomycin was even more poorly absorbed (about 5%), but since the remainder was not destroyed it was available in active form for use in purely intestinal infections. Aureomycin was absorbed fairly well from the intestine and was unique amongst the antibiotics in current use in that it was taken up by the reticuloendothelial system, from which it was then slowly released into the blood-stream. Chloramphenicol was the most rapidly and efficiently absorbed antibiotic, while terramycin, though fairly readily absorbed, seemed to show a threshold of maximum absorption for a dose of about 1 g. every eight hours. No additional uptake occurred when this dose was increased.

IMPACT OF ANTIBIOTICS

Prof. C. JIMÉNEZ-DIAZ (Madrid) spoke of the various harmful effects of the antibiotics and also of certain of their beneficial actions other than the eradication of infections. Among the harmful effects, he discussed in some detail the toxicity of antibiotics, especially in relation to allergic phenomena. Though these were manifested frequently by simple cutaneous responses, sometimes there were more serious reactions such as the polyarteritis occasionally seen after penicillin administration. Direct toxic effects of antibiotics were uncommon. Lesions of the 8th cranial nerve might follow the use of streptomycin, and occasionally this drug was responsible for thrombocytopenic purpura, leucopenia, and aplastic anæmia. Of considerable importance among the harmful effects was the development of resistance of bacteria to antibiotics. The frequency of occurrence of penicillin-resistant staphylococci had risen markedly in recent years, and resistance had been observed in various bacteria after treatment with terramycin, aureomycin, and chloramphenicol. Sometimes an organism developed resistance simultaneously to two antibiotics during treatment with one of them. This phenomenon of "crossed resistance" was seen most frequently between aureomycin and terramycin or chloramphenicol.

Dr. Jiménez-Diaz laid great stress on the importance of normal bacterial symbiotic relationships in the body and on the disorders that may result from their disturbance. By interference with the intestinal bacteria which normally assisted digestion, antibiotics might give rise to malnutrition. This had been seen both in experimental animals and in clinical practice. Digestive disturbances, varying from mild dyspepsia to severe diarrhœa and vomiting, might result from the disturbance of bacterial symbiosis, which opened the way to secondary invasion by organisms resistant to the antibiotic in use. In the intestinal tract these organisms were usually yeasts, while in the respiratory system coliform bacilli or resistant staphylococci might assume predominance.

From harmful effects Dr. Jiménez-Diaz then turned to some aspects of antibiotic usage very different from those which are generally familiar. These reactions, whose character is still little known, concern the metabolism and respiration of tissues and organs, general nutrition and growth, and the repair of tissue injuries. As an example of such activities he cited the beneficial effect of aureomycin in infective hepatitis. It seems that the antibiotic has no direct action on the virus, but acts by improving the nutrition of the hepatic cells. Some cases of hepatic cirrhosis had, he said, shown surprisingly good response to aureomycin. Terramycin, too, seemed to be of considerable value in the treatment of experimental cirrhosis in animals. He predicted, in conclusion, that the future would bring to light many useful actions of the antibiotics apart from their purely antibacterial rôles.

DISCUSSION

The discussion which followed the opening papers covered a wide variety of aspects of antibiotic action, ranging from electron micrographs illustrating the effect of penicillin on *Salmonella typhi* to the treatment of peptic ulcers with terramycin (Dr. NAJIB-FARAH, Alexandria). In the latter instance it seemed that many factors other than the terramycin must have played their part in the beneficial responses of the patients described, and it would be premature to conclude that terramycin is now the remedy of choice for these conditions.

Commenting on the so-called barriers to the passage of antibiotics into certain tissues, Prof. C. D. DE LANGEN (Utrecht) spoke of the importance of adequate capillary pressure and described the case of a severely shocked patient with pneumonia. Initially this patient showed no response to penicillin, but after a blood-transfusion the infection rapidly subsided under the influence of the same antibiotic. Professor de Langen interpreted this response as indicating that the penicillin could not reach the infected tissues unless there was enough pressure to drive it out of the capillaries.

Among the speakers who discussed the harmful effects of antibiotics was Dr. K. G. BENGTSSON (Stockholm), who reported a case in which typical pernicious anæmia developed in a patient who had received about 100 grammes of chloramphenicol in about six weeks. The anæmia responded satisfactorily to liver therapy.

A new note of caution was struck by Dr. B. OLHAGEN (Stockholm), who described several cases in which acid-fast bacilli had appeared in the sputum of patients receiving antibiotics. Guineapig inoculation showed that these organisms were not tubercle bacilli, and it was thought that they were a species of acid-fast fungus. Dr. Olhagen thought it advisable to carry out animal inoculation tests whenever acid-fast bacilli are found in a specimen of sputum; but such a procedure, however desirable, would certainly present difficulties in laboratories handling large numbers of tuberculous specimens.

☞ Members of the congress paid visits, in small parties, to many of the principal London hospitals, and also travelled more widely. Those attending numbered more than 500, from over 30 countries.

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sometimes, apoplectic—and at other times lumbar tenderness. Despite very high counts in the cerebrospinal fluid recovery was usually complete in 14 days.

Dr. R. E. SMITH (Rugby) said that just as anterior poliomyelitis was more severe in the adult, so also was posterior poliomyelitis or herpes zoster. Reports on treatment with vitamin B suggested that the ageing posterior-horn cells could be supported in their combat with the virus. Two clinical types were recognisable, one of which was associated with chickenpox.

Prof. E. OLIVER (Madrid) described cases of Coxsackie-like infections associated with disease of the central nervous system and hepatic and pancreatic lesions.

No-one answered categorically the only question asked: Does lumbar puncture aggravate in poliomyelitis?

ANTIBIOTICS IN MAN

AT the concluding session, with Sir LIONEL WHITBY in the chair, Sir ALEXANDER FLEMING, F.R.S., discussed antibiotics in general terms, with more special reference to the factors to be taken into account in selecting the right drug or combination of drugs in the treatment of any infection. All the antibiotics, he said, were to some extent selective in their action: though some might be effective against a wider range of micro-organisms than others, yet none were inhibitory to all bacteria. Consequently in antibiotic therapy there were two main problems. First it was necessary to use an antibiotic effective against the infecting microbe. This necessitated a considerable amount of laboratory control, not only for identification of the organism but also for determination of its sensitivity in vitro to the various antibiotics. Secondly, the physician must ensure that the antibiotic reached the organisms in the body in a concentration high enough to destroy them. This problem, Sir Alexander said, was often neglected. It was necessary to think further than the mere introduction of an antibiotic into the blood-stream, for this was often insufficient to allow penetration into an abscess cavity or across the blood-brain and other barriers.

He then turned to the question of combinations of antibiotics in therapy. Such combinations might be considerably more effective than the simple summation of the individual actions of the drugs alone, though it appeared from the work of Jawetz and his colleagues that in many cases the addition of one antibiotic to another might cause a diminution of the activity of both. To illustrate the complexities of the subject, the example was quoted of an organism which was sensitive to penicillin in vitro. The addition of aureomycin caused a lessened response to penicillin, the two drugs being antagonistic to each other. When, however, the same organism was made artificially resistant to penicillin, the addition of aureomycin caused an increased response, the two drugs now acting synergistically.

Finally, Sir Alexander mentioned the subject of nomenclature. By definition, one of the fundamental features of an antibiotic, he said, was its production by a living organism. But 'Chloromycetin' was now produced solely by synthetic means. Should this substance, therefore, be cast out of the antibiotic fold and listed merely as a chemotherapeutic agent, like arsphenamine, the sulphonamides, or isonicotinic acid hydrazide? One might drop the term antibiotic and call all these substances chemotherapeutic agents, but on the whole he felt it would be better to continue the present practice of calling a substance an antiobiotic if it was originally produced by a living organism.

DOSES AND COMPLICATIONS

Dr. F. MAGRASSI (Naples) devoted his talk to various aspects of the posology of penicillin, streptomycin, aureomycin, and chloramphenicol, and to the complications which can arise from the use of these substances. In the earliest days of penicillin therapy, he said, there was thought to be an exact correspondence between the antibacterial power of the antibiotic in vitro and its activity in vivo, and participation by the defensive mechanisms of the body was held to be insignificant. Today this conception had lost most of its value, not only for penicillin but also for streptomycin, aureomycin, and chloramphenicol. Though in many cases one found a correspondence between the sensitivity of an infecting organism in vitro and its response to an antibiotic in vivo, there were cases in which antibiotics were clinically effective even though the organism appeared resistant in vitro. Similarly, in some instances the organism might be highly sensitive in vitro to an antibiotic which had negligible value clinically. Many of these latter results could be explained by the failure of the antibiotic to reach the organism in sufficient concentration by the route employed.

The complications sometimes associated with antibiotic therapy might arise through various mechanisms. Direct toxicity varied considerably with different antibiotics. The toxicity of penicillin was so low that it could be regarded as practically non-existent, whereas that of streptomycin was considerable. Complications arising from hypersensitivity to antibiotics were numerous: they were similar to allergic reactions to other drugs and affected commonly the nervous, cutaneous, and digestive systems. In this category of complications Dr. Magrassi discussed the blood dyscrasias following chloramphenicol. There was, he said, no evidence of direct toxicity of the drug on the bone-marrow, and it seemed likely that the disorders were allergic manifestations in patients hypersensitive to the antibiotic.

Another important group of complications of antibiotic therapy were those resulting from the action of the drugs on the bacterial flora of the body. The organisms causing the infection for which an antibiotic was being administered might become resistant to the drug and necessitate a revision of treatment. Alternatively, elimination of the infecting organisms might be followed by overgrowth of other bacteria or fungi resistant to the antibiotic. These might cause extension of the disease if their pathogenic propensities were sufficient. Finally, the possibility of disturbances in the synthesis or utilisation of vitamins and other substances by interference with the normal intestinal bacterial ecology must be taken into account in the management of antibiotic therapy.

EFFECTIVE CONCENTRATIONS

Prof. ALAN KEKWICK (London) said that the standard doses of the drugs were, in the main, designed to produce bacteriostatic or bactericidal concentrations in the blood, but such levels did not necessarily reflect an equivalent therapeutic effectiveness in other tissues. Knowledge of the distribution of antibiotics throughout many of the tissues in man was still largely incomplete, though *a good deal of information was available regarding the concentrations attainable in many body-fluids and cavities. Penetration through the blood-brain barrier*—notoriously poor for penicillin, even after large doses—continued to give cause for concern. *Hardly any* terramycin reached the cerebrospinal fluid *from the* blood, while the level of streptomycin was *only* a fifth to a tenth of that in the plasma. Aureomycin concentrations of about half that in the plasma might be attained only after a delay of several days. Chloramphenicol, however, penetrated with the greatest facility, giving levels up to three-quarters the plasma level in a very short time. Ease of penetration of these five antibiotics into body cavities followed a similar *pattern to that of the cerebrospinal fluid.* In the pleura *the concentrations of penicillin,* streptomycin, and terramycin that might be attained were about half to a quarter of the plasma levels. Aureomycin penetrated better, but only after considerable delay, while chloramphenicol rapidly gave high concentrations. Similar penetrative powers were observed for the pericardial sac and the peritoneal cavity, concentrations in the latter being somewhat higher than those in the pleural cavities. In the nasal sinuses and the aqueous and vitreous of the eye the levels of each antibiotic attainable were considerably lower than those elsewhere.

All five substances were excreted by the kidney. About 75% of the penicillin or terramycin administered might be recovered in biologically active form from the urine, while about 50% of streptomycin was recoverable. Both aureomycin and chloramphenicol were largely destroyed in the body, and only 15% of the former and 10% of the latter were excreted in the urine in a form active against bacteria.

Penicillin and streptomycin had the advantage over the other three antibiotics that they were largely non-irritant and could be introduced in quite large doses into the subarachnoid space, from which some absorption into the blood-stream occurred, giving levels about 10% of those in the cerebrospinal fluid. There was very little absorption from the pleural and peritoneal cavities, especially when these were inflamed.

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INTERNATIONAL CONGRESS OF NEUROPATHOLOGY

The first International Congress of Neuropathology, held in the Palazzo Barberini, Rome, between Sept. 8 and 13, was attended by 414 people from 37 countries. Dr. Mario Gozzano (Rome) was the president, Dr. Lucio Bini (Rome) the secretary-treasurer, and Dr. Armando Ferraro (New York) the secretary-general.

If, said the President in his opening remarks, there was an inherent danger in excessive specialisation, then the remedy lay in collaboration. This was the reason for this first international meeting of neuropathologists; and he was firmly of the opinion that neurology, far from being the loser, would be gaining. The specialty called for new techniques—techniques of thought as well as new methods of investigation—and this was the occasion to pool knowledge so far as the tyranny of time permitted.

DEMYELINATING DISEASES

I. **Hallevorden** (Giessen) rejected outright the hypothesis that multiple sclerosis had its origin in vascular thrombosis: such vascular changes as occurred were to be expected in any inflammatory process. In multiple sclerosis inflammation preceded sclerosis, while demyelination preceded inflammation. The disease was essentially one of myelin dissolution, the ganglion cells and axis-cylinders being relatively spared. The location of the foci suggested that the specific demyelinating substance diffused through the capillary vascular bed and was perhaps also conveyed by the cerebrospinal fluid.

Professor Hallevorden drew an analogy between von Balo's concentric sclerosis and the "ringspot disease" of plants which was known to be viral in origin. The Liesegang phenomenon so clearly represented in the former disease had been accurately mimicked by means of silver-chromate precipitation in a gelatin medium. In von Balo's disease the stratification of the concentric rings was probably the result of the repeated production of antibodies: in the plant disease such antibodies had already been isolated. In his opinion multiple sclerosis was a specific disease and there were no intermediate forms, as had sometimes been postulated, between it and the various varieties of encephalomyelitis; certainly it had no resemblance to the experimental forms of allergic encephalitis. He believed that multiple sclerosis was viral in origin.

J. G. **Greenfield** (London) agreed with the views expressed by King and Meehan (1950): the demyelinating diseases of animals had no similarity to those of man. One could learn much of the process of demyelination by a study of the œdema to be found around tumours, abscesses, and contusion; this was rarely complete and the main commissural tracts, such as the optic radiations and corpus callosum, as well as the subcortical U fibres, tended to be spared. In the affected areas there was comparatively little katabolism of the myelin into neutral fat, the axons showed only a minimal disturbance, and the capillaries remained healthy. The microglial cells were mobilised early and the astrocytes soon began to swell: the oligodendroglia, on the other hand, showed little change. Myeloclasts of either microglial or oligodendroglial origin were to be found in many of the distended myelin-sheaths. Doubtless it was all due to stasis of the tissue fluids and interference with the process of metabolic exchange, but this form of demyelination secondary to œdema might at times be so severe and widespread as to mimic diffuse sclerosis.

Dr. Greenfield said that it was becoming increasingly evident that the subacute form of encephalitis of Dawson (1933) and that described by van Bogaert (1945) were one and the same. Demyelination and sclerosis of the white matter were to be found in both, whether or not inclusion bodies could be found in the nerve-cells. In some instances alteration of the white matter was widespread and severe, but in others slight. The changes in fact might simulate those of diffuse sclerosis except that the U fibres were not spared as in the latter disease and the inflammatory process involved the cortex. He now agreed with van Bogaert that this disease was primarily one of the white matter. The presence of intranuclear inclusion bodies in the oligodendroglia suggested that the demyelination might be secondary to damage to these cells.

Researches on allergic encephalitis led now to the view, long held by Glanzmann and van Bogaert, that acute postexanthematous disseminated encephalomyelitis (characterised by perivenous demyelination), and to an even greater extent the acute hæmorrhagic leucoencephalitis described by Weston Hurst (1941), were essentially allergic in character. In the latter, which differed from the former only in the prominence of the leucocytic exudate and in its tendency to be confined to the central grey matter, acute necrosis of the vessel walls was clearly evident and accounted for the exudation of œdema fluid and fibrin.

He agreed that there was no evidence that demyelination was preceded by inflammation in multiple sclerosis: rather was the reverse the truth. In a recent case where a plaque gave rise to clinical evidence of its appearance eight days before death there was already almost complete loss of myelin, and the only evidence of reaction was to be seen in the earliest phase of microglial activity.

Dr. Greenfield held that our imperfect knowledge of the various forms of diffuse sclerosis justified further analysis. It was in fact customary in pathology to separate our diseases on the basis of a particular cell reaction. He proposed therefore to subdivide these diseases on a basis of myelin metabolism. The first group consisted of those cases in which sudanophilic lipid, some of it anisotropic, was plentiful, suggesting a breakdown of the myelin on classical lines as was to be found in multiple sclerosis, encephalomalacia, and wallerian degeneration. The bulk of the spontaneous cases came into this group. The second group comprised the metachromatic leucodystrophies: in them sudanophilic lipid was either absent or present only in the walls of vessels, its place being taken by material which appeared to be a galactolipid. He believed that in this variety of the disease, which was often familial, there was a constitutional fault in the myelin. In a special late form of it there was evidence of a primary degeneration of the oligodendroglia. The third group comprised those rare instances in which one found clusters of globoid cells containing some relatively immovable substance which was not sudanophilic.

A. **Wolf** (New York) reviewed the various forms of demyelination which had been produced experimentally, and also the spontaneous and allergic diseases of man and animals in which demyelination was apparently the primary process. There were basic similarities between them in that the myelin appeared to be the vulnerable element, but one could not pursue the analogy too far. A disease of known ætiology might show in many forms, whilst a histological picture might be common to more than one ætiological factor. Those diseases of the white matter in man which were thought to be due to an endogenous myelinotoxic agent (eclampsia, porphyria, subacute combined degeneration of the cord, and dysentery) yielded valuable information on the pathology of myelin, but proof was lacking that there was any such toxin in multiple sclerosis. He knew of no evidence to suggest that in multiple sclerosis there was a disorder of lipid metabolism; nor was there evidence of a nutritional factor. Vascular occlusion, when it occurred, surely played only a secondary part. He concluded from a study of the experimental disease, which could now be produced readily not only in the monkey but in the guineapig, the dog, and the mouse, that there was no pathological picture which could be regarded as specific of an allergic reaction. Because of the enhancing effect of the adjuvants of Freund and the preventive action of cortisone, one would have supposed that the experimental allergic encephalomyelitis had for its basis an immunological mechanism, but the value of this hypothesis was lessened by the facts that this disease could not be transmitted passively and that no parallelism had been observed between the production of antibody-fixing complement and the development of the pathological process. Efforts to isolate an active antigen had produced contradictory results.

In the discussion G. **Steiner** (Detroit) produced photomicrographs showing convincingly the presence of leptospira in the lesions of multiple sclerosis. There were three diseases at first thought to be viral in origin which were now known to be due to leptospiræ; multiple sclerosis might turn out to be a fourth. He could not agree that the inflammation was secondary to tissue damage; he regarded it as primary because he had found inflammation in the leptomeninges at some distance from the plaques and even down in the cauda equina.

H. **Pette** (Hamburg) maintained that the pathogenesis of multiple sclerosis must be assessed from clinical studies as well as in the laboratory. He could not accept any evidence so far adduced as being in favour of a viral origin. Virus diseases were expected to show periodic outbreaks. Moreover we had no knowledge of a virus causing demyelination and would not expect that a virus could; a virus by its very nature was parasitic in the cells of the host, but in the disease we were dealing not with cells but with a labile lipid membrane. He knew of no virus which could thrive in a lipid medium. Multiple sclerosis was a specific reaction on the part of the nervous system; but it might, as was believed now to be the case in Boeck's sarcoidosis, be due to one of many ætiological factors. He thought that the disease often depended upon allergy for its manifestations, but he knew of no instance of perivenous encephalomyelitis that had developed into multiple sclerosis. The theory of neuroallergy, which he had advanced in 1931, was now on a firm basis.

D. J. **Trevan** (Beckenham) produced important evidence in the field of comparative pathology. He reported that myelin destruction could occur in dogs infected with a distemper-like virus. The damaged myelin, he argued, might act as an antigen to a reaction of antibody-producing type set up by the myelin, by the virus, or even by both. The antibody produced could react with, and damage, more myelin, which in turn would be released to act as a further antigen. In this way the antibody-producing changes might be prolonged indefinitely after the virus had died out.

C. L. **Cazzullo** (Milan) and G. **Gomirato** (Turin) believed that histobiochemical analysis had been neglected in the study of multiple sclerosis; the rôle of enzymes in this disease might turn out to be important.

G. **Schaltenbrand** (Würzburg) gave a statistical analysis of the occurrence of multiple sclerosis in Central Europe. The incidence appeared to have risen since the beginning of the century. There had, however, been no rise in the number of necropsies in the years immediately after the late war as had been the case after the first world war. In his series the necropsy incidence had varied from 0·73 to 1·6%, the maximum being reached in the year 1936. Constitution, he thought, played an important part. Tuberculosis, syphilis, and rheumatism were more commonly found in subjects with multiple sclerosis than in the general population, while arteriosclerosis was a little rarer and malignancy considerably rarer.

F. **Lüthy** (Zürich) was highly critical of Hallevorden's deductions. We had no proof that multiple sclerosis, diffuse sclerosis, and concentric sclerosis were the same disease. Why then had he paid so much attention to concentric sclerosis, which was admittedly extremely rare? The analogy with ringspot disease was purely superficial. No antibody had been demonstrated in multiple sclerosis.

O. T. **Bailey** (Indianapolis) had studied a case of multiple sclerosis in which the plaque concerned was only eleven days old; his findings were the same as those of Greenfield. Experimental methods were justified if they contributed to knowledge of the formation and maintenance of the myelin-sheath. This was more important than trying to read into them an identity with human demyelinating diseases.

C. **Davison** (New York) was certain that processes of demyelination, which could never be attributed to a single specific factor, were governed by both qualitative and quantitative factors; while A. **Ferraro** (New York) put in a plea that we should not dismiss experimental work as being something too far apart from the human diseases. He was opposed to evaluating either human or experimental material simply on a pathological picture. One must define as clearly as possible the clinicopathological features of each demyelinating disease.

W. **Blackwood** (London) described evidence that the globoid cells in multilocular cerebral sclerosis were of microglial origin and that they contained a non-lipid material of uncertain nature.

L. **van Bogaert** (Antwerp) and J. **Bertrand** (Paris) summed up the discussion. The cellular infiltration sometimes seen in the lesions of multiple sclerosis was only symptomatic; the primary disease was in the myelin. They admitted, with Hallevorden, that there was a myelinolytic substance, but could not agree that the analogy between tobacco mosaic and concentric sclerosis permitted one to postulate a viral origin for Balo's disease and still less for multiple sclerosis. Concentric patterns were to be found in many physicochemical phenomena, including the aurora borealis, but did not argue in favour of a virus. They doubted if there was yet sufficient evidence to place perivenous encephalomyelitis with the allergic disorders. Allergic reactions in the brain were hardly comparable with those elsewhere in the body, for fibrinoid necrosis of the vessels of the brain could be observed in purely toxic states such as carbon monoxide poisoning. They recognised that for the proper understanding of the demyelinating diseases further clinical and biochemical observations were necessary; but they believed that histology, far from having exhausted its usefulness, could still yield much information.

VASCULAR DISORDERS OF THE BRAIN

J. H. **Globus** (New York) discussed the ætiology of massive cerebral hæmorrhage. His hypothesis was an elaboration of that originally proposed by Rouchoux (1844), who held that bleeding was the indirect result of a diseased blood-vessel which first gave rise to an area of softening into which bleeding occurred. Durant-Fraidel (1842) also had this idea of an area of diminished resistance of the brain substance into which bleeding took place. Globus and Strauss in 1927 set out the stages in which a massive hæmorrhage developed, and now there was experimental work to support these observations originally made on clinical material. Infarction had been produced surgically in animals, and hæmorrhages produced afterwards spontaneously or by means of the intravenous administration of arsenical compounds. Evidently several factors were concerned in the causation of a hæmorrhage, but it seemed likely that conditions favourable to bleeding were brought about when a small vessel traversed an area of softening; a naked vessel in this way would be temperamental and liable to give way if the intravascular tension was increased.

W. SCHOLZ (Munich) discussed the changes in the parenchyma of the brain when the vessels were subjected to oxygen deprivation, and showed many examples both in the early stages of nerve-cell damage and in the reactionary stages of neuronophagia and gliosis. He referred at length to the vulnerability of the various forms of nerve-cells and adduced evidence that it was determined in part by the vascular supply of the area concerned, and in part by the peculiar metabolic requirements of the particular nerve-cells. A variety of gross pathological findings might result from oxygen deprivation. His thesis permitted of a reconciliation between the opposing views of Spielmeyer (who held that nerve-cell damage was the result of a local impairment of blood-supply) and of the Vogts (who believed in the theory of pathoclisis). He recognised a difference between simple oxygen deprivation and cerebral oligæmia; in the former the circulation was maintained and metabolites could be removed, while in the latter this was not so.

R. D. ADAMS and J. J. MICHELSEN (Boston, Mass.) contributed a classification of inflammatory lesions of the cerebral blood-vessels. Endarteritis could now no longer be regarded as specific for syphilis; for it was found also in tuberculous and other forms of meningitis, while the smaller vessels had now been shown to be involved, giving rise to a picture which Nesil and Alzheimer would have regarded as specific of syphilis, in such varying diseases as anthrax, glanders, schistosomiasis, and those caused by rickettsiæ. The disorder which we knew as polyarteritis nodosa represented the *end-stage of a variety of different conditions.*

K. T. NEUBUERGER (Denver) evaluated the histopathology of vascular disorders of the brain. Too much emphasis had in the past been placed on vasospasm. In his opinion vasoparalysis, stasis, and peristasis were more important. He did not think it possible or advisable to make a strict separation between functional and organic disorders of the blood-vessels. It was important to establish whether or not a change was reversible. We tended, too, to overlook the importance of the venous circulation; interference with this was often responsible for red softenings.

HISTOPATHOLOGY OF SCHIZOPHRENIA

J. L'HERMITTE, P. GUIRAUD, and L. MARCHAND (Paris) admitted that confusion existed because patients with schizophrenia-like disorders had been found at necropsy to have histological changes which we associated with other diseases. The same had been said years ago of general paralysis, but now we knew that this was a specific disease and that it could be simulated by others. They believed that schizophrenia was an organic disease of the brain.

W. L. BRUETSCH (Indianapolis) dealt with those cases in which demyelination or changes associated with rheumatic arteritis had been found; while C. and O. VOGT (Neustadt) believed that a cell loss occurred in schizophrenia, but that the symptoms were to be attributed to the behaviour of the cells which survived.

D. BOLSI (Turin) and V. M. BUSCAINO (Naples) both dealt with the extraneural pathology of schizophrenia, and L. VAN DEN HORST (Amsterdam) compared the findings in schizophrenia and in schizophrenia-like disorders.

G. PETERS (Bonn) did not believe that schizophrenia had yet been established as a disease entity. It was a syndrome which could be caused by different ætiological factors. This view was supported by L. BINI (Rome) who, on behalf of Professor Marchiafava, demonstrated a case clinically diagnosed as schizophrenia which turned out to be one of rheumatic encephalitis. Other speakers agreed that there was no constant histological pattern, and that when changes did occur they were due to accompanying psychosomatic states, to convulsive therapy, or to terminal diseases. Experts usually could not distinguish the brains of schizophrenics from those of patients who had died of other diseases. One speaker, who held that schizophrenia represented a plurality of syndromes, urged that further clinical analysis was necessary. Simple syndromes, he said, facilitate research.

The difficult task of summing up was left to A. MEYER (London). We had to agree that many cases of schizophrenia showed few lesions, and we had the paradox that the most classical cases were those that showed the minimal change. Even after leucotomy brains had been found to be normal. He hoped that the references which had been made to histological lesions attributable to convulsive therapy would not discredit a treatment of proved value. Secondary changes in the brains of schizophrenics could be due to so many associated disorders—of the autonomic system, for instance, and even liver damage. He hoped that those who favoured a somatic rather than a psychosomatic origin for the disease would not feel defeated. There would always be a somatic factor in schizophrenia. In the course of his communication Professor Meyer described the necropsy findings in twenty-six cases of schizophrenia and in sixteen cases in which biopsy had been carried out. He confirmed not only the essentially negative findings but also the ease with which other diseases could be diagnosed as schizophrenic.

HISTOPATHOLOGY OF MENTAL DEFICIENCY

C. E. BENDA (Waverley, Mass.) described a series of mentally deficient patients. Of these 35% were mongols; in 24% the cause was circulatory disorder, including cystic degeneration of the white matter, subcortical encephalomalacia and cortical atrophy, and status marmoratus. In 14% the cause was infection, mostly postnatal but sometimes occurring during the period of gestation; occasionally mental deficiency resulted from disease of the mother (rubella). Disorders of metabolism accounted for 7% and neoplastic malformation for 5%. The remaining 15% he styled true oligophrenia or oligoencephaly: these were the imbeciles who showed only minor structural abnormalities in the brain.

M. MINKOWSKI (Zürich) confined his remarks mostly to mental deficiency caused by prenatal factors and demonstrated material collected by Monakow and his pupils. W. E. MAFFEI (Sao Paulo) discussed nutrition in relation to mental deficiency; while K. INGLIS (Sydney) reviewed the various forms of extraneural pathology associated with it.

G. A. JERVIS (New York) directed attention to the metabolic causes of mental deficiency. Wilson's disease he believed to be due to an error of amino-acid metabolism, and therefore it fell into the same category as phenylpyruvic oligophrenia. Galactosuria and glycogenosis might both give rise to disease of the brain. All the metabolic disorders had in common their genetic behaviour, which was in accord with a recessive gene. The number of observed cases in families of several forms of metabolic disease of the brain had been in striking agreement with the number to be expected on the basis of a single recessive gene. He believed that one was born with a particular biochemical individuality, just as one was born with a certain physical and psychological personality.

G. de Morsier (Geneva) discussed the causation of agenesis of the corpus callosum and of various forms of cerebral agenesis and hemiatrophy on the basis of vascular lesions. W. G. P. Mair (London) described the findings in seventeen cases of cerebral hemiatrophy; the condition probably dated from birth or from early postnatal life. R. M. Norman (Bristol) described two cases of cystic degeneration of the brain which were undoubtedly prenatal in onset. The first was a twin, the other child having been dead for about ten days before birth. Death occurred at the age of one year and ten months, and confluent cystic cavitation of the white matter was found. Possibly strangulation of the cord had accounted for the death of the one and for encephalomalacia in the other. The second case lived for one month although the mother had had severe transfusion reactions superimposed on profound anæmia. The anoxic origin in both these cases could hardly be doubted.

C. Berlucchi (Pavia) described recent experimental work carried out in his department on toxoplasmosis. N. Malamud (San Francisco) agreed with Benda that some diseases were genetically determined while others were of prenatal origin. But a pathologist found it impossible to say whether a disease was due to birth trauma or anoxia on the one hand, or to some infection in early postnatal life.

SENILE PSYCHOSES

F. Bonfiglio (Rome) said that we had no true knowledge of the causation of senile plaques and of the neurofibrillary change of Alzheimer. These were not found in ageing animals and were not constant in old age in man. Senile dementia had been regarded as an accentuation of normal decay of the brain; but mental decay could not be regarded as physiological in old age, because many never showed it. One could only conclude that factors, be they endogenous or exogenous, other than the process of normal senile involution were necessary for the production of these characteristic lesions. There was, however, an obvious identity between the pathological picture in Alzheimer's disease and senile dementia; in fact an experienced pathologist would find it difficult to distinguish between them. He did not agree with Grünthal that Alzheimer's disease was heredofamilial. He had found no such evidence in some hundred cases of which he had knowledge. In spite, however, of the histological similarity he believed Alzheimer's disease to be different from senile dementia.

P. Divry (Liège) gave a detailed study of the plaques and neurofibrillary alterations, enumerating the varieties of the former which he had encountered. Histochemical analysis showed that they were largely caused by the appearance of amyloid which had precipitated out of the interstitial colloidal medium of the brain. The characteristic changes of Alzheimer's disease could be designated, he thought, disseminated paramyloidosis of the brain.

F. Morel and E. Wildi (Geneva) described further evidence of the histochemical nature of the lesions. The amyloid substance, in their opinion, emanated from the capillaries, or from the capillaries and arterioles; in the former instance one found senile plaques, in the latter instance senile plaques together with the perivascular deposits which they termed, as a pathological process, dyshoric angiopathy.

H. Spatz (Giessen) suggested that Pick's disease was a system disorder; and he classified it in the same main group as cerebral and spinal progressive systemic atrophies along with amyotrophic lateral sclerosis, the various heredo-ataxias, Huntington's chorea, Parkinson's disease, and Leber's primary optic atrophy. At times the disease was widespread, but it was never generalised. The postcentral gyrus, the paracentral lobule, the occipital lobe, the auditory field, and the caudal part of the superior temporal gyrus were usually spared. The affected parts, in fact, were those which were the last to be myelinated. He agreed with Hallevorden that the disease had its origin in the periphery of the neurone.

R. Estrada and F. Fusté (Havana) believed that senile plaques had their origin in degenerating neurofibrillary elements, and that the amyloid and other deposits were the result of this degeneration. They had noticed in patients with senile dementia that when the blood-pressure was low they tended to be not so well.

J. de Ajuraguerra (Paris) believed that in the group of presenile dementias we had to look for factors capable of activating the involutionary process to which all were subject. Circulatory dysfunction, rather than arteriosclerosis, should be looked for in the ætiology of these diseases. This approach was recommended also by C. M. Fisher (Montreal), who described cases of dementia in associating with occlusion of the carotid arteries.

H. Jacob (Hamburg) confined his remarks mostly to the Jacob-Creutzfeld disease; while W. H. McMenemey (London) dealt with the heredofamilial element in the presenile dementias. E. Grünthal (Berne) and W. J. C. Verhaart (Amsterdam) were both of the opinion that Professor Spatz's classification of the progressive cerebrospinal systemic atrophies was rather oversimplified; there were many facts which could not be entirely explained by his hypothesis of degeneration at the periphery of the neurone.

L. Bini (Rome) referred to the reported cases which appeared to be something between Pick's disease and Alzheimer's disease. J. Solé-Sagarra (Barcelona) described new work on Parkinson's disease and compared it with Huntington's chorea. It was left to G. R. Lafora (Madrid) to sum up, which he did with a masterly review of the present position with regard to this group of diseases.

Public Health

Paratyphoid-B Fever in Cardiff

There have been 54 cases of paratyphoid-B infection in Cardiff since the epidemic in South Wales began in the early part of May.[1] In the rest of the South Wales area the total is now approximately 400.

Dr. W. Powell Phillips, deputy medical officer of health for Cardiff, writes:

> "The epidemic has shown that it is relatively simple to trace the immediate vehicle of infection when there is a group of cases whose incubation periods roughly correspond. For instance, in the area there have been 10 or 12 bakehouses involved. Commonly a mild case or a symptomless excretor is discovered at the bakehouse, and that particular source of trouble is eradicated. What remains to be discovered is how the infection gets into the bakehouse and the source of infection among the staff. Naturally all common products, their origin, and method of handling and distribution have been studied. Bacteriological investigations have so far failed to give the answer. On the other hand it is too much to expect that a chance infection has occurred in bakery staffs when such a number of separate undertakings are involved and when there are considerable distances between the various establishments."
>
> "We are now having to deal with cases which are being diagnosed at irregular intervals, and on investigation it is now rare to find any common factor. A certain number of these cases are probably secondary infections, but the continuing incidence gives rise to concern because it is possible that there is some source of infection which is from time to time being distributed outside the city and causing the more localised outbreaks with a common incubation period in the surrounding districts. In other words the infection has tended to persist sporadically in the city since May, whereas elsewhere there have been groups of cases occurring together in districts some distance apart."

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[1] See *Lancet*, July 19, 1952, p. 128.

In England Now

A Running Commentary by Peripatetic Correspondents

THOSE of us who have not yet been to the regions of heat hyperpyrexia and thermogenic anhydrosis are, I suppose, in no position to criticise the recent D.T.M. & H. papers; but one cannot help regretting all the valuable information that has proved, in the end, of no avail. The questions, if I may say so, seemed very ill designed to elicit a number of important facts—for example, that Pruner's hedgehog in the Sudan is particularly susceptible to yellow fever; that if the housefly bred unchecked it would, in a year, cover the whole Earth's surface to a depth of 47 ft.; that tsetse flies can be collected by drawing a baby crocodile on a small cart through the fly belts; and that not only humans but also carnations are susceptible to sporotrichosis.

* * *

Since leaving school my pooled store of words from the Latin languages has been limited. It was, therefore, with some relief that I reached the house of my friend in Paris. He, however, had not yet come in, and his wife, who was preparing the meal, left me in the sitting-room exposed to the tender mercies of their oldest toddler. Shoving his picture book under my nose, "Qu'est-ce-que c'est?" he crowed, with the delight of the born examiner, who senses that the examinee is on *terra incognita*. "C'est un bœuf," I ventured. "Non, une vache," he corrected. And to make sure that I, at least, derived some profit from the experience he added: "Elle donne le lait." So it went on. I failed to identify the "wolf," whom I called "un reynard." For the world I could not remember the French for "monkey" or "elephant's trunk," though I managed to score with "cheval." When my hostess at last rescued me I was glad to talk again in coherent sentences. Before long, however, the youngster, like an examiner prematurely deprived of his prey, staged a comeback. Tugging at my sleeve, annoyed that now he was left guessing, he cried: "Parlez français, parlez FRANÇAIS!" And to make it clear how reprehensible my conduct was he held forth with irrefutable Gallic logic: "En France on parle français, en Angleterre on parle anglais, et en Chine—en Chine . . ." he halted momentarily, but not for long, for the solution was obvious: "en Chine on parle jaune!"

* * *

Dog-owners are seldom at a conversational loss, and a chance encounter I had the other day with a middle-aged Norwegian medical cynophil lasted about an hour—the first ten minutes being devoted, rather perfunctorily, to shop, and the rest of the hour to a monologue (his, not mine) on his dog. It must have been of a ripe old age, for its saga began in the spring of 1940 when it was part of a small expeditionary force sent by the French Army to the West coast of Norway to remove the Germans. But it was the French who had to evacuate Norway; and the dog was left behind, very much in the lurch, the only attention paid it at first being a charge of buckshot still lodged in one of its legs. Fortunately it found a good friend, and dog and doctor soon became inseparable. Indeed, after they settled in the suburbs of Oslo the dog would meet the doctor every evening when his bus deposited him some way from his house. But one evening its reception of him was as cold and aloof as it had usually been warm and friendly: all its attention was focused on plants and trees and little birds, while Master was icily ignored. At first puzzled and hurt, he could not understand the cause of this sudden estrangement, till he remembered that, a few moments earlier, on stepping off the bus, he had exchanged friendly greetings with another dog, an arch enemy of his own dog.

* * *

It has been said that a man may be described in three ways—as he supposes himself to be, as he appears to others, and as he really is. The third of these descriptions may surely be dismissed; for who is entitled to decide what a person really is? As for the other two, reconciliation is difficult, perhaps impossible. Nobody can take simultaneously a subjective and objective view of anything, and perhaps this is just as well. There may be a few who indulge in the self-depreciation of Robin Oakapple in *Ruddigore*, who protested that people had no idea of what a poor opinion he had of himself and how little he deserved it. The majority are happy in their fool's paradise, and it is cruel to disturb them.

I have been inveigled into this somewhat pessimistic philosophy by the experience of hearing my own recorded voice after a broadcast. I was horrified. I had hitherto plumed myself on the possession of an attractive, cultured, nicely modulated, musical timbre; and I was confronted with a monotonous, nasal, uncouth declamation, the sole recommendation of which was that it was audible.

I am told that everybody, on hearing his voice reproduced for the first time, is surprised and perturbed. That, to a certain extent, is comforting, for the element of instrumental distortion can be invoked. But the fact that those who heard my broadcast, while complimenting me with the observation that it came over well, invariably added that it was a perfectly true reproduction compels me to abandon this consolation. It would have been better to have been left undisturbed in my illusion. And this, I feel sure, applies to a good many other conditions, particulars, and attributes besides the sound of one's voice.

* * *

Notice in a New York florist's window: All Our Flowers Contain Chlorophyll.

* * *

He was a foundry-worker aged 68 who had been admitted to hospital some months ago with a severe coronary thrombosis. When I saw him again after a period of convalescence he had done well and I referred him to the almoner in the hope that she would find lighter employment for him. In a brief note she replied that she'd do what she could but his age made it rather a problem. Later she wrote that his wife, very sensibly, had persuaded him to retire completely.

At the clinic today he looked spruce and remarkably fit and happy. "How do you occupy yourself these days?" I asked. His face lit up. "You'll remember, doc," he said, "I was an acrobat before I went to the foundry. I do handstands and jump from table to table." I suppose I looked surprised. "A chap's got to keep fit," he explained.

* * *

A clinical colleague of mine lately came upon a number of old examination papers lying on my desk. Unfortunately the internal evidence was too strong for me to disclaim authorship, and knowing his incisive scorn of the more academic aspects of medicine I expected unflattering comment. However, his love of English outran his reaction to unclinical science—and also his experience of examining. "What do you mean by 'indicate'?" he asked. "Oh," I said airily, "I meant 'I am tired of saying 'describe,' 'discuss,' 'give an account of,' 'state,' and 'mention,' but you can jolly well answer the question in the usual way all the same!'" This didn't satisfy him, and he pointed an accusing (second) finger at me and thundered "Indicate: to point with the index finger. How do you expect your candidates to do that in their written paper?" I have since consulted my dictionary, which does not support him; but at the time I fell for the authoritarianism of the born clinician and turned to musing on the possibilities of using other fingers. Annulate? Minimate? Mediate, forsooth. I set out wearily for home, and, as the buses were full, I felt I should have done better to have pollicated a lift.

* * *

Midwife: "You go and bath the baby while I wash Mother."

Student (several minutes later, with ashen face): "For God's sake come quickly. I've dropped it in the bath."

Midwife: "Well take it out."

Student: "I can't, the water's too hot."

Letters to the Editor

ISONIAZID

SIR,—Strains of tubercle bacilli insensitive to isoniazid have been isolated from the sputum of tuberculous patients before, during, and after therapy with the drug.[1] It seems that isoniazid-resistant bacilli may become more numerous after about 8 to 12 weeks' treatment.[2] Since the appearance of drug-resistant bacilli foretells the loss of effectiveness when other drugs, notably streptomycin, are given, some clinicians have expressed doubts as to the efficacy of isoniazid.

We believe that the phenomenon of drug resistance should not be used as the chief criterion of a drug's value. The real evaluation must always depend upon clinical tests of efficacy. By this criterion, isoniazid has not failed.

The most rapid and definitive clinical test of an anti-tuberculous drug is its use in treating miliary and meningeal tuberculosis.[3] Isoniazid is proving at least as effective as streptomycin in controlling miliary disease.[4] Results in other forms of tuberculosis are generally satisfactory so far as can be judged at present, and it is suggested that no adverse conclusions can be drawn until the current extensive clinical trials are completed.

The phenomenon of isoniazid resistance is of great theoretical and practical interest particularly because it may not be exactly analogous to bacterial resistance to other drugs. In the early investigations at the Squibb Institute for Medical Research, *Mycobacterium tuberculosis* easily became resistant to isoniazid, and subsequent reports have confirmed this observation. Resistant strains appear in vitro after prolonged culturing of a single inoculum in the presence of isoniazid,[5–7] and after repeated subculturing in increasing concentrations of the drug[8]; iproniazid, the isopropyl derivative, gives similar results. In general, isoniazid-resistant strains are difficult to maintain in culture, which probably indicates greatly increased metabolic requirements,[9] in contrast to the characteristics of streptomycin-resistant strains. Further, isoniazid-resistant, but not streptomycin-resistant, strains may again become sensitive when cultured in media not containing the drug.[10] Although some strains resistant to isoniazid in vitro are also resistant to the drug in vivo,[11] at least some of the resistant organisms have lost their virulence. These observations may explain why no-one has yet demonstrated a close and consistent correlation between the appearance of isoniazid resistance and clinical relapse. They raise the question as to what observed changes in the isoniazid sensitivity of tubercle bacilli are of significance to the clinician treating tuberculous patients.

While this question will be answered in time, the clinician cannot wait to plan treatment for his present patients. Several considerations can guide him in his decisions. No cross-resistance exists between isoniazid and the streptomycin drugs, *p*-aminosalicylic acid (P.A.S.), or amithiozone,[12–14] and it has been shown in vitro that no tubercle bacilli resistant to either agent emerge when cultures are exposed simultaneously to isoniazid and streptomycin[10, 15]; admixture of these two agents also appears to potentiate their antibacterial action.[16] It was suggested at the recent annual conference of the British Tuberculosis Association[2] and elsewhere[5–7] that isoniazid be used with streptomycin. We have received personal communications about the treatment of more than 500 patients with a combination of isoniazid and one of the streptomycin drugs, and the safety of this combination has been demonstrated.

We have always regarded isoniazid as a valuable new therapeutic adjunct rather than as a complete cure for tuberculosis. Obviously we do not yet know how isoniazid can be used most effectively; some five years were needed to find and test the presently accepted streptomycin régimes. We can, however, use our experience with streptomycin and P.A.S. to guide us in administering isoniazid until more definite information is available. At present it would appear that isoniazid should usually be given in daily doses of 3 to 5 mg. per kg. body-weight by mouth, with streptomycin in intramuscular doses of 1 to 2 g. twice weekly, but only as a part of the complete treatment which includes bed rest and surgical care. The truly threatening forms of tuberculosis, such as miliary, meningeal, and extensive pneumonic disease, probably should be treated more vigorously with larger doses of both drugs; and perhaps with P.A.S. as well.

The results so far available indicate that combined treatment with isoniazid and streptomycin is likely to prove superior to older methods of treatment. Our present lack of information only emphasises the need to continue the orderly search for the best isoniazid régime. Until this search is ended, the profession must reserve judgment on the ultimate value of isoniazid. We must remember that streptomycin, now regarded as the standard of comparison for other antituberculous drugs, was itself treated with reserve until the current methods of use were evolved.

Medical Division,
E. R. Squibb & Sons.

GEOFFREY W. RAKE.
LAWRENCE B. HOBSON.

STATUS IN THE SERVICES

SIR,—It has come to our notice that officers fulfilling their National Service obligations are occasionally appointed to posts that carry a specified rank and rate of remuneration which are denied to them by the central authorities concerned. They have perforce to seek the assistance of professional organisations to establish their rights in this matter, though these rights are patent to anyone who is familiar with establishment of the units concerned. Already in three instances solicitors have been instructed to make representations to central authorities to observe their own rules and regulations by conceding the higher rank to which the medical practitioner is entitled and making payment of remuneration on the enhanced scale.

Medical officers who fail to receive the acknowledgment of rank and pay to which they are entitled should communicate with their professional organisations as soon as practicable to enable representations to be made on their behalf before valuable time has been lost and tempers have been ruffled. That this intervention should be necessary is deplorable since the authorities concerned ought to be anxious to observe their regulations, at any rate to such an extent as to prevent any medical officer from suffering loss of status or remuneration to which he is clearly entitled.

It is hoped that medical officers will not accept these indignities with complaisance, and that they will not

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1. McDermott, W. Personal communication.
2. See *Lancet*, July 5, 1952, p. 19.
3. Hobson, L. B., McDermott, W. *Ann. N.Y. Acad. Sci.* 1949, 52, 782.
4. McDermott, W., et al. *Amer. Rev. Tuberc.* 1952 (in the press).
5. Thomson, W. A. R. *Practitioner*, 1952, 169, 87.
6. Knox, R., MacLean, K. S., Robson, J. M. *Brit. med. J.* 1952, i, 1981.
7. Grace, E. J., Bryson, V., Szybalski, W., Demerec, M. *J. Amer. med. Ass.* 1952, 149, 1241.
8. Buck, M., Schnitzer, R. J. *Amer. Rev. Tuberc.* 1952, 65, 759.
9. Donovick, R. Personal communication.
10. Pansy, R., Stander, H., Donovick, R. *Amer. Rev. Tuberc.* 1952, 65, 761.
11. Goulding, R., King, M. B., Knox, R., Robson, J. M. *Lancet*, July 12, 1952, p. 69.
12. Szybalski, W., Bryson, V. *Amer. Rev. Tuberc.* 1952, 65, 768.
13. Domagh, V. G., Offe, H. A., Siefken, W. *Dtsch. med. Wschr.* 1952, 77, 573.
14. Offe, H., Siefken, W. *Naturwissenschaften*, 1952, 39, 118.
15. Middlebrook, G. *Amer. Rev. Tuberc.* 1952, 65, 765.
16. Ilavsky, J. *Ibid*, p. 777.

hesitate to register their views and to inform those who can help them by intervention on their behalf; and also that this letter may result in an improvement in the Services whereby medical officers are granted their rights without protestation and protracted correspondence.

Medical Defence Union,
Tavistock House South,
London, W.C.1.
ROBERT FORBES
Secretary.

HÆMOPHILIOMETER

SIR,—The techniques for diagnosing the presence of hæmophilia seem to be getting more reliable, but there remains a crying need for a simple, reliable, and harmless means of determining the "degree" of hæmophilia at any given time.

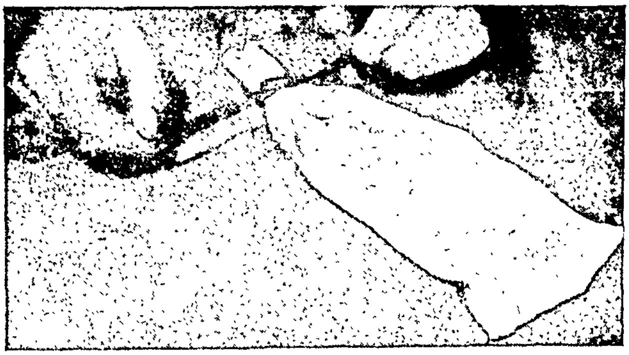
It does not seem to be fully realised that, whilst the hæmophilic is "constantly" hæmophilic, the extent of the hæmorrhagic diathesis may vary widely, sometimes slowly over a long period of time but sometimes rapidly in a matter of hours. The lack of any reliable means of determining the patient's hæmophilic state at any given time imposes a great strain on patient and doctor alike.

A "Hæmophiliometer" is therefore very urgently needed, and I appeal to research-workers to give this problem their attention.

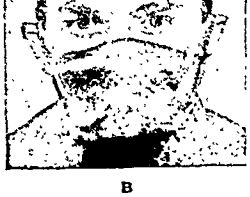
International Hæmophilia Society,
94 Southwark Bridge Road,
London, S.E.1.
FRANK A. SMITH
President.

A CHEAP SURGEONS' CAP

SIR,—For the surgeon who is operating there are many models of headwear, most of which are secured by tape. They are made from various materials, some expensive; and hospital seamstresses and commercial firms spend a lot of time on the intricate suturing. The end-result is a sweaty rag which constricts the venous return of the scalp, gives the surgeon a headache, and commonly slips out of place. Surgeons, being by nature ingenious, overcome these difficulties by their pet modification, such as a sweat band round the forehead.


A

During and since the late war I have used for operating a hat which takes less than thirty seconds to make, cannot cost more than a few farthings, is light and comfortable, absorbs the sweat, and stays in position. It is made by cutting a short length (about 12 in.) of orthopædic stockinette, of suitable diameter according to the size of the head; a knot is tied in one end with a piece of string to make a small pom-pom (fig. A), and the hat is then ready for use (fig. B). Theatre sisters can exhibit their artistry and regard for their surgeons by embroidering the lower edge of the hat, if they wish; but this is unnecessary as the stockinette can be rolled up to form a natural hem and, incidentally, a sweat band.


B

I heartily commend this hat, for which I claim no originality whatever, although I have never seen it used anywhere else. It would save the Ministry of Health a lot of money, time, and labour; and its comfort would save many surgeons headache and fatigue which inevitably lead to ruffled tempers.

I am grateful to the photographic department of St. Bartholomew's Hospital for the photographs.

St. Bartholomew's Hospital,
London, E.C.1.
JOHN HOWKINS.

CURE OF TOBACCO-SMOKING

SIR,—It is remarkable that no reference has so far been made to the silver nitrate cure.

The method is simple and inexpensive. Immediately after meals the smoker strokes the tongue two or three times with a stick of silver nitrate and then rubs the tongue against the palate and buccal mucosa for half a minute or so. Thereafter he finds that the taste of tobacco-smoke and silver nitrate combined is so peculiar that he derives no pleasure from smoking. If this procedure is carried out for, say, three consecutive days, the smoker who is really in earnest about his cure finds it much easier to abstain. The treatment should not be continued for more than three days because of the risk of argyria from the prolonged use of silver salts.

What matters most is the attitude of the smoker. I have recommended the treatment to many of my friends, and I am able to report that without exception they have given up the silver nitrate. *Vouloir c'est pouvoir.*

Department of Materia
Medica and Therapeutics,
The University, Glasgow.
STANLEY ALSTEAD.

SIR,—Dr. Lennox Johnston has avoided the main difficulty confronting most heavy smokers—namely, how to give up smoking without admitting that it is a habit, and possibly a bad one, and so losing face. To make an oath of total and everlasting abstention is a terrible thing for any man to do. But there is a way out of his dilemma. Let him vow only to smoke tobacco that he has grown and cured himself. His own cure is then certain and, if he is married, rapid.

Upton on Severn,
Worcestershire.
H. F. GREEN.

SIR,—My critics (Sept. 13) do not appear to have grasped my most fundamental point—that tobacco-smoking is not a habit but a specific infectious disease. Like other drug addictions, it is an intermittent intoxication, and habit and vice are incidental.

I do not agree with Dr. E. C. Cordeaux that smoking is easy to stop. Even with medical assistance, supported by strong economic pressure, I estimate that less than half of those who try to stop smoking succeed. Difficulty varies with the strength of acquired craving for tobacco, and inversely with the strength of resolution to stop.

I agree with Dr. Gordon Ambrose that some smokers can be cured by suggestion; but unless suggestion is supplemented by undeception and re-education, relapse is extremely probable. I also agree with most of Dr. Ellis Stungo's observations; but is not auto-suggestion on the lines he indicates in fact auto-analysis, a procedure which clarifies knowledge about smoking and which brings with it resolution to abstain?

I shall take Dr. Christopher Howard's criticisms (Sept. 20) seriatim. The immediate soothing (and *apparently* beneficent) effects of smoking on smokers are not disputed. Nor are the soothing effects of smoking other drugs—e.g., marihuana and opium—but these soothing effects are inevitably followed by toxic after-effects.

umber of cured smokers interviewed.—Scarcely a smoking ient has consulted me during the past 24 years who has been subjected to a harangue (!) on the ill effects of smoking te "ill effects," not "evils," for this is a medical, not a al, issue). As my proficiency in presenting the case against acco, and in refuting arguments in favour, has increased, as evidence in support of my views has accumulated, my portion of cures has increased. An average of 10 cured kers per week—although not necessarily permanently ed—during the past 24 years is not, I consider, an overimate.

etoxication.—It is surely justifiable to assume that when individual ceases to take a toxic drug, such as nicotine, oxication and consequent improvement in health begin once.

efinite proof that cancer of the lung is related to smoking.—ll and Bradford Hill[1] discuss the possibility that improved gnosis might account for the great increase in deaths from cer of lung, and conclude that "there is sufficient evidence reject that factor as the whole explanation, although no one ld deny that it may well have been contributory."

rsenic.—I merely mentioned its occurrence in tobacco oke. Dixon[2] wrote: "Arsenic is a constituent of American baccos in amounts many times greater than those permitted foods."

Wallasey, Cheshire. LENNOX JOHNSTON.

EMPLOYMENT OF REGISTRARS

SIR,—Dr. James Fairley, Deputy Senior Administ ative Medical Officer of the South-East Metropolitan egional Hospital Board, said in his letter last week at he was "directed" to state that candidates for nior registrarships are not required to have held a gistrar appointment at a teaching hospital for two ears, but that preference is given to applicants who ave had such experience.

Will Dr. Fairley's assurance comfort Mr. Thomas and is colleagues in the Bromley group (and their anxiety bout the future registrar position is common to all on-teaching groups)? To a potential applicant for a egistrarship in a non-teaching hospital it would appear o be as reassuring as the paratroop instructor's reply o the inquiry "what do I do if the parachute don't pen, sarg.?": "Don't worry, son, we gives you a ew one—free!"

The problem could be solved practically by making ll registrarships below the senior grade joint appointnents between the teaching hospitals and the regionaloard hospitals. A tour of duty by a registrar in the ospitals of the region would be of great benefit to all oncerned, not least to the registrar himself.

South Shields. TERENCE G. ROBINSON.

FRESH BLOOD

SIR,—My committee have been told that the medical taff in some hospitals are under the impression that the reater London Red Cross Blood Transfusion Service as ceased to function. I can assure you that this is not so, and that to the end of last July the service had nswered 74,000 calls. May I take this opportunity of explaining the functions of the service?

It is the oldest organised blood-transfusion service in the world, having been inaugurated in 1921 by the late Percy Oliver. When the National Health Service came into operation this Red Cross service was requested by the Ministry of Health to continue its work of providing voluntary blood donors to hospitals in the Greater London region for cases where freshly drawn blood was considered essential or preferable. To meet the administrative costs a per-capita payment of one guinea was agreed, but at the request of my committee this was reduced to 16*s*. in January, 1951.

The members of the service are medically examined on enrolment, and their blood is tested and grouped by the medical officer of the service, Dr. H. F. Brewer, of the pathological department of St. Bartholomew's Hospital, where they are also grouped for the Rh factor.

The service is a day-and-night one. A telephone call to Stamford Hill 0091 will receive immediate attention, and donors of the group or groups required will at once be supplied. Donors are also supplied for hospitals and nursing-homes outside the National Health Service at a minimum donation to the funds of one guinea, and a number of these calls are received each year.

Greater London Red Cross Blood
Transfusion Service,
324, Seven Sisters Road, N.4.

A. W. PILGRIM
Chairman.

SORE THROAT AND RHEUMATIC FEVER

SIR,—With reference to the letter from Dr. Stewart and Mr. Hewitt (July 19), there is an important point not generally taken into consideration when statistics are studied.

At one time I was an "onlooker" at an investigation into the incidence of upper respiratory tract infections in (*a*) children who had had the tonsils and adenoids removed and (*b*) those who had not.

The investigator's method was to ask each child: "Have you had your tonsils and adenoids removed?" No examination was made. Of twelve of the children who had answered "yes" and whom I was able to examine later, all had tonsillar tissue in the fauces—in two or three it was almost impossible to detect that tonsillectomy had ever been performed. In several of the children with whom posterior rhinoscopy was possible, quite large pads of adenoid tissue were also noted. These children, however, were rated as having had the tonsils and adenoids removed.

One would suggest, therefore, that when tonsillectomised and other children are to be compared for any purpose, those who are found still to have tonsillar tissue in the fauces or nasopharynx should not be included in the investigation as having had the tonsils and adenoids removed. Obviously the children should be examined by an experienced person.

Brisbane, Queensland,
Australia.

HERBERT EARNSHAW.

SUCCINYLCHOLINE

SIR,—Following the excellent contributions of Dr. Bourne[1] and Dr. Evans[2] and their colleagues, a number of cases of delayed recovery after injection of succinylcholine were reported. In the 2 further cases described here the blood-cholinesterase levels were determined.

CASE 1.—The first patient was an apparently healthy man, aged 60, weighing $9^{1}/_{2}$ st., who was to have radium needles inserted through a fenestration in his thyroid cartilage. He was premedicated with morphine sulphate gr. $^{1}/_{6}$ and atropine sulphate gr. $^{1}/_{100}$, and one hour later anæsthesia was induced with 0·45 g. thiopentone sodium and 75 mg. succinylcholine. A cuffed oral endotracheal tube, lubricated with 1% amethocaine ointment, was easily passed and connected to a semiclosed Boyle's machine delivering nitrous oxide 6 litres per minute and oxygen 2 litres per minute. Apnœa lasted for 75 minutes and respiration was adequate at the end of the operation 5 minutes later. The patient was awake when seen in bed 15 minutes afterwards. Several times during the operation when surgical stimulation was intense (e.g., chiselling thyroid cartilage) "bucking" occurred, but complete respiratory arrest followed withdrawal of the stimulus.

Six days later the patient was given 0·4 g. thiopentone sodium and 25 mg. succinylcholine for removal of the radium. Apnœa lasted 15 minutes and breathing was quite adequate 3 minutes later.

CASE 2.—The second patient was a boy, aged $6^{1}/_{2}$ years, weighing 2 st. 13 lb., who was to have an œsophageal stricture dilated with a Negus bag dilator. Premedication consisted of 'Omnopon' gr. $^{1}/_{8}$ and scopolamine gr. $^{1}/_{375}$ 75 minutes before induction with 0·3 g. thiopentone sodium and 50 mg. succinylcholine. It was 75 minutes before spontaneous respiration returned. "Bucking" occurred when the Negus

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1. Doll, R., Bradford Hill, A. *Brit. med. J.* 1950, ii, 739.
2. Dixon, W. E. *Ibid*, 1927, ii, 719.

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1. Bourne, J. G., Collier, H. O. J. Somers, G. F. *Lancet*, 1952, i, 1225.
2. Evans, F. T., Gray, P. W. S., Lehmann, H., Silk, E. *Ibid*, p. 1229.

dilator was fully inflated, and mucus was aspirated from the lungs on several occasions. Nikethamide 2 ml. and picrotoxin 3 mg. produced no response.

Whole-blood cholinesterase levels in these patients and in five others who responded *normally* to succinylcholine (i.e., about 5 minutes' apnœa) gave the following results:

Case no.	*Response to succinylcholine*	*Cholinesterase**
1	Delayed (75 min. apnœa)	94
2	Delayed (75 min. apnœa)	91
A	Normal	125
B	Normal	115
C	Normal	113
D	Normal	124
E	Normal	114

* The cholinesterase number was determined by the Michel electrometric method,[3] and should be considered with reference to the normal range of 80–129.

The differences in cholinesterase number between patients with normal and those with delayed response are thus not so great as the differences cited by Bourne et al.; but the simplicity of the Michel method makes it very suitable for screening cases in which the use of succinylcholine is proposed. We hope to carry out further work to ascertain whether plasma or erythrocyte levels would show a wider divergence by this technique.

Royal Victoria Hospital,
Belfast.

J. E. REID
D. W. NEILL.

AVERSION TO ALCOHOL

SIR,—Dr. Pullar-Strecker refers (Sept. 13) to aversion to alcohol in Hodgkin's disease.

I have suffered from Hodgkin's disease for five years at least. Very early on I became aware that about ten minutes after the ingestion of alcohol I had a pain at the site of the lesion.

I have told this to many doctors, and most of them have, I suspect, thought that it was a psychoneurotic symptom but that I must be humoured. One professor, however, told me that it was a well-known phenomenon and that I must be absolutely teetotal. Another very famous physician said: "Well, alcohol is a vasodilator, so why not?" The radiotherapist who has successfully treated me has found another patient who volunteered the same information; so I am convinced that this is real. The sensation is so unpleasant that I have not persevered in experiments into its cause, but it seems that it might be worth investigating in our search for the cause and cure of this baffling disease.

ANON.

CANADIAN UNIVERSITY APPOINTMENTS

SIR,—I note in your issue of Aug. 16 an advertisement for an assistant or associate professor of anatomy in a Canadian university at $4600 per annum. May I make this the occasion of some general observations on the state of affairs in Canada?

In the first place, your readers should be aware that Canadian *universities* rarely advertise for staff for medical schools, and that almost the only appointments advertised are those which Canadian doctors will not consider because they regard the salary as too low. Canada is the richest country in the Commonwealth and soon will be the richest country in the world. Correspondingly, the cost of living is high, and in the city where this associate professor of anatomy is to live it is higher than in most parts of the United States. My own estimate is that to have the same standard of living as a reader in anatomy in the United Kingdom, an associate professor here would require at least $8000 per annum. Commencing salaries are maximum salaries.

The Canadian medical profession, in my view, ought not to tolerate a situation whereby few (or no) Canadians will accept preclinical posts in their medical schools. And until the Canadian Medical Association lays down a salary scale for all hospital and medical school appointments, intending candidates for Canadian posts should exercise due caution.

Canada.

TEACHER.

ACHALASIA *v.* CARDIOSPASM

SIR,—In the interests of accuracy I should like to point out that Ryle's patient with cardiospasm was not cured by the laying-on of hands. His symptoms were completely relieved and he was able to take part in vigorous athletics, but X-ray examination showed that the dilatation of the œsophagus and the hold-up at the cardia remained unchanged.

The Radcliffe Infirmary,
Oxford.

L. J. WITTS.

WHAT OF GENERAL PRACTICE?

SIR,—It seems a just summary of the discussion in your columns to say that since the demise of unspecialised consultant physicians the G.P. is the only comprehensive doctor left. As such he is the only one with the practical experience necessary to gain an over-all view of medicine.

It would now seem high time he concerned himself with the subjugation of this unruly machinery of hospital and "scientific" medicine to the needs of his patients. That the machine is in part human must be allowed for, but this complication of evolutionary regression, by which a proportion of his colleagues have become cardinals of the machinery, must not distract the G.P.'s attention in his over-all view of the mechanism.

As in all similar modern devices, the man—the whole man—must be master, or nothing but ill will come of it.

London, S.W.10.

B. M. O'SULLIVAN.

SIR,—It has been suggested that a part of my letter of Sept. 20 might be interpreted as a criticism of certain services in this area. If this is so, may I quickly state that the general practitioners of Shropshire are fortunate in having access to an excellent and comprehensive pathological service. It is this happy experience which makes me feel that such an arrangement should be universal, and that it ought to be possible to provide access to X-ray departments in a similar way.

Shrewsbury.

JOHN C. RYLE.

SALT-LOSING NEPHRITIS

SIR,—We are grateful to Dr. McGowan (Sept. 20) for drawing attention to an error in our paper on salt-losing nephritis (Sept. 6). We would point out, however, that the mistake was not one of biochemical estimation. The figures for serum-chlorides given in the table for case 2 actually represent chlorides as sodium chloride and should have been written and calculated as such. Thus the correct milliequivalent values for chlorides in this case lie between 61·0 and 79·0, levels which are quite compatible with the low serum-sodium figures and with a diagnosis of marked salt depletion.

The suggestion of Dr. Atkinson and Dr. Prankerd (Sept. 13) that in 2 of our patients the state of salt loss might have been secondary to tuberculosis is interesting but, we think, untenable. In the first place, as they point out, the cases of Westwater et al. showed *no obvious* renal damage to account for their low serum-sodium levels; our cases, on the other hand, all showed *gross* disorganisation of the kidneys. Secondly, we do not consider that our cases (the one with a small *unilateral* apical lesion and the other with healed miliary disease) are comparable with a *group* of patients who were seriously ill or dying from their pulmonary tuberculosis, for it was among such a group that Westwater *et al.* found the low levels of serum-sodium. Thirdly, no less than 9 out of 24 of their patients who died showed "unequivocal proof of adrenal injury," evidence which was sought but not found in our cases, though the adrenals were not, it is true, actually cultured for tubercle bacilli.

As regards case 1 we had, as we admitted, no biochemical evidence of salt depletion in life. Since the publication of our paper, however, we have received information about the sodium chloride content of the grey matter of the brain tissue in this case. Estimations were performed at the time by Dr. H. G. Close, and he has kindly allowed us to quote his results. In six out of seven specific areas of the patient's brain sodium chloride levels were below average (for between 42 and 71 brains), while in the seventh it was above average. The mean of Dr. Close's values for the seven areas are:

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[3] Aldridge, W. N., Davies, D. R. *Brit. med. J.* 1952, i, 945.

"Average": 0·286 g. per 100 g. (wet weight) as NaCl.
Case 1: 0·258 g. per 100 g. (wet weight) as NaCl.

We cannot, of course, put forward these figures as confirmation of renal salt loss, but they do suggest that, in this case, salt levels were in fact lowered.

Finally, we agree with your correspondents that in case 3 the diagnosis of salt-losing nephritis was made largely on clinical and therapeutic grounds. But while we would have preferred to have been able to give more biochemical evidence, we do not think the diagnosis is in reasonable doubt because that information is lacking.

Guy's Hospital,
London, S.E.1.

M. G. THORNE
C. L. JOINER.

Medicine and the Law

Responsibility in Hospital

THE Court of Session in Edinburgh has contributed a fresh decision on the important issue of the liability of hospital managements for the negligence (if established) of the surgeons and physicians on their staffs. A woman met with a riding accident and was thrown from her horse in such a way as to sustain a fractured nose and facial abrasions. The wounds were ingrained with dirt and stone particles. Her family doctor applied temporary dressings and sent her, with a note explaining what had happened, to the outpatient department of the hospital. She complained that the two doctors who treated her at the hospital had failed to carry out a thorough surgical cleansing of the wounds and that, in consequence, there was unsightly discoloration of her forehead and nose, permanently spoiling her personal appearance. She claimed £3000 damages from the board of management of the Royal Infirmary at Edinburgh and from the two doctors. The Court of Session dismissed the claim against the board and remitted to a jury the claim against the doctors. The board had contended that, as the doctors were exercising their professional skill in the treatment of the patient, the hospital authorities could not be vicariously liable for any negligence on the part of the doctors. The court upheld this contention. Reference was made to two sections of the National Health Service (Scotland) Act of 1947 which roughly correspond with similar sections in the English Act of 1946. These were sections 12 (dealing with the functions of regional hospital boards and boards of management) and 14 (dealing with the conditions of service and appointment of officers). The latter declares that "All officers employed for the purposes of the functions of a Regional Hospital Board under the Act shall be officers of that Board." The court held that this statutory provision had not displaced the common law of Scotland so as to create the relationship of master and servant between the board of management and the two doctors who treated the patient.

There seems in this respect no reason why the law of Scotland should differ from that of England. The legal position in England, however, has undergone some change since the often quoted case of Hillyer *v.* St. Bartholomew's Hospital in 1909 when it was held that the only duty undertaken by the governors of a public hospital was the duty to use due care and skill in selecting their medical staff. In Smith *v.* Martin and Hull Corporation (1911) Lord Justice Farwell held that the hospital undertakes towards its patients nothing more than the obligation to provide premises where they will be treated by experts; the experts he defined as "surgeons, physicians, or nurses of whose professional competence the governors have taken reasonable care to ensure themselves." "I see no ground," he continued, "for holding . . . that the hospital authority makes itself liable for damages if members of its professional staff . . . act negligently towards the patient in some matter of professional care or skill." The learned judge, it will be noted, placed nurses in the same category as a senior consultant surgeon. Lord Justice Kennedy, whose judgment in Hillyer's case is usually relied upon, conceded that the hospital authority *might* be legally responsible for its servants' acts inside the hospital if the acts were "purely ministerial or administrative"—for example, if a nurse had to summon medical aid in an emergency. Any idea, however, that the hospital authority could always escape liability by regarding its medical staff as independent experts rather than servants was dispelled in 1937 by the decision in Lindsey County Council *v.* Marshall. There the medical officers in charge of a county council's maternity home were alleged to have admitted a mother for her confinement without warning her that there had been a recent case of puerperal fever in the home and that she ran the risk of infection. The county council was held liable to pay damages.

The most important review of Hillyer's case occurred in Gold *v.* Essex County Council in 1942 when Lord Justice Farwell's and Lord Justice Kennedy's opinions were critically examined. A child had suffered facial injury because the radiographer (fully competent, according to the evidence, to do his work) had omitted to provide adequate screening material when giving Grenz-ray treatment. The county council was held responsible. The radiographer was under a contract of service with the council and the doctrine of *respondeat superior* applied. The earlier rulings about nurses were criticised and, although in Evans *v.* Liverpool Corporation consultant physicians and surgeons had been held in 1906 not to be the servants of hospital authorities, Gold's case furnished a dictum that medical practitioners on the permanent staff might be servants of the hospital authority if they had entered into a contract of service. Lord Justice (now Lord Chief Justice) Goddard was unable to see why a hospital should be exempt from liability if a nurse carelessly administered a dose of poison instead of medicine and yet liable if the cook mixed some deleterious substance in the patient's food. Hospitals, he added, employed many specialists—solicitors, accountants, engineers, electricians, and the like; why should a hospital be responsible for those servants' acts and not for those of nurses who were equally in their service? Then came an important passage. "That they are not liable for the doctor's negligence is due simply and solely to the fact that he is not their servant. I desire, however, to say that for the purpose of this judgment I am not considering the case of doctors on the permanent staff of the hospital. Whether the authority would be liable for their negligence depends, in my opinion, on whether there is a contract of service, and that must depend on the facts of any particular case."

On top of all this came the dicta of Lord Justice Denning in Cassidy *v.* Ministry of Health, early in 1951. There the trial judge held that neither the doctor nor any member of the hospital staff had been negligent; the Court of Appeal, however, held that a jury could have found a verdict of negligence as the evidence stood. Lord Justice Denning used language which indicated that a hospital doctor is a hospital employee for whose negligent acts the hospital is legally responsible. If the opinions of the learned Lord Justice have occasionally been overruled by the House of Lords as somewhat too progressive, they are nevertheless entitled to high respect. We must wait for the appropriate set of facts to enable the House of Lords to say the last word on the law as it now stands.

Obituary

ALFRED FRANK TREDGOLD

M.D. Durh., F.R.C.P., F.R.S.E.

BORN in 1870, A. F. Tredgold came of a Cornish family which has latterly had a strong medical tradition. He trained at Durham University College of Medicine and at the London Hospital, where he was a prize-winner in anatomy, biology, physiology, pathology, and medicine. On qualifying in 1899, he was offered a research scholarship, recently founded by the London County Council, for the study of insanity and mental diseases. He chose mental defect as his subject—one little enough studied before that time—and for two years worked in the L.C.C. mental hospitals, and the central laboratory at Claybury Hospital on its causation, pathology, and clinical varieties. He hoped to make the pathology of mental disease his life study, but, as so often happened in those days, he was not in a financial position to follow his bent, and instead he went into general practice. He still kept his clinical interest in mental disease, however, and in 1905 was appointed as a medical investigator to the Royal Commission on the Feeble-Minded. This enabled him to gain additional experience, which helped to form the background of his classical *Textbook of Mental Deficiency*, first published in 1908. This was easily the most comprehensive work on the subject which had ever appeared, and it was warmly welcomed. During the next few years he lectured widely in support of the Mental Deficiency Bill, based on the recommendations of the commission. The Bill was passed in 1913, and by 1914 Tredgold, now an accepted authority on his subject, was able to enter consultant practice in London.

He had been interested in the Volunteer movement for many years, and had been commissioned, in 1905, as a combatant officer in a Volunteer battalion of the Queen's Regiment. In 1914 he was in command of a company, but as doctors were scarce when war broke out he asked the War Office whether they wished him to transfer to the R.A.M.C. Since he was a neurologist and psychiatrist, the War Office of those days was under the impression that his services would not be needed, and he was told to remain as a combatant. A combatant he accordingly remained, seeing service at Gallipoli, as adjutant of his battalion with the rank of major. After Gallipoli was evacuated he served in Egypt and Sinai, until ill health led to his return to England. He was posted to the command of his local Territorial depot until the end of that war.

In 1919 he had leisure, at last, to take the M.D. of Durham University, and in 1921 he became M.R.C.P. His practice as a consultant steadily increased, but he gave up much of his time to committee work, serving on the deficiency committees of the Board of Education and the British Medical Association, the Ministry of Health committee on sterilisation, and many others. He was appointed neurologist to the Royal Surrey County Hospital, and physician in psychological medicine to University College Hospital, and he lectured at Bethlem and the Maudsley Hospitals, and at the London School of Economics. He also instructed a very large number of school medical officers and public authorities in the features of mental defect, lecturing and demonstrating, over many years, to classes of 70–80 graduates, under the auspices of the National Association for Mental Defect. In 1929 he was elected F.R.C.P. He contributed on neurological subjects, and on the clinical and social aspects of mental defect, to many scientific journals. He was invited to give the Galton lecture to the Eugenics Society, and was president of the section of psychiatry of the Royal Society of Medicine. His *Textbook of Mental Deficiency* was regularly revised, and at the time of his death had reached its 8th edition. His *Manual of Psychological Medicine*, first published in 1943, was also widely read.

The death of his wife in 1947, within a year of two of their golden wedding, was a great grief to him; and shortly afterwards he lost the sight of one eye through glaucoma. The gradual failure of sight in the other eye, and a cerebral vascular lesion last year, combined to disable him; but with the help of his son, Dr. Roger Tredgold, he was able to get the new editions of his two books ready for the press. He died on Sept. 17.

E. O. L. writes: "Of very few workers in any field of science can it be said that they initiated a new era. Dr. A. F. Tredgold is one of this select few. Without disparagement of textbooks on mental deficiency written previously, it can be maintained that with the publication of Tredgold's book in 1908 a new era began in this branch of medicine. Earlier textbooks had been mainly descriptive; Tredgold was the first writer to present what was known about mental defect at the beginning of this century as a systematic body of knowledge, with a scientific classification based upon well-defined theories of causation. His extensive and thorough clinical knowledge of mental defectives and his researches in the cognate pathology enabled him to write a book that was lucid, comprehensive, coherent, and in many respects original. For nearly half a century his *Mental Deficiency* has been the standard textbook in this and other countries—surely a unique achievement in medical literature. Moreover, on the day we receive the sad news of his death we find a new edition of his book being placed on the bookstalls: and it is safe to predict that the book will remain the standard work on the subject for several years again.

"A comparison of the eight editions of Tredgold's textbook enables the reader to obtain a fairly complete picture of the progress made in the study of mental deficiency during the last fifty years. Throughout this period, and even in these last few months when over eighty years of age, Tredgold kept himself informed of the work of other investigators; and he incorporated the latest findings, with admirable impartiality, in the successive volumes. He welcomed with zest the researches of others in mental deficiency, and gave their findings most thorough and painstaking consideration. His thoroughness is well exemplified by the way he assimilated each new finding and integrated it with his own views, theories, and teaching. So masterly is this assimilation that the young student who reads the latest edition of the textbook will not be confused by the conflicts that exist in this field of science. Tredgold himself, however, recognised that some recent researches, such as those in genetics, challenged the validity of his theories of causation, and more especially his advocacy of the hypothesis of *blastophoria* or germ corruption.

"Whilst his textbook was Tredgold's chief contribution, he rendered great service to medicine in many other ways. He had been a member of almost every important committee set up by Government departments and voluntary bodies concerned with the welfare of the mentally defective during the last fifty years. In all discussions he held fast to what he regarded as true and sound; but, when other members of the commission or committee held contrary views with equal tenacity, Tredgold always sought a practical compromise. For many years he has been the chief consultant physician in mental deficiency in this country. By his tact and very genuine sympathy, he enabled many parents to orientate themselves rightly to the acceptance of one of the greatest disappointments of life—to the fact that one's child will never be normal mentally. In the course of my official visits, I heard nnumerable spontaneous tributes by many workers mongst those who are mentally handicapped to the eadiness with which Dr. Tredgold invariably responded o requests for guidance and assistance. He was highly ndowed with many talents, and these he invested in he service of those who had but a single talent."

MILLAIS CULPIN

M.D. Lond., F.R.C.S.

Millais Culpin—the Christian name is a family one—was born in 1874, the son of a doctor in general practice in Stoke Newington. His education began at the local school and was continued at the Grocers' Company School where he obtained a scholarship and incidentally acquired his lifelong interest in entomology. Soon after he had matriculated, his father, for health reasons, decided to leave England and set up in practice in Brisbane. Here Millais tried many ways of earning a living, including gold-mining—at which, as he frequently remarked, he had no success. After that experience he travelled to Cape York Peninsula and worked as a schoolmaster for four years. In later life he often referred to this period as a very happy one, and asserted that if the educational authorities had not promoted him to the nearest town, Townsville, he might have remained in his remote post for life. At Townsville he found himself one of a large staff, and this he disliked intensely. So, having saved some money, he returned to England to study medicine. He gained a scholarship at the London Hospital and qualified in 1902. His training here gave him plenty of opportunity for his critical faculties, and he found many current theories of disease causation unsatisfactory. As a student he used to marvel that a celebrated physician or surgeon could make a diagnosis on what to him seemed inadequate data. He found surgery, probably because of its relative objectivity, more satisfying than medicine.

Having qualified, he returned, for family reasons, to Queensland. In 1907 he took his F.R.C.S. and settled in practice in Shanghai, where he was very happy and developed a lasting interest in China and its problems. He married Ethel Maude Bennett and in 1913 decided to return home, hoping to set up in practice in the South of England. However before he reached England the 1914–18 war had broken out, and as soon as possible he joined the R.A.M.C. His war-time experiences made him more and more sceptical of the reliability of many diagnoses. As a surgeon he was very successful, but he often found that there was nothing to warrant the diagnosis. There was evidently here a problem for which he had had no training.

Accordingly he sought further training that might help, and went to Maghull where under Bernard Hart, T. H. Pear, and others he learned something of the psychoneuroses. An appointment as a lecturer on the psychoneuroses at the London Hospital was offered to him and he settled down as a psychotherapist.

Meanwhile from another angle a similar problem had arisen. Eric Farmer and May Smith had been appointed by the Industrial Health Research Board to investigate Telegraphists' Cramp, supposed to be due to some neuromuscular disability. By comparing a group of telegraphists already diagnosed as having cramp with a similar group telegraphically efficient, it was found that among the former there were many who had no disability except for certain letters. It looked as if the disability was not entirely due to neuromuscular inefficiency, but that some other factor was involved. The suggestion that this was probably psychological was not well received by the board. Professor Greenwood proposed that Dr. Millais Culpin should be asked to interview the subjects already tested, and, in ignorance of the experimental findings, should classify them from the point of view of psychoneurotic symptoms. The report is now ancient history, but it brought Dr. Culpin into the field of industrial psychology and proved to be the first of a number of researches. His appointment as professor at the London School of Hygiene and Tropical Medicine extended his influence, and students training for medical and industrial work in the field of public health had some training in the psychological problems likely to be encountered.

Throughout his life Culpin was a rebel against the accepted order. If some theory or attitude of mind was generally accepted it tended by that alone to be of doubtful value and to need criticism. Often he was right, but sometimes this attitude led to a disregard of something valuable even though it might be linked to apparent error. He often criticised what he called academic psychology, and it was only with difficulty that he was led to see that there had been many developments since his student days. Having been convinced of the value of psycho-analysis, he could not understand why there was so much opposition to it. His highly developed critical faculty tended to make him over-simplify the problems of life, and he thought that if a theory or general principle was clear to him it must be equally clear to others. Once, however, convinced that he had been mistaken, or that two apparent incompatibles had to be accepted in the absence of adequate differentiating data, he could tolerate the two. He once said that an uncle of his, who was a member of one of the more rigid religious sects, was perfectly convinced that his nephew was damned, but on this basis they got on excellently, and the latter bore him no ill-will.

To those in trouble he was the perfect physician, never grudging time or sympathy if he could help. Many a student and "interviewee" has cause to be thankful that he met Dr. Culpin at the right time. Sometimes during interviews for research purposes, he would come across some problem for which the time available was insufficient and he would then arrange for the person concerned to see him privately.

He retired in 1939 but continued to do some clinical work. Temperamentally he was well balanced, never likely to lose his head in an emergency, and he had to an unusual degree the capacity for preventing one experience from impinging on the next. He rarely read novels, for he said he found people much more interesting. He excelled at and enjoyed bridge and was an adept at the more learned crosswords.

He died on Sept. 14, as he had lived, without fuss.

SAMUEL WILLIAM ALLWORTHY

M.A., M.D. Dubl., D.P.H.

Dr. Allworthy died in Belfast on Sept. 13 at the age of 85. He was consulting physician both to the Royal Victoria Hospital, Belfast, and to the Old Charitable Institution.

Entering Trinity College, Dublin, at the early age of 15, he graduated in arts at 19 and in medicine at 20. On qualifying he worked for a time in Darlington before settling in Belfast where he combined general practice with specialist work in dermatology. For many years he was physician to the Benn Hospital for Diseases of the Skin, and it was on his initiative that this hospital was amalgamated with the Royal Victoria Hospital. He had studied for a time at the Finsen Institute in Copenhagen and he became a pioneer radiologist in Belfast. In those early days few precautions were taken, and like others of his generation he suffered later from the frequent exposure to X rays. His hands were disfigured by old X-ray burns and in the last years of his life the skin began to break down: a finger was removed in 1951 and two more fingers had to be amputated in the spring of this year.

During the 1914–18 war he served in the R.A.M.C. with the rank of major. At first he was specialist in dermatology and superintendent of the department of radiology at the Lord Derby Hospital, Warrington, and later he was radiologist at No. 1 Casualty Clearing Station, B.E.F.

Allworthy was a foundation member of the Jenner Institute (later called the Lister Institute of Preventive Medicine), a fellow of the Chemical Society, and a former president of the Belfast Natural History and Philosophical Society. He took a prominent part in the public life of Belfast and was an alderman of the city, thus following a family tradition: his maternal grandfather was the first alderman elected when Belfast became a municipality, and his father was also an alderman. An interest in public health led to his becoming a water commissioner and later he was chairman of the Belfast water commissioners. He was also a justice of the peace.

His family on his father's side had many links with Ireland, and his grandfather, a district inspector of the Royal Irish Constabulary, married a daughter of the Knight of Glin. His wife, the widow of William Boyd Bennet, died in 1933.

GUY JOSEPH BRANSON

B.A., M.D. Lond.

Dr. G. J. Branson, who died at his home in Edgbaston on Sept. 2 at the age of 82, had practised medicine in Birmingham for over half a century. He had been born and bred in that city, and his father was a member of the firm which in 1850 built the Bingley Hall in nine weeks. He was educated at Mason College, Birmingham, in the days before the University of Birmingham had been incorporated, and he took his B.A. Lond. with honours in 1888. Six years later he qualified in medicine and in 1895 he graduated as M.B. After holding house-appointments at Queen's Hospital he settled in practice in Birmingham. During the 1914–18 war his interest in shell-shock cases led him to the study of psycho-analysis, and after the war he continued his work in psychiatry. At the Ministry of Pensions Hospital in Birmingham he became neurologist and chairman of the neurological boards, and physician to outpatients at the psychotherapeutic clinic.

J. F. B. writes: "For nearly 60 years Guy Branson exhibited the highest traditions of medicine to the great benefit of his patients and to the honour and glory of his profession. His brusque manner, his careful scrutiny of men and material, of patient and doctor, may not have brought him the recognition of a popular doctor, but his rigid integrity, his firm honesty of purpose, his searching inquiry into all things reported to be good for his patients entitled him to the term wise physician. He was one of the old school of family doctors and those who were fortunate enough to be his patients found in him always a true guide, philosopher, and friend. He respected academic status and position only when it was coupled with honest endeavour, but all who came into contact with him, be he patient or consultant, experienced a chastening discipline—a discipline which has done more to establish the high standard of British medicine than all the showy exponents of the 'scientific' fashions of the time.

"He had a profound respect for, and knowledge of, psychology which gave him a clear insight into human thought and conduct, and this, coupled with his wide reading and experience, his love of the truth, and sound appreciation of all modern advances, fitted him to assess values. He did not tolerate the shallow enthusiast, but he was kind and encouraging to all who showed an earnest desire to render honest service. He was opposed to the exploitation of medicine, be it private or public. The profession has been ennobled by his services, for he set a high pattern throughout a long and useful life."

Dr. MAX LEDERER, director of laboratories at the Jewish Hospital in Brooklyn, New York, from 1918 until his retirement in 1943, died on Sept. 13 at the age of 67. Dr. Lederer first described, in 1925, the form of acute hæmolytic anæmia which now bears his name.

Notes and News

ALL ROUND THE UNIVERSE

To read the report of the Nuffield Foundation[1] is to experience some of the astonishment of Miranda at what goes on in the world—and outside it. The Foundation exists to advance health and social well-being in Great Britain and the Commonwealth, to prevent sickness, foster research, to favour the care and comfort of the aged poor, and to advance education. In addition, the trustees administer the Oliver Bird Fund for research into the relief and prevention of rheumatism.

Their main interests at present are in fundamental research in biology and sociology; but they are not at all narrow in outlook, for almost the first thing they report is a grant of £200,000 towards the cost of a steerable radiotelescope for the University of Manchester. With this, it seems, we may hope to achieve in radio astronomy during the next twenty years what the Mount Wilson telescope, in America, did for visual astronomy between the two world wars. Already workers in England and Australia, by applying radio and radar techniques to astronomy have found a new and different universe from the one which sufficed for former watchers of the skies. Radio emissions come from space not diffusely but from localised sources which do not correspond with prominent visible stars. These dark "radio stars" interlard the visible stars, and, not unlike their namesakes on the air, await some explanation. A diametrically opposite project supported by the foundation is the sinking of a borehole at Cambridge to determine the geological succession of the rocks. Returning from these astronomical and geodesic excursions to the earth's crust the trustees have granted £25,000 to the University of Cambridge to build a new high-speed electronic calculating machine, which is to be more reliable and slightly faster, and is to have more storage capacity than the already famous EDSAC.

Studies of more direct medical interest include the continuing research on blood-groups at the Nuffield centre in the Royal Anthropological Institute; work at the Lister Institute on bacterial antigens, which may lead to the preparation of materials more suitable for immunisation than crude bacterial vaccines; X-ray and infra-red studies at Leeds University on the molecular structure of collagen; investigations at University College Hospital of the biochemical activities of red cells, and of liver regeneration, and of course, research on the processes of ageing. In the obstetric department of U.C.H. a study, to which the foundation has contributed, is being made, by means of sensitive electronic recording apparatus, of uterine contractions in childbirth. At Oxford the mechanism of drug-resistance in bacteria is being studied, while Cambridge is hard at work on the action of hormones on tissue cultures. Sociological studies are to include the making of a set of social accounts, classifying and presenting all the transactions taking place in the administrative county of Cambridgeshire in the tax year 1953–54. Like those ancient records, the Saxon pipe-rolls, these accounts should tell us a good deal about local, and hence perhaps national, economy. As for personal economy, that forgotten art, Oxford, the home of lost causes, is conducting a statistical survey of the saving habits of a national sample of the populace. On the subject of town and country planning the Foundation displays a frankly inquisitive spirit: "Planning itself needs to be investigated." To this end the trustees have granted £4000 to the department of town-planning at University College, London, for an inquiry into the processes of planning, including the natural history of representative plans, from conception to birth. Moreover, the whole field of social research is to come under the scrutiny of Prof. Barbara Wootton, who is to resign her chair as professor of social studies in the University of London and accept a research fellowship for three years from the foundation. She will assess the results of current sociological research and point out the gaps, beginning with social deviation—"a term which includes not only crime but other forms of social failure, irresponsibility, incompetence, and nonconformity."

Sociology, however, is but one aspect of the study of mankind, and a tame one perhaps compared with those enjoyed by anthropologists in different parts of the Commonwealth. Dr. D. F. Thomson, for instance, of the University

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[1] Report for the year ending March 31, 1952. Nuffield Foundation, 12, Mecklenburgh Square, London, W.C.1.

Melbourne, went to live with the natives of Arhem Land the Northern Territory of Australia. Even their fellow atives considered these people to be difficult, and at the me they had been attacking pearling vessels in a way that emed to invite reprisals. Dr. Thomson found, when he ot to know them personally, that those who respected their aditions had little to fear. The Foundation has made a rant towards his expenses in visiting this country and ublishing his material. Then, the Pretorian discoveries f fossil remains of new types of ape-men in 1936, 1942, and 948, have thrown new light on the theory of evolution; nd the foundation is contributing to further excavations on he site of the last find.

For biologists, however, man is but one living organism mong many, and not by any means the most fascinating. hus the foundation has had the pleasure of encouraging tudies on such things as the reproductive behaviour in the en-spined stickleback, the hormonal control of ovulation, regnancy, and lactation in marsupials, the evolutionary elationships of the rannuculus in New Zealand, the nervous ystems of sea-anemones, and the family habits of the uatara, the most primitive reptile now living. The report ells of these many projects with enough detail to make the oint of them clear, and with enough reticence to whet the ppetite for more news of them. Any young man hoping o enter research could read this delightful work as a rospectus.

BRISTOL HEALTH CENTRE

On Sept. 16 Mr. Iain Macleod, the Minister of Health, on opening Bristol's new £20,000 health centre at Knowle West housing estate, congratulated the council on making history. Although a few dispensaries and other buildings were taken over as health centres when the National Health Service Act came into being and one cottage hospital had since been adapted, Bristol's health centre, as Mr. Macleod pointed out, is the first to be designed and built for this purpose.[1] It contains 6 suites for general practitioners, each consisting of a consulting-room, examination-room, and waiting-room. These suites have communicating doors so that a pair may be used for maternity and child-welfare clinics out of surgery hours. Eight doctors will use the centre, which has a staff of 12, including 5 nurses and 2 secretaries.

Since the National Health Service began, shortage of building labour and materials have made it impossible to develop health centres widely over the whole country. "Apart from that," Mr. Macleod declared, "it would be foolish to encourage authorities to build large numbers of health centres until it is known what type of health centre is likely to be most useful and popular with patients and at the same time acceptable to doctors. It is better to allow a few health centres of different types to be tried first in areas where there is a real need for better accommodation for doctors' surgeries and clinics." By studying these first experimental health centres the Minister hoped to discover the sort of centre which would enable doctors to give their best work and which would also be liked by their patients. "It is no use," he said, "putting up a palatial building with every modern facility if, in order to justify itself economically, it has to serve so large an area that the patients are obliged to travel inconveniently far. On the other hand, we expect that patients will be content to travel a little further than usual if the consulting and waiting rooms are pleasant and comfortable and, most important of all, the doctors a little less pressed for time." But he did not intend to prejudge the future of health centres. He would watch this and other experimental centres closely, and he would be "interested to know to what extent general practitioners, accustomed to practice from their private surgeries, find benefit from working with their colleagues under one common roof—whether this will lead to a desire for more co-operation or to a confirmation of a preference for working as individuals."

INSTRUCTION IN BREAST-FEEDING

The Central Council for Health Education is issuing a set of thirteen wall charts as an aid to teaching medical and nursing students the technique of breast-feeding. These charts have been produced with the coöperation of Dr. R. C. Mac Keith and the department of medical illustration, Guy's Hospital Medical School. The authors suggest only that breast-feeding is more enjoyable and simple, and is associated with rather better health in the baby, than artificial feeding; they make no dogmatic assertion that breast-feeding is essential. Some of the reasons for success and failure in breast-feeding are illustrated; and details are given of a technique based mainly on Dr. H. K. Waller's successful work. A small pamphlet is available for distribution to individual students. The set of charts may be hired, at a cost of one guinea a week, from the council, Tavistock House, Tavistock Square, London, W.C.1.

University of London

On Nov. 10, 11, 12, 13, and 14, at 5.15 P.M., at the London School of Hygiene, Keppel Street, W.C.1, Prof. Henry E. Sigerist (Yale University) will deliver a course of Heath Clark lectures on Landmarks in the History of Hygiene.

Royal College of Surgeons of England

A course on anæsthetics will be held at the college from Sept. 29 to Oct. 10. There will be two lectures in the morning and two in the afternoon. A course of lectures on pharmacology will also be given from Oct. 13 to 17 at 5 P.M. and 6.15 P.M. daily. A course of surgery lectures and clinical conferences will also be held at these times from Sept. 29 to Oct. 16. Further particulars may be had from the secretary of the faculty of anæsthetists at the college, Lincolns Inn Fields, London, W.C.2.

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held next year from April 23 to 25 at 1, Wimpole Street, London, W.1, under the presidency of Mr. Alex. MacRae. Prof. Arnold Sorsby, Prof. Robert Cruickshank, and Mr. Derek Ainslie will open a discussion on the Scope of Antibiotics and Chemotherapeutic Agents in Ophthalmology, and Sir Geoffrey Jefferson, F.R.S., will deliver the Bowman lecture. Further particulars may be had from the hon. secretaries of the society, 45, Lincoln's Inn Fields, W.C.2.

British Postgraduate Medical Federation

A further series of lectures on the *Scientific Basis of Medicine* has been arranged for the coming session. The lectures are specially designed for research-workers and specialists in training. The first lecture will be given by Prof. J. Z. Young, F.R.S., in the Beveridge Hall of the Senate House, London, W.C.1, on Oct. 7 at 5.30 P.M. His subject will be the Influence of Language on Medicine. Subsequent lectures will be given on Tuesdays and Thursdays at 5.30 P.M. at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1. *Admission is free without ticket.*

King's College Hospital Medical School

Willshire Memorial Research Scholarship.—Applications are invited for this prize which was founded in 1948 to encourage research in cardiology. It may be held for the purpose of study and travel abroad. Further particulars may be had from the dean of the school, Denmark Hill, London, S.E.5.

B.M.A. Scholarships and Prizes

The council of the British Medical Association is offering an Ernest Hart scholarship (£250), a Walter Dixon scholarship (£250), one or more research scholarships (£200 each) to candidates qualified to undertake research in any subject (including State medicine), and an Insolde scholarship (£250) for research into venereal diseases. Application must be made not later than March 31, 1953, and further particulars may be had from the secretary of the association, B.M.A. House, Tavistock Square, London, W.C.1.

The council is also offering during 1953 an Occupational Health prize (£50) for essays or studies in this field; a Katherine Bishop Harman prize (£75) for research on the disorders incident to maternity; a Sir Charles Hastings prize (50 guineas) and a Charles Oliver Hawthorne prize for an essay on a clinical subject by a general practitioner. Further particulars may be had from the secretary of the association.

Hunterian Society

At the annual party to be given by this society to fellows and their friends on Oct. 2 at 41, Portland Place, London, W.1 (by kind permission of the Ciba Foundation), the books, manuscripts, &c., acquired by the society during the year will be on view in the library. The exhibition is open for the week following (Oct. 3-10), from 4.30 to 6 P.M., to all who are interested.

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[1] Wofinden, R. C., Parry, R. H. *Lancet*, 1952, i, 1297.

Memorial to Dr. J. C. Muir

A memorial tablet has been erected to Dr. Muir at Whipps Cross Hospital, Leytonstone, London, E.11, where he was superintendent for over 20 years. It will be unveiled at 3 P.M. on Saturday, Oct. 18, and his friends are invited to attend the ceremony.

W.H.O. Committee for South East Asia

At the fifth session of the South East Asia regional committee of the World Health Organisation, which ended in Bandung on Sept. 9, Dr. M. Soerono, the chairman, laid stress on the desire of delegates to place the emphasis of W.H.O. help on supplies of equipment, rather than on procurement of foreign personnel. The committee adopted a strong resolution urging further modification of W.H.O. policy in this respect. Health projects for 1954, involving W.H.O. assistance and totalling over 2 million dollars, were endorsed. These projects will require a further $1^1/_2$ million dollars from UNICEF and other sources, making a total international expenditure of 4 million dollars.

Contraceptive Technique

A lecture and demonstration on contraceptive technique will be given by Mrs. Marie Stopes, D.SC., at the Mothers' Clinic, 108, Whitfield Street, London, W.1, on Thursday, Oct. 2, at 2.30 P.M. Tickets must be obtained in advance from the clinic.

Biology of Deserts

The Institute of Biology is holding a symposium on the Biology and Productivity of Hot and Cold Deserts at the Royal Institution, 21, Albemarle Street, London, W.1, on Sept. 25, 26, and 27. The 30 speakers will include scientists from Australia, France, the Gold Coast, North Africa, Israel, and the United States. Papers are to be given on the physical environment in deserts, the means by which plants and animals are able to exist in desert regions, the effects of hot and cold on man, how man can adapt himself to extreme conditions, and the economic aspects of obtaining increased food-supplies from arid regions. Further particulars may be had from the institute, Tavistock House South, Tavistock Square, London, W.C.1.

Eighteen doctors and others concerned in the health of industrial workers from 13 Western European [illegible] arranged by the British Council, o[illegible] Britain, which opened in Manche[illegible] continued in West Cumberland an[illegible] the course is being directed by P[illegible] [illegible]hn Craw, m[illegible] [illegible]irmingham the Birmingham branch of the [illegible] Medical Officers, of which Dr. F. H. Tyrer is hon. secretary, has coöperated in arranging the programme.

Diary of the Week

SEPT. 28 TO OCT. 4

Wednesday, 1st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of History of Medicine.* Dr. George Edwards: A Note on John Snow and the Institut de France. Dr. W. H. McMenemey: The Water Doctors of Malvern.
5 P.M. *Section of Surgery.* Prof. F. A. R. Stammers: The Surgeon's Environment.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. H. Haber: Histology of Normal Skin.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (University of Manchester.) Prof. J. Crighton Bramwell: Heart-disease and Pregnancy.

[illegible] OF ANÆSTHETISTS
[illegible]ral Infirmary.) Dr. H. O. J. Collier: New in Muscle-relaxant Drugs.

Thursday, 2nd

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of United Services.* Surgeon Lieut.-Commander W. H. B. Ellis: The Human Factor in Naval Aviation; wit[illegible] to Deck Landings.
8.15 P.M. [illegible] Dr. Macdonald Critchley: Tactile Th[illegible]ference to the Blind.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Mycology—Diagnosis of Mycotic Infections.

Friday, 3rd

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. E. M. Wigley: Eczema. (Clinical demonstration.)

Births, Marriages, and Deaths

BIRTHS

AUMONIER.—On Sept. 13, at Guy's Hospital, to Nell (née Col wife of Dr. F. J. Aumonier—a daughter.

BARRY.—On Sept. 20, at Royal Simpson Memorial Pavilio Edinburgh, to Monica (née Craig), wife of Dr. Claude Barry— [illegible]

[illegible] at the Bristol Maternity Hospital, to Joy [illegible] wife of Dr. F. G. Bolton—a daughte

CLARK.—On Sept. 7, at Bromley, Kent, to Mary Rose (née Harr wife of Dr. David Clark—a son (Alan Trelawney).

DELLER.—On Sept. 20 to Patricia (née Palmer), wife of Dr. Pete Deller, 49, Chester Square, S.W.1—a daughter.

RUTTER.—On Sept. 13, to Mary (née Milton), wife of Dr. Frank Rutter, of [illegible] a daughter.

SMITH.—On Sep[illegible] Hospital, London, to Lily Janet, [illegible] daughter.

MARRIAGES

BROWN—RICHARDSON.—On Aug. 27, Robert W. W. Brown, M.B., to F. C. Ruth Richardson, F.R.C.S.

HUTCHISON—PRICE.—On Sept. 13, in Toronto, James Graham Pinney Hutchison, M.B., to Margaret Jane Price.

DEATHS

CULPIN.—On Sept. 14, Millais Culpin, M.D. Lond., F.R.C.S., 78, of 17A, Hatfield Road, St. Albans, late of Queens Shanghai, Loughton, and Park Village East.

GOW.—On Sept. 19, at Robinwood Cottage, Kingston Vale, S.W Alexander Edward Gow, M.D. Lond., F.R.C.P.

GRAHAM-SCOTT.—On Sept. 18, at Eastbourne, Thomas Gra Scott, M.R.C.S.

HODGSON.—On Sept. 18, 1952, Stanley Hodgson, M.D. Lo LL.B., J.P.

ROW.—On Sept. 13, at Stanton Lodge, Fleet, Hants, Ch Martin Row, M.B.E., Croix de Guerre, M.R.C.S., lieut.-col R.A.M.C. retd.

TREDGOLD.—On Sept. 17, at St. Martin's, Guildford, Alfred Tredgold, M.D. Durh., F.R.C.P., F.R.S.E., consulting ph to University College Hospital, London, aged 81.

Appointments

JONES, G. A. H., M.B. Birm.: appointed factory doctor, W district, Cumberland.

MACMILLAN, S. C., M.B. Glasg., D.P.M.: consultant psych (deputy medical superintendent), Cefn Coed Hospital, Swansea.

O'CALLAGHAN, ANNE, M.B. N.U.I., D.C.H.: asst. school M.O., Brig

PERRY, KENNETH, M.A., M.D. Camb., F.R.C.P.: cons physician, Royal Masonic Hospital, London.

REID, J. J. A., M.B. St. And., D.P.H.: asst. county M.O., Buc hamshire.

WALLIS, A. L., M.B. Edin.: appointed factory doctor, Da district, Cumberland.

WARD, A. B., M.B. Durh., D.A.: asst. anæsthetist (consu to the West Cumberland group of hospitals.

Sheffield Regional Hospital Board:

[illegible] M.B. Leeds, F.R.C.S.: consultant sur [illegible] Infirmary, and Derby City Hospital.

[illegible].M. Oxfd, M.R.C.P.: consultant phys [illegible]istrict Hospital, and Victoria Hos [illegible]

WILD, G. D., M.R.C.S.: asst. chest physician with duti chest clinics in the South Derbyshire area.

Colonial Service:

BARNES, G. T., M.B. Birm.: senior pathologist, Nigeria.
BATEMAN, F. J. A., M.B.: resident M.O., Northern Rhodesi
BUCK, S. C., M.A., M.B. Camb.: senior pathologist, Nor Rhodesia.
COTTON, S. P. F., M.B.: M.O., Fiji.
DE BEAUX, J. L. M., M.B. Madras: M.O., Fiji.
DELANEY, JOYCE, M.B. N.U.I.: M.O., Federation of Malaya.
DURHAM, N. A., M.D. Bombay, M.R.C.P.: M.O., Federation of Malaya.
GARDINER, A. S., B.M. Ox[illegible] Malaya.
GATT, E. J., M.D. Malta: [illegible] a.
GRAVES, JOHN, M.R.C.S.: [illegible] of Malaya.
LESLIE-SPINKS, A. J., B.M [illegible] Trinidad and
SIUNG, O. H., M.B. Edin[illegible] Tobago.
SUTHERLAND, J. A., M.B. Glasg.: M.O., Federation of Malaya.
SWAN, T. T., M.CH. N.U.I.: M.O. (special grade) Aden.
TANNER, J. W., M.B. Birm.: M.O. Uganda.
THORNTON, T., M.B. St. And., F.R.C.S.: surgeon specialist, Federation of Malaya.
TUDOR, C. E., M.R.C.S., D.A.: anæsthetist, Trinidad.
WOLF, J., M.B. N.U.I.: M.O., Federation of Malaya.
YHAP, SHEILA A., L.R.C.P.E.: M.O., British Guiana.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

CORRIGENDUM: *New Atropine Substitute.*—In our annotation last week the reference to J. A. Marks's paper should have been *N.Y. St. J. Med.* 1952, **52**, 1783.

PERMANENT FACIAL PARALYSIS

THE RÔLE OF SURGICAL SUPPORT *

C. R. McLaughlin
M.B. Camb., M.B. Edin., F.R.C.S.E.
ASTIC SURGEON, QUEEN VICTORIA HOSPITAL, EAST GRINSTEAD

[HE problem of permanent facial paralysis is both ious and complex. Its various aspects have been plored by a host of experts with specialised interests neurologists, otologists, and general surgeons—and erefore the precise scope of this paper should at once defined. It is concerned with the rôle of static and namic support by surgical methods for those patients th permanent and irrecoverable lesions of the facial rve, who, for whatever reasons, are unsuited to urosurgery.

It includes a review of 55 cases which I have treated plastic surgery.

SELECTION OF CASES

It is very important that patients should be properly lected before they are submitted to such operations.

Unquestionably, reconstitution of the facial nerve, ether by suture, graft, or decompression, is the best eatment where it is possible (Cawthorne 1952). There e, however, many cases in which nerve repair is likely be hopeless; for instance, after radical removal of a alignant parotid gland, in certain middle-fossa fracres, in persistent congenital lesions, in birth injuries, in long-standing palsies—and these are the cases st suited to plastic surgery. In quite a different type case, where there is very slow recovery, it may be *ise to give temporary* support. The patient's age is ot very significant, and it may even be justifiable do this type of operation in children. Electromyoraphy is sometimes of value in assessing cases before peration; but it is an ancillary method, of only econdary value. Clinical judgment is, as usual, the ost important factor.

With each patient the defect has to be analysed arefully. In a fully developed case there will be sagging f the mouth and of the cheek, ectropion of the lower d, and lowering of the eyebrow on the affected side. he patient himself may complain of dribbling, of ifficulty in chewing, or of asymmetry of his mouth ith an appearance of depression and stupidity; also f epiphora and lagophthalmos. Corneal ulceration s rare.

MATERIALS

A great variety of materials has been used by different urgeons to support the face.

Silk has often been tried, but is unsatisfactory because t tends to cut out. There is, however, no serious objection o its use with proper precautions as a fixation suture in relation to fascia.

Wire slings have had a great vogue in the past, particularly in the form of stainless steel and tantalum; they have been strongly recommended by Sheehan (1946) and other surgeons. However, wire is now regarded by many as dangerous and unreliable. Even tantalum is prone to electrolytic action, and this reaction has been reported as occurring between buried tantalum and lead. It could also occur in relation to dental fillings.

Wire gauze, usually fine stainless-steel or tantalum gauze, has been used. It has proved satisfactory in the repair of certain large hernias; but it is unsatisfactory in the face, because it is still liable to undergo fragmentation, and a wide dissection is required to insert it.

Fascia lata is, in my view, the ideal material. It is strong and not prone to stretch. It should be taken, preferably by open operation, from the toughest portion of the fascia lata—namely the iliotibial tract. This is in fact the tendon of the tensor fasciæ latæ, and is covered with paratenon. For clinical purposes it may be regarded as a flattened tendon and it retains all the characteristic advantages of a tendon even under tension. When transplanted it behaves as a living graft nourished by small ingrowing blood-vessels.

Lastly one may use *muscle*. Strips of muscle, partly torn from their parent muscle belly, are not ideal. They are likely to become separated from their nerve-supply and blood-supply, and they will then undergo fibrosis and cease to act as muscles. But the use of a complete muscle with its tendon intact, in conjunction with fascia lata, is a different matter. This undoubtedly is a very satisfactory combination with a wide sphere of usefulness.

STATIC VERSUS DYNAMIC SUPPORT

It is proper at this stage to set down the indications for dynamic as opposed to static support.

In a normal person the face is highly mobile, and ideally there is no doubt that for paralysed patients dynamic support is best; but it must be of such a kind that it also offers static support while the face is in repose (fig. 1). With technique as it is at present, dynamic support to the forehead or the eyelids is often unsatisfactory, and in my opinion static support is best in these areas. Dynamic support is certainly applicable to the mouth and cheek if the patient is suitable—i.e., if he is not stupid or too old. But it always requires patience and effort for anyone to overcome the difficulties of dissociating and reassociating two such primitive functions as chewing and smiling. Also there are likely to be some involuntary mouth movements which cannot be entirely suppressed when the patient is eating. Finally it must be remembered that, technically, static support is much the simpler operation.

TECHNIQUE OF STATIC SUPPORT

In static support one must have two fixed points. The lower point lies at the corner of the mouth, though it is also linked medially with the functioning half of the oral sphincter on the unaffected side. The upper point of fixation can be either the temporal fascia, 4 or 5 inches away, or round the zygoma; but it has been argued that the best point lies nearer the mouth (McLaughlin 1949). The nearest bony structure in the right direction is the malar, only $1^3/_4$ inches away. A hole can easily be drilled near the lower edge of the anterior part of this

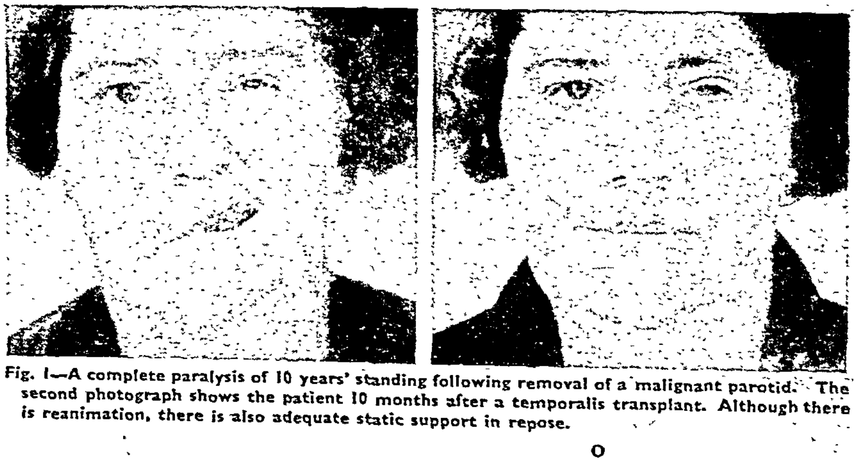

Fig. 1—A complete paralysis of 10 years' standing following removal of a malignant parotid. The second photograph shows the patient 10 months after a temporalis transplant. Although there is reanimation, there is also adequate static support in repose.

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* Based on a lecture given at the Royal College of Surgeons on April 21, 1952.

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bone. This is close to the origin of zygomaticus major, and the sling will finally follow the course of this important muscle.

The operation is carried out as follows :-

Three tiny incisions are made, one on the upper lip, one on the lower, and one on the lateral side of the mouth on the paralysed side. Two $^1/_4$-inch strips of fascia lata have already been cut, one 7 inches and the other 5 inches long. The longer of these is then inserted with the Blair needle in a figure-of-eight so that it reaches the unparalysed portion of the sphincter just beyond the midline in both upper and lower lips. The two ends are brought out of the lateral incision and sutured together with silk. The second strip is looped round the double loop at the corner of the mouth.

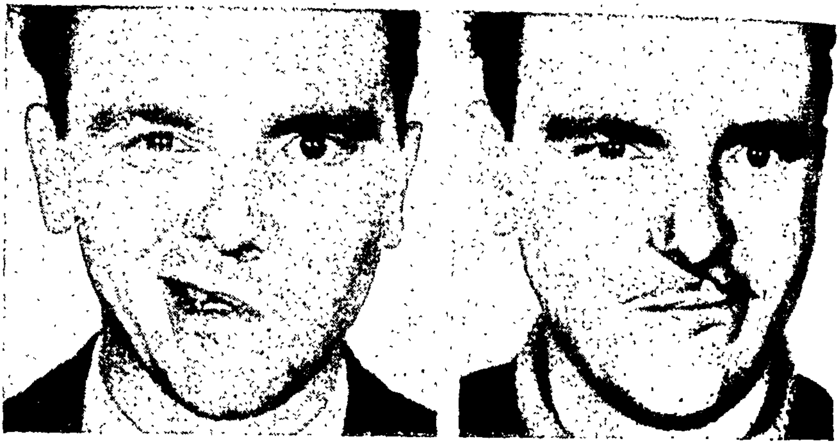

Fig. 3—Left facial paralysis. Range of cheek movement before and after total temporalis transplant. With practice the patient can also produce a natural-looking smile. *In this case the coronoid was approached by sectioning the zygomatic arch and turning down the bone together with the masseter origin.*

The malar bone is exposed through a separate incision. After stripping a small area of periosteum, a hole is made with a dental drill and enlarged sufficiently to admit a small sucker-nozzle. Using a wire noose, one end of the fascia lata is drawn through this hole; the other end is then brought up, but not through the hole, and the two ends are twisted together and finally sutured together. The device of twisting is useful, because in this way the correct tension may be gauged.

In all these manœuvres it is important, by the use of small towels, to prevent the fascia coming in contact with the face. With silk sutures it is particularly necessary to preserve asepsis. The four small incisions should lie so that they are virtually self-closing, and when sutured they will then not leave conspicuous scars. It is always wise to apply pressure to the cheek with a crêpe bandage to prevent postoperative œdema.

In this technique certain points require emphasis. First a considerable degree of so-called overcorrection has to be produced, because the muscles on the unparalysed side are without tone under the anæsthetic. As soon as the patient is conscious, most of this overcorrection will disappear. Secondly, it is important to adjust the tension of the figure-of-eight so that the mouth is not made too small. If the tension is rightly assessed it will correct the ectropion of the lower lip but will avoid a rigid mouth. Relaxation of the normal half of the sphincter then allows a wide enough opening of the mouth.

A well-judged static operation will tend to straighten the nose, and centre the philtrum; it will control any bulging of the buccinator muscle, and it should also restore the normal curve of the cheek (fig. 2). One may note in passing that the so-called face-lift operation tends in these patients to do the opposite and to achieve only a flat cheek.

REANIMATION BY DYNAMIC SUPPORT

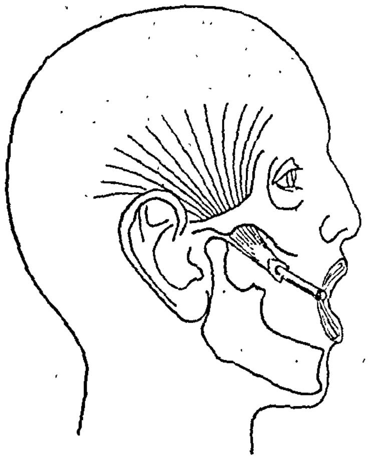

Fig. 4—Diagram of temporalis sling showing relationship of transplanted temporalis and fascial slings.

This brings us to the question of dynamic support. Muscle transplantation cannot hope to give the *quality* of reanimation that nerve surgery can achieve; but where nerve surgery is not feasible muscle transplantation offers the best alternative. It is the method of choice where there is an irrecoverable nerve lesion, where the patient is over twelve but under fifty years of age, and where he is coöperative and intelligent enough to make the best use of an unusual and anomalous means of expression (fig. 3).

There are a number of alternative ways of using a muscle transplant to achieve facial movement. First the masseter may be used in strips. It is however a bad principle to split a muscle belly, and there is inevitably some risk to the nerve-supply of this muscle. Secondly, fascia lata brought up from the corner of the mouth may be sutured to the masseter; but this may not give secure fixation. Similarly, fascia lata attached to the temporalis muscle may be used: this has the definite disadvantage of conferring only a small range of movement, but it is appropriate to certain rare cases of bilateral paralysis, where a fixed malar sling is too

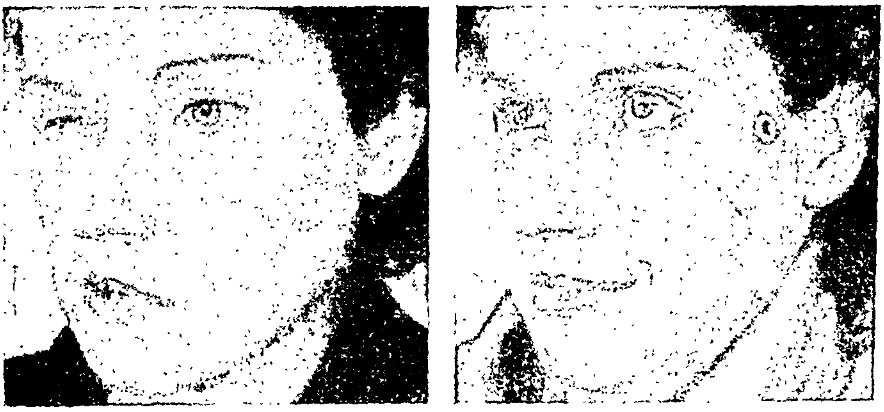

Fig. 2—Partial paralysis of 25 years' duration, following otitis media. *Gross asymmetry of face with skeletal distortion.* Treated by fascia lata sling to malar, with Bunnell type of removable wire for later adjustment; seen 10 days after operation.

igid. Or, a portion of the temporalis muscle may e turned down as a muscle flap after the method of illies (1934). This is a very difficult operation, and s apt to give rather a cumbersome result.

The last, and probably the best, method is to use the emporalis in its entirety, firmly secured to a strip of ascia lata (fig. 4). As this appears to me to be the nethod of choice and has never been published, it may be wise to describe it fully.

It involves a direct open approach to the coronoid process of the mandible, so that the insertion of the temporalis muscle may be preserved intact. There are several possible routes to the coronoid:

1. It may be approached through the masseter muscle. But this is an unsatisfactory route and involves serious trauma.
2. It may be approached by dividing the zygoma on each side of the masseter origin, and turning down a large single flap of bone and muscle. This gives a very good view, but involves a major dissection which seems hardly justified.
3. One may go through the skin in front of the masseter in the narrow space between the zygoma above and Stensen's duct below. This is a good method, but it is usually impossible to reach the coronoid by this route unless the temporomandibular joint is dislocated forward *on* that side.
4. The coronoid may be approached from within the mouth.

This last may appear a difficult approach, but it involves very little trauma. There is no skin incision. The condyle of the mandible is held in dislocation, and the jaw is jacked widely open with a cleft-palate gag. It might be thought that this would involve a serious risk of sepsis, but with the routine use of antibiotics the risk appears to be very small, particularly if no sutures are buried near the intra-oral incision. The function of the temporomandibular joint is not disturbed by this procedure, nor is the power of mastication curtailed.

Whatever the anatomical approach to the coronoid, the technique of dynamic support should be a standard one:

> After the necessary dissection to expose the upper part of the coronoid, a hole is drilled in the bone near the apex. A wire loop is then passed through this hole, and the coronoid is divided a little below the hole. The loop of wire is used to draw the fascia lata through the hole, and both ends of the fascia are then brought through a single subcutaneous tunnel down to the figure-of-eight at the corner of the mouth. This must be done in such a way that the fascia and the small portion of coronoid are free to follow a direct line and to run easily in the soft tissues.

In the early postoperative phase it is important to encourage gentle active movements within the limits of comfort, for adhesions are the most likely difficulty with this type of operation.

CONSERVATIVE METHODS

It may be well to refer to some conservative methods of support, that either avoid surgery or require a less complex technique. First, a hook to lift the corner of the mouth may be fixed to the denture, or externally to the ear. This, except after a nerve repair, is a bad device unless for very temporary use, since it stretches the oral sphincter and deforms the mouth. Secondly, an intra-oral flange may be built into the denture to give support in the upper buccal fornix. This is a good method for elderly patients; but if the patient is edentulous, as is usual, it may be difficult to hold the heavy denture in position. Thirdly, the method of supporting the face by skin advancement alone, the so-called face-lift operation, has a limited use, but it is insufficient in the very old, where it might otherwise be most helpful. However, while it is not as effective as fascial slings, it may enhance the result produced by fascia, and it has its uses on occasion.

The best device for supporting the face temporarily in cases of Bell's palsy (or any other paralysis which is likely to recover spontaneously) is plain zinc oxide strapping. This is certainly unsightly, but it *does* give the proper kind of temporary support if applied carefully, and in any case about 80% of Bell's palsies make a full and rapid recovery, usually without any treatment (Muller 1952).

EYELID SURGERY

We now come to the problem of eyelid surgery, including the relief of frontalis paralysis. Both symmetry of the face and also vision may be marred by a sagging eyebrow, when the frontalis muscle is paralysed. Transposition of the frontalis is an operation which has been advocated and is easy to do, but the effect of reanimation usually wears off as the muscle becomes scarred. As so often, the simplest operation is probably the best. This consists in excising an ellipse of skin and of paralysed muscle immediately above the affected eyebrow. It may be necessary to remove as much as half an inch in height at the centre of the ellipse.

As regards eyelid surgery we should in a severe case have four objectives—to relieve the patient's epiphora, to narrow the palpebral fissure, to lessen the lagophthalmos, and to prevent corneal ulceration or conjunctivitis due to exposure.

With regard to epiphora it is necessary to understand the physiological process of lacrimal drainage. Normally

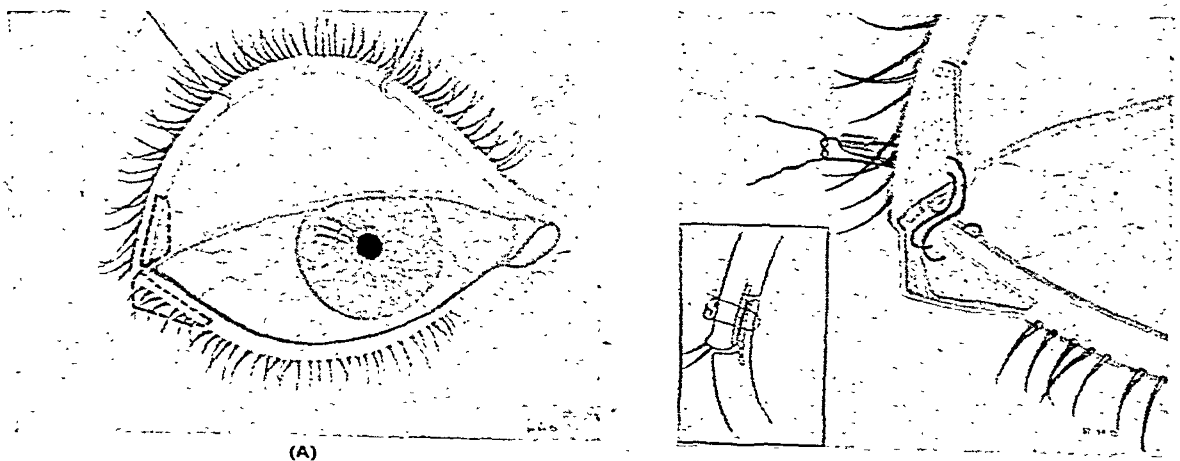

Fig. 5—Diagrams showing (A) the incision and (B) the method of suturing recommended for a lateral tarsorrhaphy, with overlapping of the tarsal plates. The operation is designed both to elevate the lower lid and to draw it in a lateral direction.

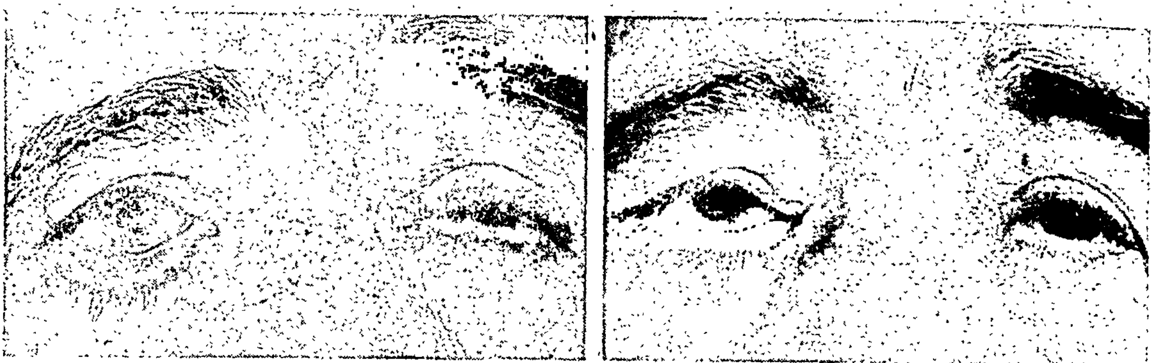

Fig. 6—Elderly patient (73) with severe epiphora. Relieved by lateral overlapping tarsorrhaphy, transposed flap at inner canthus, and "three-snip" to canaliculus.

tears tend to collect and form a tear lake at the inner canthus. The further passage of the tears into the lacrimal sac is assisted by the action of the orbicularis oculi. The lacrimal portion of this muscle is attached to the fascia covering the lacrimal sac. When the muscle contracts it pulls on the fascia and dilates the sac. It also shortens and widens the lower canaliculus and inverts the punctum. This occurs each time the patient blinks. It is probable that the tears pass from the lacrimal sac into the nose by gravity aided by capillary attraction. Thus in paralytic epiphora the following factors are likely to cause difficulty: there is no contraction of the orbicularis to dilate the sac; the punctum is not in contact with the eye and is usually stenosed; the caruncle is unduly exposed and becomes enlarged; and the tear lake lies in the middle of the sagging lid away from the punctum. Finally, undue exposure of the eye leads to excessive lacrimal secretion.

Ectropion of the lower lid is best relieved by an overlapping lateral tarsorrhaphy (McLaughlin 1951) (fig. 5). This will carry the tarsal plate both up and out, and will restore not only its proper position but its normal tension. At the same operation as the tarsorrhaphy, it is also necessary to enlarge the lacrimal opening. This is done by what is known as the three-snip operation. First the roof of the canaliculus is slit for a short distance after dilating the punctum; secondly, a vertical cut is made on the inner aspect of the punctum; and thirdly a triangle consisting of the posterior wall of the canaliculus is excised. This makes a new ostium much nearer the sac. If trouble arises from an enlarged caruncle, this is best treated by partial excision. In the worst cases internal canthoplasty, using a transposition flap, is useful. If these methods are properly carried out, the tears will drain into the nose quickly enough for the eye to remain dry under normal conditions (fig. 6). The eye will be sufficiently covered when the lids are open, and the cornea will be safe when the patient is asleep.

ANALYSIS OF OPERATIONS

This series of 55 patients does not include the small number for whom no surgical treatment of any kind was indicated. The great majority of the lesions, including some that were incomplete, were permanent and therefore required operation. Most of the palsies were due to gross damage to the facial nerve, the commonest causes being mastoid surgery, parotidectomy, and birth trauma.

Owing to the unwarrantably pessimistic attitude of many doctors, only a few patients were seen within a year of onset of the paralysis, and many had waited twenty years or more. For the whole series, the average duration of paralysis before surgical treatment was fifteen years, and in 2 cases it exceeded fifty years. The age of patients ranged from thirteen to eighty.

As has been emphasised, the temporalis transplant is not suited to every patient, and a careful and critical selection is necessary. On this basis a malar sling has been used on 34 occasions, and a temporalis transplant on 11, in each case using the methods described. The need for surgery to relieve the associated epiphora can be judged from the fact that 44 patients have required surgery to the lower canaliculus and 38 have had a tarsorrhaphy by the overlapping technique.

Sepsis in relation to fascial grafts is alleged to be a serious and not infrequent complication. In this series it has occurred on 3 occasions (just over 6%) and in each instance it was related to silk fixation sutures. When these were later removed, healing followed without delay, and the efficiency of the sling was unaffected.

The following summary shows the operative methods used:

Number of patients	55
Range of age at operation	13–80 years
Average duration of paralysis	15 years
Number of operations:	
Malar sling	34
Temporalis transplant	11
Lateral tarsorrhaphy	38
Three-snip to canaliculus	44
Face-lift	4

The results can be roughly assessed by the photographs, though these unfortunately give little or no idea of the degree of reanimation achieved. The object of illustrating results ought to be not so much to advertise the success of new procedures as to demonstrate their scope and limitations. However, from the patient's point of view, symmetry of the face in repose is a major achievement, and a little reanimation greatly enhances the result.

CONCLUSIONS

I would like to summarise certain points which seem to me of special importance.

It is essential to avoid a fixed routine; each patient must be assessed as an individual problem. Even in cases of established facial paralysis there is a wide variety of clinical circumstances. Therefore, the most effective operation suitable to the patient must be selected. For most younger patients a temporalis transplant is best; but static support to the malar bone is easier to carry out, though less effective.

Permanent overcorrection by fascial slings is almost impossible, owing to limitation by the buccinator and mucosal attachments to the mandible. There should be no serious risk of progressive loss of support after the operation, through stretching and so on. Fascia lata does not stretch, and the fixation at both ends should be secure if the operation is properly carried out. There is always the appearance of deterioration due to return of tone on the normal side, but when the patient is re-anæsthetised overcorrection reappears. A dental flange is a useful but inferior alternative.

Most of these patients suffer from epiphora in some degree, and it should never go untreated. 95% of those with this symptom have been greatly improved by very simple methods.

It is wise to remember the gravity of the whole roblem. Bunnell (1927), describing the untreated atient, says: "In facial paralysis, joy, happiness, orrow, shock, surprise, all the emotions have for their ommon expression the same blank stare." But Tagliacozzi, writing in 1597, strikes a more cheerful and onstructive note. He says:

> "We bring back, refashion and restore to wholeness the eatures which nature gave but chance destroyed . . . not as a mean artifice but as an alleviation of illness . . . For although the original beauty of the face is indeed restored, yet this is only accidental, and the end for which the physician s working is that the features should fulfil their offices according to nature's decree."

SUMMARY

The indications for surgical support by reconstructive methods in patients with permanent facial paralysis are discussed.

The relative advantages of reanimation by dynamic rather than static support are described. A new method is suggested, using transplantation of the entire temporalis muscle.

The indications for treating epiphora by simple methods are set out.

Experiences with a personal series of 55 patients are summarised.

I am very grateful to my colleagues at East Grinstead, whose kindness in referring many of these patients has made it possible to collect this material in the past five years. It is also a pleasure to acknowledge my debt to Mr. T. G. Ward for valuable help in working out an approach to the coronoid, to Mr. R. H. Dale for the drawings, and to Mr. G. Clemetson for the photographs.

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OCCUPATIONAL AND PERSONAL FACTORS IN THE ÆTIOLOGY OF CARCINOMA OF THE LUNG

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> "The pressing problems of our time are not, with the knowledge available to us, amenable to the usual methods of preventive medicine. They are diseases obscure in origin and chronic in their course, such as the several forms of heart and arterial disease, diabetes, cancer, rheumatoid and other forms of arthritis."—Boas 1947.

Some of these diseases have a clearly defined social incidence and affect to a greater degree particular classes of our society; others are more prevalent in workers in certain occupations. Some cancers more commonly affect the lower strata of society, and, until recently, hypertension and coronary thrombosis were seen more often in the professional classes. Ryle (1948) aptly remarked that with ætiology—the first essential for prevention—and with prevention itself, the majority of physicians and surgeons have curiously little concern. The problem of the ætiology of carcinoma of the lung remains unsolved and the results of present methods of treatment are poor. Although surgery has placed it among the curable diseases, Brock (1948) reported that only 11% of 666 cases seen over the seven years 1941–47 were operable. A reasonable figure for the present operability-rate is 15%.

INCIDENCE

Whereas twenty-five years ago it was a rare disease, carcinoma of the lung now occurs nearly as often as carcinoma of the stomach and more often than cancer of the colon: indeed at certain hospitals in America it has become now the commonest visceral cancer in men. The third annual report of the Liverpool Cancer Control Organisation (1947–48) states that "there would appear to be little doubt that there is an actual increase in the incidence of this disease, which, in man, is now assuming numerical importance comparable to that of malignant disease of the breast in the female." In 1944 cancer of the lung and mediastinum constituted 8% of the 2668 cases of cancer registered with this organisation; this proportion rose in 1947 to 10·4% of 3875, and in 1949 to 12·2% of 4384. In 1947 and 1949 only carcinoma of the breast and rodent ulcer were registered more frequently than cancer of the lung and mediastinum; the percentages of carcinoma of the breast (which had the highest incidence) were 15·9 in 1944, 14·9 in 1947, and 12·5 in 1949. The corresponding figures for carcinoma of the stomach were 7·4, 9·6, and 7·5. Kennaway and Kennaway (1947) in a careful statistical study of death-certificates in England and Wales from 1928 to 1945 present evidence that the increase is at least partly real. In our opinion the increase is real and cannot be accounted for solely by improved diagnostic methods and a greater awareness of the disease amongst doctors.

POSSIBLE CAUSES OF THE INCREASE

In considering this disease we must consider certain facts about the development of tumours in animals. Following the application of tar to the skin there is a long latent period between the cessation of tarring and the appearance of tumours. A locally applied carcinogen may also act on a tissue remote from the scene of application; 60–80% of mice receiving tar application to the skin developed lung tumours (Murphy and Sturm 1925). Constitutional factors are important, and strains of mice especially sensitive to the action of polycyclic hydrocarbons can be bred. The successive actions of carcinogens are cumulative and also injury or non-specific irritation may precipitate tumour formation in a carcinogenically prepared field.

A number of substances are known to be carcinogenic and 9:10 dimethyl 1:2 benzanthracene is the most active hydrocarbon so far discovered. Amounts as small as 0·0004 mg. have produced sarcoma in mice (Shear 1936). A single intratracheal injection of 0·1 mg. methyl cholanthrene is followed by the development of multiple lung tumours in mice (Shimkin 1939). Active carcinogenic agents can be produced by heating a great number of substances to a temperature of 700°C—e.g., skin, yeast, voluntary muscle, and cholesterol. In a review of carcinogenic and anti-carcinogenic substances Dodds (1948) notes that there are a great many ways of producing cancer with no fundamental connections between them. He calls attention to objections to the accepted theory of a long-term action of carcinogenic substances.

If it is correct that the occurrence of carcinoma of the lung is increasing, the cause may be found in some factor or factors to which the general population has been more exposed in this century. For instance, the tarring of roads and the exhaust fumes of motor-cars have for many years been suggested as possible factors. The evidence, however, points to the disease being as prevalent among the general population in some wide open spaces—such as Western Canada,

SMOKING

An obvious possible factor in the causation of carcinoma of the lung is smoking. It has increased greatly in recent years, especially cigarette-smoking. Also there is still a sex difference, though it will be interesting to study this again after a sufficient lapse of time.

Roffo (1939) and Florey (1941) demonstrated that tobacco tar is carcinogenic in animals. Muller (1939) found suggestive evidence of smoking as a factor in an investigation of 86 patients with cancer of the lung; and in 1950 two large-scale inquiries were published. In America, Wynder and Graham (1950) questioned 605 men with carcinoma of the lung and found that 51·2% were excessive or chain smokers (more than 20 cigarettes per day for more than twenty years), compared with 19·1% in the general male hospital population without cancer. Only 1·3% of the cancer patients were non-smokers, compared with 4·6% of the non-cancer patients. They concluded that excessive and prolonged use of tobacco, especially cigarettes, seemed to be an important factor in the induction of carcinoma of the lung.

Doll and Hill (1950) published the findings on smoking which they obtained in the M.R.C. investigation referred to earlier. A carefully conducted inquiry with other cancer and non-cancer control groups, it is the most important contribution to our knowledge of this aspect of the ætiology of carcinoma of the lung yet published. Altogether 709 patients with carcinoma of the lung were interviewed—489 confirmed by necropsy, biopsy, or exploratory operation. Of the 649 men 0·3% and of the 60 women 31·7% were non-smokers. The corresponding figures for the non-cancer control groups were—men 4·2%, women 53·3%. Of the lung-cancer patients 26% of the men and 14·6% of the women who smoked gave as their most recent smoking habits, before their illness, the equivalent of 25 or more cigarettes a day; only 13·5% of the male, and none of the female non-cancer control patients smoked as much. Cigarette-smoking was more closely related to carcinoma of the lung than pipe-smoking. No distinct association was found with inhaling. They concluded that smoking was an important factor in the cause of carcinoma of the lung.

All the 300 patients interviewed in our series were asked the same questions:

1. The age-periods during which they had smoked.
2. The amount they habitually smoked before coming into hospital.
3. Details of their smoking history and the distinction between smoking pipes and cigarettes.

Soon after the investigation started it became apparent that many of the patients did not understand what was meant by inhaling, or else attached meanings to it different from the usual one of drawing some of the smoke into the lungs. To many it meant taking a very deep breath after drawing some smoke into the mouth and to a few it meant swallowing the smoke. As the investigation continued, we became more and more convinced that the answers we were receiving to this question were unreliable, and finally we gave up asking. It is our opinion that anyone who smokes cigarettes must inhale a certain amount of tobacco smoke, at least as far as the main bronchi.

The patients were placed in four groups according to their smoking history: non-smokers, cigarette-smokers, those who had only smoked pipes, and those who had smoked both a pipe and cigarettes. A non-smoker was defined as one who had never smoked more than an occasional cigarette at widely spaced intervals. Anyone smoking as much as one cigarette per day for three months would have been assessed as a smoker. In practice we found no difficulty, for all our 300 patients had either smoked for periods over two years or fell easily within our definition of a non-smoker. The cigarette-smokers were subdivided into heavy (more than 20 per day), medium (10–20 per day), and light (less than 10 per day), by estimating their average consumption over the years they had been smokers. This was not always easy, for many of the casual-labourer class smoke as many as they can afford, and so their consumption may vary from 2 per day when out of work, to 15 per day when working, or perhaps 30–40 per day during overseas military service. If they had been heavy smokers for a third of their smoking life, or for more than six years, they were allotted to that group. Several men over 50 had smoked heavily for three or four years during the first world war but since had been medium smokers; they were allotted to the medium group. By including both 10 per day and 20 per day in the medium group, that group has been enlarged, but we feel that thereby the heavy and light groups become more accurate and significant. Pipe-smokers were divided into heavy (more than 4 oz. per week), medium (2–4 oz. per week), and light (less than 2 oz. per week). Those who had smoked both pipe and cigarettes were subdivided into heavy, medium and light groups by taking into account only their cigarette-smoking and classifying them accordingly.

TABLE VI—NUMBERS OF SMOKERS AND NON-SMOKERS IN CANCER AND CONTROL GROUPS, WITH SEX-INCIDENCE

—	Non-smokers	Smokers	Probability test
Males			
Cancer (93)	5 (*5·4%*)	88 (*94·6%*)	$\chi^2 = 0{\cdot}0078$ $n = 1$ $P > 0{\cdot}0$
Control (186)	12 (*6·5%*)	174 (*93·5%*)	
Females			
Cancer (7)	4 (*57·1%*)	3 (*42·9%*)	Exact test $P > 0{\cdot}05$
Control (14)	11 (*78·6%*)	3 (*21·4%*)	

RESULTS OF SMOKING INQUIRY

Smokers and Non-smokers.—Of 100 cancer cases, 9 were classified as non-smokers. Of the 93 men, 5 (5·4%) were non-smokers, and of the 7 women 4 (57·1%) were non-smokers. The corresponding percentage in the 186 control men was 6·5 and in the 14 control women 78·6. These figures are shown in table VI.

Both sexes show no significant difference between the percentage of non-smokers in the cancer and control groups. In contrast Wynder and Graham (1950) and Doll and Hill (1950) found significant differences in the incidence of smoking in the cancer and control groups for both men and women, though this may perhaps be accounted for by the much larger samples which they used. It is of interest, however, to compare our figures with those of Doll and Hill, and this is done in table VII.

TABLE VII—COMPARISON OF SMOKING INCIDENCE IN MALE CANCER AND CONTROL GROUPS WITH THAT GIVEN BY DOLL AND HILL

—	Non-smokers	Smokers	Probability test
Cancer patients			
Doll and Hill (649)	2 (*0·3%*)	647 (*99·7%*)	$\chi^2 = 17{\cdot}26$ $n = 1$ $P < 0{\cdot}001$
Present series (93)	5 (*5·4%*)	88 (*94·6%*)	
Control patients			
Doll and Hill (649)	27 (*4·2%*)	622 (*95·8%*)	$\chi^2 = 1{\cdot}23$ $n = 1$ $0{\cdot}20 < P < 0{\cdot}30$
Present series (186)	12 (*6·5%*)	174 (*93·5%*)	

It will be seen that in the male cancer group Doll and Hill have found a significantly greater incidence of smoking than is suggested by our figures (99·7% compared with our figure of 94·6%). This difference in incidence of smoking is not found significant in the control group, where the corresponding figures are 95·8% and 93·5%. In the female patients, neither the cancer nor the control group show any significant difference in incidence: Doll and Hill gave 68·3% and 46·7% smokers for the cancer and control groups respectively, compared with our figures of 42·9% and 21·4% smokers.

The proportion of non-smokers in this series (9%) is higher than that found in previous series, and particularly so is the proportion in the males (5·4%). It was thought possible that some other factor might be at work in these patients, but a careful review of their histories did ot bring anything to light. 4 lived in suburban and in rural surroundings; 5 had no possible occupational actors; the other 4 had been exposed to cotton-dust, ailway fumes, mineral-oil, and flour. None had lived ear a gas-works or other industrial source of atmospheric ollution.

Type of Smoking.—The male and female patients ave been taken together for this comparison since, lthough few women smoke pipes, the proportion of women who are smokers is sufficiently small to make no ppreciable difference in the results. Of the 91 smokers in the cancer group, 68 (74·7%) were cigarette-smokers, 8 (8·8%) were pipe-smokers, and 15 (16·5%) smoked both a pipe and cigarettes. The 177 smokers in the control group contained 138 (78·0%) cigarette-smokers, 7 (4·0%) pipe-smokers, and 32 (18·0%) who smoked both. Table VIII shows the percentages of the different types of smokers, divided into age-groups; and it will be seen that there is a remarkable similarity in the percentages in the cancer and control groups. Doll and Hill, to distinguish between cigarette and pipe smoking, excluded those who had smoked both, and found that of the lung carcinoma patients who had smoked either pipes or cigarettes but not both, 5·7% were pipe-smokers compared with 9·7% in the corresponding section of the control patients. A similar comparison with our figures is given in table IX, and in contrast it will be seen that the percentage of pipe-smokers in the cancer group (10·5) is greater than that in the control group (4·8) though the difference is not significant.

TABLE VIII—PERCENTAGE OF CANCER AND CONTROL SMOKERS (MALE AND FEMALE) WHO SMOKE CIGARETTES OR PIPE OR BOTH, AND AGE-DISTRIBUTION. CONTROLS IN PARENTHESES

Age-group	Cigarettes	Pipe	Pipe and cigarettes
30–39 ..	5·5 (*6·8*)	0 (*0*)	2·2 (*0·6*)
40–49 ..	29·7 (*28·2*)	1·1 (*1·1*)	4·4 (*5·6*)
50–59 ..	25·3 (*28·2*)	5·5 (*1·1*)	3·3 (*7·3*)
60–69 ..	14·3 (*14·7*)	2·2 (*1·7*)	6·6 (*4·5*)
Total ..	74·7 (*78·0*)	8·8 (*4·0*)	16·5 (*18·0*)

Comparison of our figures for the incidence of pipe-smoking with those given by Doll and Hill reveals no significant differences, however. For the cancer patients $\chi^2 = 1{\cdot}85$, $n = 1$, $0{\cdot}10 < P < 0{\cdot}20$ and for the control patients $\chi^2 = 2{\cdot}77$, $n = 1$, $0{\cdot}05 < P < 0{\cdot}10$.

Amount Smoked.—The figures shown in table X were compiled according to our definition, given above, of heavy, medium, and light smokers. Considering the cigarette and pipe-and-cigarette smokers together as cigarette-smokers, we found that 38·5% of the cancer smokers were heavy cigarette-smokers compared with 23·2% of the control smokers. This difference is statistically significant $\chi^2 = 6{\cdot}19$, $n = 1$, $0{\cdot}01 < P < 0{\cdot}02$. Similarly only 7·7% of the cancer smokers are light cigarette-smokers, compared with 22·5% of the control smokers, and this difference is also statistically significant $\chi^2 = 8{\cdot}23$, $n = 1$, $0{\cdot}001 < P < 0{\cdot}01$.

TABLE IX—COMPARISON OF INCIDENCE OF PIPE-SMOKING IN CANCER AND CONTROL PATIENTS WHO SMOKE CIGARETTES OR A PIPE BUT NOT BOTH

—	Cigarette-smokers	Pipe-smokers	Probability test
Cancer (76) ..	68	8 (*10·5%*)	$\chi^2 = 1{\cdot}74$ $n = 1$ $0{\cdot}10 < P < 0{\cdot}20$
Control (145) ..	138	7 (*4·8%*)	

The numbers who smoke a pipe only, and the numbers who smoke a pipe and cigarettes are too small to make useful comparison between cancer and control of the amount of smoking done by each of these types of smokers. This has been done for the cigarette-only smokers in table XI, and the result is highly significant, indicating that the amount of smoking in the cancer group is larger than that in the control group.

This agrees with the conclusions of Doll and Hill, who, using 25 or more cigarettes per day as the definition of a heavy smoker, found 26% of lung carcinoma males fell into this category against 13% of non-cancer males.

Duration of Smoking.—The number of years during which the cancer and control smokers had smoked regularly is shown in table XII. In those patients who had smoked a pipe and cigarettes consecutively rather than concurrently, the total number of smoking years was used; thus the figures in the table do not differentiate between pipe and cigarette smoking. The numbers in the two lowest groups are small, but on combining these groups it will be seen that there is a significant difference between the cancer and the control smokers. This difference does not appear to be a simple one since there are more cancer than control smokers in the 20–29 group (50·5% against 32·2%) but less cancer than control smokers in the extreme groups (8·8% against 13% in the under-20 group, and 40·7% against 54·8% in the over-30 group).

The fact that the control patients had smoked for longer periods than those with lung carcinoma suggests that those who develop this disease may be more susceptible to any carcinogenic effect of smoking than normal people; but the difference is not enough for us to draw any definite conclusion.

Arsenic in Tobacco.—If smoking is a possible factor, it is interesting to note that tobacco smoke contains an appreciable quantity of arsenic.

Thomas and Collier (1945) have described a method of analysing the concentration of arsenic in tobacco smoke, employing combustion in the peroxide bomb, arsenic evolution, and titration of mercuric arsenide. The method of analysis attempts to simulate actual smoking

TABLE X—PERCENTAGE OF CANCER AND CONTROL SMOKERS WHO SMOKED CIGARETTES ONLY, A PIPE ONLY, AND A PIPE AND CIGARETTES, SUBDIVIDED BY AMOUNT SMOKED AND IN AGE-GROUPS

Age-group		Cigarettes only			Pipe only			Pipe and cigarettes		
		Heavy > 20	Medium 10–20	Light <10	Heavy > 4	Medium 2–3	Light <2	Heavy > 20	Medium 10–20	Light <10
30–39	Cancer	3·3	1·1	1·1	—	—	—	—	2·2	—
	Control	1·1	4·0	1·7	—	—	—	—	0·6	—
40–49	Cancer	12·1	16·5	1·1	—	1·1	—	3·3	1·1	—
	Control	6·8	17·5	4·0	—	—	1·1	0·6	3·4	1·7
50–59	Cancer	13·2	11·0	1·1	—	5·5	—	1·1	2·2	—
	Control	7·9	12·4	7·9	—	0·6	0·6	2·8	2·3	2·3
60–69	Cancer	4·4	6·6	3·3	—	2·2	—	1·1	4·4	1·1
	Control	2·3	9·0	3·4	0·6	1·1	—	1·7	1·1	1·7
Total	Cancer	33·0	35·2	6·6	—	8·8	—	5·5	9·9	1·1
	Control	18·1	42·9	16·9	0·6	1·7	1·7	5·1	7·3	5·6

TABLE XII—NUMBERS OF CANCER AND CONTROL SMOKERS WHO HAD SMOKED FOR DIFFERENT LENGTHS OF TIME

—	Number of years of regular smoking					Probability test
	<10	10–19	20–29	30–39	> 40	
Cancer (91)	3 (*3·3%*)	5 (*5·5%*)	46 (*50·5%*)	21 (*23·1%*)	16 (*17·6%*)	$\chi^2 = 8·62$
Control (177)	4 (*2·3%*)	19 (*10·7%*)	57 (*32·2%*)	57 (*32·2%*)	40 (*22·6%*)	n = 3 (first two groups combined) $0·02 < P < 0·05$

conditions. They found that the smoke contained 11–23% of the arsenic on the average, the remainder being distributed between the ash and butts. The concentration of arsenious oxide in the puffed smoke was 0·2–3·0 mg. per cubic metre with cigars, 1·7–5·7 mg. with pipe tobacco, and 3·3–10·5 mg. with cigarettes. It appears that a third to half of the arsenic in tobacco may be found in the smoke.

Using a similar apparatus we arranged the following experiments.

Puffs of air, 10 ml. in volume, were drawn through the burning cigarette, each puff lasting $1^1/_2$ sec. with a 10 sec. interval between each puff. The puffed smoke was drawn through an electrostatic precipitator and the arsenic in the precipitated material determined. The arsenic content of the ash, the butts and the whole cigarette was also determined—the method used consisting of wet oxidation, distillation in the magnuson microstill and calorimetric estimation by the *molybdenum-blue method.*

The results are shown in table XIII.

It must also be noted that tobacco-smoke provides an additional source through which tarry substances of known carcinogenic quality may enter the respiratory system. Tobacco tar has been proved to be carcinogenic when applied to the skin. It would be interesting to know if there is an increased incidence of bronchial carcinoma in the tobacco industry. The operations in processing leaf tobacco are dusty and workers are exposed to lead arsenate, but according to McCormick and his colleagues (1948) the arsenic content of the dust is low (<0·095 mg./As/m³). Daff and Kennaway (1950), and Daff, Doll, and Kennaway (1951) have estimated the arsenic content of 27 brands of cigarettes. The results do not suggest that there is a relation between the arsenic content and the incidence of lung cancer in different countries.

TABLE XI—NUMBERS OF CANCER AND CONTROL SMOKERS WHO SMOKE ONLY CIGARETTES CLASSIFIED ACCORDING TO AMOUNT OF SMOKING

—	Heavy > 20	Medium 10–20	Light < 10	Probability test
Cancer (68)	30 (*44·1%*)	32 (*47·1%*)	6 (*8·8%*)	$\chi^2 = 11·54$
Control (138)	32 (*23·2%*)	76 (*55·1%*)	30 (*21·7%*)	n = 2 $0·001 < P < 0·01$

SUMMARY

Published work on the cause of cancer of the lung has been reviewed.

An investigation has been made into the environmental, occupational, and smoking history of 100 patients with carcinoma of the lung, living in the Liverpool area; 200 inpatients of the same age and sex, suffering from diseases other than cancer, were also interviewed. The 93 men and 7 women in the 100 studied were proven, by biopsy, necropsy, or operation, to have carcinoma of the lung.

Careful questioning showed that 47% of the cancer patients had been exposed appreciably to various dusts, fumes, and smokes; 43% of the controls had been similarly exposed, and in approximately the same proportions. Only a slightly higher proportion of the cancer patients lived in industrial areas (60% as compared with 54·5% of the controls). An equal proportion of the two groups (16–17%) had lived near a gas-works or other industrial source of atmospheric pollution.

No significant difference was found in the incidence of smoking, or of the proportion of cigarette-smokers, in the two groups. A significantly higher proportion (33·0%) of the cancer smokers had smoked more than 20 cigarettes per day than had the non-cancer smokers (18·1%). There was a slightly higher proportion of pipe-smokers among the smokers with cancer than among the smokers without cancer.

It is possible that heavy smoking of cigarettes may be a factor in the ætiology of carcinoma of the lung.

TABLE XIII—*DETERMINATION OF ARSENIC CONTENT OF CIGARETTES, AND OF THEIR SMOKE*

		Sample A	Sample B	Sample C
Portion of cigarette smoked ..		80–85%	80%	77%
Vol. of air drawn through cigarette, per g. of tobacco consumed ..		0·64 l.	0·69 l.	0·67 l.
Arsenic * in :	Puffed smoke ..	2·1, 2·5	1·7, 1·8	1·7, 1·9
	Ash	30·6, 26·0	19·6, 21·8	32·9, 32·4
	Butts	17·7, 16·8	10·8, 10·9	17·1, 15·6
	Whole cigarette ..	70·6, 64·4	38·3, 38·0	73·0, 70·0
Concentration in smoke—mg. As_2O_3/m^3		3·6	2·6	2·7

* Parts per million of As_2O_3 calculated on original weight of cigarette.

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FURTHER STUDIES ON THE NATURAL RANSMISSION OF THE COMMON COLD

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THAT the common cold may be transmitted from man o man by the instillation into the nose of bacteria-free ltrates of infective nasal washings has been established y several workers and fully confirmed at the Common old Research Unit, Salisbury. This information, howver, throws little light upon the ways in which colds re transferred under natural conditions. The present eport is concerned with attempts to study the transission of colds under conditions closely resembling those f normal social intercourse.

EARLIER EXPERIMENTS

Earlier attempts to study the natural transmission of olds at this Unit had proved difficult. As already reported Andrewes 1949), 19 normal persons in one trial were xposed for ten hours to others with early colds, and nly one infection developed as a result; this was in a erson exposed to another in the presymptomatic ncubation period. In a second test none of 4 exposed eople, and in a third attempt only 1 of 5, caught colds. imilar difficulty in producing naturally transferred nfection was reported by Kerr and Lagen (1934).

In 1950 an experiment was made on an island off the orth coast of Scotland (Andrewes et al. 1951):

> The hope was that people conditioned by three months' omplete isolation would have acquired enhanced suscepti-bility and thus permit us to answer questions about the oute of transfer of infection. The possibility of transfer by means of droplet nuclei or by contamination of the environment was explored by much the same techniques as are described below. 12 people thus exposed to 10 people with profuse colds failed, to our surprise, to contract infection. The colds to which they were exposed were of one of our "pedigree strains"—i.e., one which had been artificially passed in series from one person to another by nasal instillation of stored washings. When later, in contrast to earlier failures, a natural or "wild" cold in a crofter did "jump" naturally to 3 of 8 of the exposed "islanders," we were led to consider the possibility that "wild" colds might have better powers of "jumping" than had the "pedigree" ones which had been used not only in the experiment on the island but also in all our previous tests at Salisbury.

We therefore decided to make more transmission experiments, using people with natural colds as "donors" of infection. In several trials we used children, since Lidwell and Sommerville (1951) have produced evidence indicating that they spread colds more readily than do adults.

EXPERIMENTAL METHODS

The organisation of the Common Cold Research Unit and methods used in experiments with human volunteers have already been described (Andrewes 1949). In the present experiments all the volunteers were examined clinically on arrival at the Unit and on each morning of their subsequent stay. On the day of arrival the volunteers were placed in isolation. Most of them were accommodated in pairs, but some remained in single isolation. Those who were passed as fit to take part in the experiments were all in good general health, aged, with three exceptions, 19–45, with a preponderance of females (141 females, 90 males).

Any volunteer showing signs of a cold during the first three days of observation was excluded from the experiment, and if the volunteer was one of a pair in isolation both were excluded. Those remaining free from signs of a cold on the morning of the third day after arrival were exposed later that day to possible risks of infection by the experimental procedures under investigation. Clinical observations of the volunteers in isolation were continued until the ninth day after arrival. Allocation to the experimental groups was made by the bacteriologist, using random sampling numbers. The nature of the exposure was not made known to the clinical observer until he had written up his assessments at the end of each experiment. In the final analysis of colds induced as a result of the procedures only those volunteers developing typical symptoms and signs subsequent to exposure have been recorded as having had colds. Those with doubtful signs, or subjective evidence alone, have been classified with those having had no colds.

People with "wild" or natural colds of recent onset have been selected as "donors."

Comparison of Transmission of Colds by Different Routes

The object of these experiments was to determine whether or not colds could be transmitted by droplet nuclei alone or by indirect contact alone, these conditions being compared with full exposure allowing all normal routes of transference to operate. Five similar experiments were made, involving 82 volunteers and 22 donors. The details of the procedure are described below; not every method was used in every trial.

Exposure to infected droplet nuclei.—A room of about 2000 c.ft. was divided into two with a blanket extending to within about 1 ft. of the side walls, floor, and ceiling. A fan ensured good mixing of the air throughout the whole chamber. 5 or 6 healthy volunteers sat on one side of the partition; they were asked to read or to sew quietly throughout the experiment. After a short interval to allow particles in the atmosphere to settle again, the donors and one observer, wearing sterile gowns to minimise the secondary release of infected particles from clothing, entered and sat on the other side of the partition. The donors were encouraged to play games involving talking, shouting, or singing but little bodily movement. Sneezing-powder (o-dianisidine hydrochloride) was liberated half-way through the experiment. A wide tube, connected to a slit-sampler operated outside the chamber, enabled the bacterial content of the air to be measured at intervals. The number of colonies of *Streptococcus salivarius* grown on a selective medium (Williams and Hirch 1949) was taken as an indication of the degree of contamination of the atmosphere by secretions from the respiratory tract. After a 2-hour exposure the donors left the transmission chamber, removed their gowns, and went to another room, of similar size but without a central division, for the second part of the experiment. The volunteers returned to their flats and remained in isolation until the end of the trial.

"*Full contact.*"—The conditions of exposure in this group were those of normal social contact. The same donors as in the first experiment mixed freely with a second party of healthy volunteers for a further period of two hours, eating luncheon together and later playing cards and other games. No bacterial samples of the air were taken in this room, but an observer again noted outstanding incidents, such as sneezing, coughing, and violent nose-blowing. At the conclusion of this experiment the donors departed and the volunteers returned to isolation.

Indirect contact in contaminated environment.—The third group of volunteers was next exposed to the environment which had been contaminated by the donors in the full-contact exposure. Playing-cards and other objects handled by the previous occupants were again used, and once more the period of exposure was two hours. Before the volunteers entered the contaminated environment, the room was aired for 10 minutes by opening windows and doors, to diminish the likelihood that infective particles would remain in the air.

RESULTS

The results of these experiments are summarised in table I. In three instances children aged 8–13 years acted as donors, and in two others adults were used. Two colds developed in 25 volunteers exposed to droplet infection, three in 32 exposed to full contact, and two in 25 exposed to a contaminated environment. The two colds in the last group were in volunteers occupying the same flat. One of these had minimal symptoms on arrival but remained clear during the quarantine period and was included in the trial. Symptoms returned on the day after exposure to the contaminated environment, and next day her partner showed signs of infection. Possibly a missed quarantine cold was responsible for both these infections; all the other colds shown in table I were separate incidents in different flats.

Another experiment is best considered separately; the results are not included in table I. Of 8 volunteers exposed to 5 children with colds 4 became infected. Conditions in this trial differed from those already described in two ways: the donors were, in part, younger children, their ages being 13, 11, 6, 5, and 4 years; also games were played, including blowing and nose-to-nose passing of a matchbox, rather a closer degree of contact, in fact, than is likely to operate commonly as a means of cross-infection. From all the experiments together we cannot conclude that children were more effective donors than adults.

Bacterial counts made during the droplet nuclei experiments indicated that there was considerable contamination of the atmosphere of the chamber with organisms from the respiratory tract, although the average for one trial was considerably lower than the other three. The number of colonies of *Strep. salivarius* per c.ft. of air sampled in one trial rose from an initial figure of 0·16 in the absence of children to 0·9 shortly after their entry, and to a peak of 3·2 per c.ft. immediately after the release of sneezing-powder. These figures are about twenty times as high as those found in recent trials in infants' school-rooms (Air Hygiene Committee of the Medical Research Council, personal communication).

TRANSMISSION BY MEANS OF MISTS

Since the results of exposure to infected droplet nuclei indicated that the common cold could spread by this means, studies were made with artificial mists of infected particles. In many instances material stored at −76°C in dry ice was used.

The apparatus consisted of a Collison-type spray, the metal parts of which were plated with gold. In the first two experiments power was supplied in the form of compressed air at a pressure of 10 lb. per sq. in., but it was found more satisfactory to use nitrogen from a cylinder at the same pressure. The droplet cloud was carried through a length of wide-bore rubber tubing to the nose-piece of a B.L.B. mask as used for the nasal administration of oxygen. When the source of power was nitrogen, a separate tube added pure oxygen to the inhaled vapour in the mask.

After the face-piece had been fitted and tested for leaks, the gas supplies were switched on, and the volunteer was instructed to inhale through the nose and to exhale through the mouth. A separate mask was used for each volunteer, and the virus suspension in the spraying chamber was changed after every 10 or 20 minutes' spraying. To reduce the inactivation due to the concentration of salt in the droplets, washings collected in 0·2% sodium chloride were selected in preference to those taken in physiological saline solution, and dilutions were made in distilled water. Protein, in the form of 0·2% bovine albumin, was also added to the spraying fluid. The true output of the spray under the conditions of the experiment was calculated to be 0·035 ml. per minute, and spraying for 5 minutes should deliver about the same dose of virus as that contained in 1 ml. of a 1 : 5 dilution of filtrate.

To investigate the possible effects of spraying on the infectivity of the material, the mist produced by the spray was drawn through 5 ml. of 10% broth-saline solution in a sampler containing small glass beads. After sampling for 5 or 10 minutes, the fluid was removed and the sampler was washed with a further 5 ml. of broth-saline solution. The spray sample was next tested in volunteers by the normal technique of inserting 0·5 ml. into each nostril in the form of drops.

As a further check on the output of the spray, and on the harmlessness of the process to a virus suspension, tests were made with influenza virus. Infected allantoic fluid from an A-prime strain A/Sweden/3/50 was diluted 10^{-4} in distilled water containing 0·2% bovine albumin and a small amount of radioactive iodine (I^{131}) was incorporated in the spraying mixture. The resultant mist was sampled in 10% saline solution, and the virus content of the original fluid and of the spray sample was determined by inoculating dilutions of both fluids into the allantoic cavity of developing 10-day hens' eggs. The dilution in the spray sample was estimated by measuring the radioactivity of both fluids with a Geiger counter. The results indicated that there had been no appreciable inactivation of influenza virus by spraying. It would, of course, be unwise to assume that the common cold virus is as stable as that of influenza.

TABLE II—SUMMARY OF SPRAYING TESTS

Test	Serial nos. of trials	Colds induced	No colds induced	No. of volunteers	Percentage positive
Spray $^1/_2$ minute ..	114, 115, 116	3	13	16	20·0
Spray 3 or 5 minutes	114, 115, 120	4	11	15	26·7
Spray collected and given as drops ..	116, 120, 121	4	16	20	20·0
Drops 1 : 5 or 1 : 10	114, 115	4	4	8	50·0
Drops 1 : 50 or 1 : 100	114, 115, 116, 120, 121	11	19	30	36·7

The results of the spraying tests are shown in table II, which shows that the common-cold virus can survive the spraying, and that a cloud of infected droplets will produce colds in some of the persons exposed. The figures suggest, however, that the same volume of material was less effective as spray than as drops; they are not, however, highly significant (P=0·07).

CONTAMINATION OF EXTERIOR OF NOSE

Three experiments were made in which infective secretions were applied only to the outside of the nose.

TABLE I—SUMMARY OF CONTACT EXPERIMENTS

Trial no.	Date of exposure (1951)	Donors	Droplet nuclei					Full contact			Contaminated environment		
			Volume of air sampled (c.ft.)	Av. count of *Strep. salivarius* per c.ft. of air	No. of volunteers	Subsequent colds		No. of volunteers	Subsequent colds		No. of volunteers	Subsequent colds	
						+	−		+	−		+	−
106	Jan. 31 ..	4 Children	12	2·8	6	1	5	6	1	5	5	0	5
108	March 3 ..	4 Children	48	1·7	8	1	7	7	0	7	6	2	4
112	April 28 ..	4 Children	48	0·35	5	0	5	5	0	5	6	0	6
122	Sept. 22 ..	5 Adults	60	2·2	6	0	6	7	0	7	8	0	8
124	Oct. 17 ..	5 Adults	..	..	..	..	..	7	2	5	..	..	..
				Total	25	2	23	32	3	29	25	2	23

TABLE III—SUMMARY OF TESTS OF APPLICATION OF VIRUS TO NOSE

Trial no.	Date	Nature of exposure	Duration of exposure (hr.)	Subsequent colds in volunteers			Comments
				+	–	No. of volunteers	
124	Oct. 17, 1951	Full contact	2	2	5	7	
		Contaminated handkerchiefs ..	24	0	8	8	
125	Nov. 28, 1951	Dry pack in nose	2	0	10	10	Material produced 6 colds in 10 volunteers in trial no. 123
		Wet pack in nose	2	2	7	9	
127	Jan. 2, 1952	Drops	..	5	3	8	
		Wet pack	2	2	5	7	
		Paint	1	0	7	7	
126	Dec. 12, 1951	Virus painted around external nares	..	0	7	7	Material produced 6 colds in 10 volunteers in trial no. 123
		Virus administered as drops.. ..	..	0	4	4	

No colds developed in 22 volunteers so exposed. The details of the experiments are as follows:

(1) Sterile cotton-wool swabs mounted on wooden applicators were soaked in infected material, and about 0·1 ml. was painted on the skin round the external nares. The 7 volunteers so treated were instructed not to touch or to wipe the nose for an hour after this procedure. Four volunteers received 1 ml. of a 1 : 10 dilution of the same material by the usual dropping technique. No colds resulted in either group, although the material, a filtrate of infected washings from a young adult with a "wild" cold, had previously produced six colds in 10 volunteers.

(2) Nasal blowings from 5 adults with recent colds were collected on 'Cellophane' handkerchiefs. These were washed off with 10% saline solution, and the pool of about 15 ml. of crude material was shaken with glass beads and then centrifuged to remove gross debris. The opalescent supernatant fluid was distributed in 1 ml. quantities, on the centre of clean linen handkerchiefs, which were refolded and issued to 8 healthy volunteers. Each volunteer was instructed to blow the nose on the contaminated handkerchief immediately, and to use the handkerchief throughout the succeeding twenty-four hours. The interval between contamination of the handkerchiefs and their first use by the volunteers was usually about half an hour, during which time most had dried sufficiently to be passed as clean handkerchiefs by the volunteers using them. No colds developed as a result of this procedure, although there were two colds in 7 other volunteers who were exposed to the 5 donors of the infected secretions for two hours under conditions of full contact.

(3) Eight-inch squares of sterile gauze, folded into pads eight layers thick, were contaminated by dropping 0·5 ml. of undiluted nasal washing into the centre of each. The impregnated pads were immediately handed to volunteers, who were instructed to spread the contents of the gauze over the outside of the nares and to repeat the process at short intervals for an hour, during which time they were neither to wash the hands nor to blow the nose. Concurrently 8 other volunteers received the same material, diluted 1 : 2 in broth-saline solution, by the usual dropping technique, and a third group of 7 volunteers was infected by means of packs inserted into the nose (see below). No colds developed in the 7 volunteers who applied the material to the outside of the nose, whereas 5 out of 8 receiving drops developed colds, and two colds developed in the third group.

It thus appears that the placing of infective secretions round the outside of the nose is unlikely to produce a cold. The absence of colds in the group of volunteers using contaminated handkerchiefs for twenty-four hours was unexpected. The result suggested that the virus might be particularly sensitive to drying. To test this hypothesis infective secretions were allowed to dry on gauze before being used for transmission studies.

COMPARISON OF MOIST AND DRY PACKS INSERTED INTO NOSE

Sterile ribbon-gauze strips 12 in. in length were soaked in 0·25 ml. of material known to be infective. Each strip was then kept over calcium chloride in a sealed container at room-temperature for an hour, after which the packs appeared to be quite dry. A second series of gauze strips was impregnated with the same amount of material shortly before the time of insertions. Volunteers were allocated in random fashion to one of two groups, and the appropriate gauze strip was inserted into one nostril with a sterile wooden applicator and remained in position for two hours. The results of this experiment are shown in table III. There were no colds in 10 volunteers exposed to infection by dry packs, and two colds among 9 exposed to moist packs. The numbers do not permit a statistical comparison of the two methods, but suggest that there has been inactivation of the virus as a result of the drying.

DISCUSSION

An analysis of the results in this Unit has shown that an average of 50% of volunteers may be expected to develop colds after the instillation of infected drops into the nose, irrespective of age, frequency of natural colds, or time since last cold. Though individual susceptibility varies considerably, the sensitivity of a group of 6–8 volunteers to infection with a given strain of virus may be expected to be rather more constant. Wherever possible such numbers have been used; otherwise duplicate experiments have been made on smaller groups.

Standardisation of the dose of infective material in transmission studies presents much greater difficulties. Although donors were selected on a history of recent onset of symptoms, together with nasal obstruction and discharge, it was impossible to assess the amount of secretion disseminated by different people other than by a crude estimate based upon direct observation. By using groups of 4 or 5 donors it was hoped that the effects of this variation might be lessened. As seen in table I, two groups of donors failed to pass their colds on by any route. In one of these the observer reported that the children acting as donors were quiet throughout the experiment, and this is reflected in the low figure for aerial contamination in this group. In the other trial no colds developed after exposure to 5 adults, although the plate counts indicated a considerable degree of contamination of the atmosphere.

With such a low rate of positives comparison between the three groups is clearly unjustifiable. There is *definite* evidence that colds may pass from person to person as a result of normal social contact, and that exposure only to infected droplet nuclei will produce colds in a small proportion of those exposed. The evidence for spread by indirect contact is, as explained above, less convincing, and further experiments are needed before the importance of this route can be estimated.

The fact that colds did develop as a result of droplet spread, in spite of the relatively small amount of material which can have reached the noses of the recipients, suggested that experimental infection of volunteers with a given quantity of virus might be more readily achieved by exposure to infected droplets than by other methods.

Comparative tests were therefore made with artificial droplet mists. Using strong virus suspensions we could induce colds in about 1 in 5 of persons inhaling the ærosol for $^{1}/_{2}$–5 minutes. When, however, about the same dose of virus was introduced into the nose in the form of drops, the rate of "takes" rose to 1 in 3 or 1 in 2. Experimentally, therefore, it appeared that infection by means of mists was a less effective method of inducing colds in volunteers than our customary method of applying drops to the nose. The technique has the further disadvantages of requiring more complicated apparatus, and of using much greater quantities of virus.

The transmission of any agent by indirect contact involves three stages. The environment must first be contaminated by an infected subject, the secretions must be in a state in which they retain their infectivity, and they must be picked up by a susceptible person and transferred by him to the nose. If we apply these ideas to our trials with the common cold, the available evidence suggests that infected secretions are rapidly inactivated by drying. Further, even when the route of transmission has been shortened to the extent of applying material of known infectivity to the outside of the nose, no colds have resulted.

Experiments made earlier, with fluorescent dyes used as tracers, had shown how readily secretions could be passed directly and indirectly from one person to another (J. E. Lovelock and K. R. Dumbell, personal communication). The present results do not support the idea that this transfer is necessarily effective, and indeed suggest that indirect contact is unlikely to play a major part in the spread of the common cold. Our tentative conclusions apparently conflict with a statement which has been made on several occasions: Arctic explorers are reported to develop colds when undoing bales of clothing which have been kept packed up for many months. The implication is that the agent concerned is very stable. One must assume either that their symptoms were due to something other than the common cold, or that their isolation had conditioned them to respond to very small doses of virus. In the present experiments "takes" as a result of direct contact compare not unfavourably with the natural rate of cross-infection in homes (cf. Lidwell and Sommerville 1951); that they are rather fewer is not surprising in view of the fact that in our experiments there was a single period of exposure, whereas in the observations of Lidwell and Sommerville contact was for some days.

The question discussed here is important. We are very conscious that the low incidence of colds induced as a result of our experiments has meant that our findings are much less conclusive than we could have wished. It is probably true that the development of an overt cold in man is determined more by the varying susceptibility of the person than by the degree of exposure to the causal agent.

CONCLUSIONS

Though common-cold infection may spread from person to person by normal social contact, and through the air in the form of droplet nuclei, the rate of clinical cross-infection is low.

We found no evidence suggesting that spread by indirect contact is of major importance in the natural transmission of the common cold.

Our results suggest that the virus of common cold may be sensitive to drying.

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FURTHER INVESTIGATION INTO CAUSES OF THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS

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In a previous paper (Bolton Carter 1951) it was shown that the incidence of thrombophlebitis resulting from intravenous infusions could be diminished by limiting the duration of infusion to eight hours.

So far as practicable this procedure has been followed with all infusions set up in the surgical unit of University College Hospital over the last two years. During this period there has been no case of thrombophlebitis severe enough to cause the patient gross discomfort.

All the infusions have been carefully followed up, with inspection of the infusion sites, for a week afterwards, and all cases showing $^{1}/_{2}$ in. of venous thrombosis with $^{1}/_{2}$ in. of surrounding inflammation, or more, have been recorded as cases of thrombophlebitis.

From January, 1951, to August, 1951, the results were:

Infusions running for less than eight hours:
121
15
Infusions r hours:
3 produced no reaction.
7 " thrombophlebitis.

Thus 11% of the infusions running for less than eight hours produced thrombophlebitis.

All of these infusions consisted in some part of 5% dextrose. Since solutions of dextrose when autoclaved become acid, it was decided, as the next step in the investigation of infusion thromphlebitis, to study this factor. For three months the pH of every bottle of infusion fluid was measured electrometrically with a glass electrode, and it was found that the pH of whole citrated blood and of physiological saline solution was reasonably constant, being slightly on the acid side of normality, whereas that of the dextrose solution varied between 3·1 and 5·8, averaging 4·5. Having established that the dextrose solution was the only infusion fluid with an unstable and acid pH, a trial of buffered dextrose with a stable pH was started.

BUFFERED DEXTROSE

Previous work had shown some of the difficulties of buffering dextrose. Hudson and Tarlowski (1947) and Bryan and Grainger (1950) found that the addition of sufficient phosphate buffer to prevent the pH falling below 6 caused so much caramelisation as to render the solution unfit for use. Other methods tried by these workers are either impracticable or have the disadvantage of causing auto-agglutination and hæmolysis *in vitro*.

We have tested the effect of 0·2% and 0·5% of disodium hydrogen phosphate and 0·5% of trisodium citrate as buffers for 5% dextrose, and found the latter to give consistently a slightly higher pH. Such buffered solutions, however, have a well-marked brown colour due to caramelisation.

Since sodium metabisulphite has proved useful as an antoxidant in several injections, its effect was tested in preventing the darkening of buffered dextrose solutions. It was found that in concentration of 0·01% the colour was reduced from dark brown to pale yellow, and that with 0·1% the solutions were almost colourless or at the most pale yellow.

Although the dark-brown solutions have generally been regarded as unfit for use and pharmaceutically are unsatisfactory, there seem to be no references to clinical tests on such coloured solutions. Previous experience has led us to conclude that the coloration is not harmful. In testing the effects of buffered dextrose solutions, therefore, it was decided to try two types of solution, one coloured by caramelisation, and the other with the factor controlled, to see if the incidence of thrombophlebitis would be reduced. The following solutions were used:

(1) 5% dextrose with 0·5% sodium phosphate; after autoclaving this was deep brown and had a pH of 5·56.

(2) 5% dextrose, 0·5% sodium citrate, and 0·1% sodium metabisulphite; after autoclaving this was almost colourless and had a pH of 6·05.

Although sodium metabisulphite tends to lower the pH slightly, this is more than offset by its action in preventing oxidation of dextrose and consequent increase in acidity.

In preparing solution (2) some difficulty was encountered with the effect of citrate in causing flaking of glass in transfusion bottles, but this was overcome by washing with acid and rinsing thoroughly before use.

Results

From August to November, 1951, when the pH of all infusions was being estimated and unbuffered dextrose was used, the results were:

Infusions running for less than eight hours:
88 produced no reaction.
18 ,, thrombophlebitis.
Infusions running for more than eight hours:
14 produced no reaction.
5 ,, thrombophlebitis.

Thus 17% of infusions running for less than eight hours produced thrombophlebitis.

From November, 1951, to February, 1952, the 5% dextrose solution was buffered as described above, and in this period the pH of all bottles of infusion fluids was estimated and in all cases approximated to normal. The results in this series were:

Infusions running for less than eight hours:
109 produced no reaction.
23 ,, thrombophlebitis.
Infusions running for more than eight hours:
10 produced no reaction.
7 ,, thrombophlebitis.

Thus 17·5% of infusions running for less than eight hours produced thrombophlebitis.

The incidence of thrombophlebitis had not, therefore, been lessened by buffering the dextrose.

There were no clinical signs of toxicity from the buffered dextrose, and no difference was noted between the effects of the coloured solutions and those of the colourless solutions.

Since the institution of the eight-hour limit for infusions no case of severe thrombophlebitis has been seen in the wards of the surgical unit.

SUMMARY

In order to see if the incidence of thrombophlebitis resulting from intravenous infusions could be reduced the 5% dextrose solution used for infusion was buffered with either 0·5% sodium phosphate or 0·5% sodium citrate and 0·1% sodium metabisulphite, thereby approximating its pH to that of normal blood.

There were no toxic reactions to the buffered dextrose, but the incidence of thrombophlebitis was unchanged.

The importance of the time-factor, if the incidence and severity of thrombophlebitis is to be reduced, is confirmed.

This investigation was carried out under the guidance of Prof. R. S. Pilcher, and much of the work was done by Messrs. J. M. Doyle, A. W. Johnston, J. L. Somervell, and P. K. Thomas, house-surgeons on the Surgical Unit when the investigation was in progress.

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HEPATIC CHOLESTEROL CONTENT IN NUTRITIONAL DISORDERS

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An increase in total cholesterol of liver, mainly due to the esterified fraction, is known to occur in various types of fatty livers produced experimentally in animals by dietary means.

In the so-called "fat" fatty liver of choline deficiency resulting from the feeding of high-fat low-protein diets to rats a small but definite increase in the cholesteryl-ester content was reported by several workers (Best et al. 1934, Channon and Wilkinson 1936, Ridout et al. 1946, Gajdos 1951).

In the fatty liver of depancreatised dogs maintained with insulin a considerable increase in the cholesteryl-ester fraction was noted, although triglycerides accounted for the major part of the accumulated lipids in the liver (Kaplan and Chaikoff 1937).

The most striking increase in the cholesteryl-ester content of the liver was found in the severe fatty livers produced in rats by feeding cholesterol in the diet (Okey 1933, Chanutin and Ludewig 1933, Best et al. 1934).

Gavin and McHenry (1941) reported that fatty livers characterised by the accumulation of large amounts of cholesterol were found in rats given biotin, and that this type of fatty liver was resistant to the action of choline but could be prevented with inositol. However, Best et al. (1946) were unable to confirm these findings.

Although there is experimental evidence that cholesterol accumulates in fatty livers of dietary origin in animals, it is not known whether a similar accumulation of cholesterol occurs in human fatty livers of nutritional origin. Severe fatty infiltration of the liver, almost certainly due to malnutrition, is common in kwashiorkor (infantile pellagra, malignant malnutrition) which was first adequately described by Williams (1933) in West Africa and later studied in greater detail in Africa and the West Indies. This disease, with all its characteristic features, occurs in India (Ramalingaswami et al. 1948) and is called "nutritional œdema syndrome" by Gopalan and Patwardhan (1951). In these laboratories we also have found fatty infiltration of the liver in adults with nutritional œdema (unpublished observations). We report here our findings on the cholesterol content of the liver in 6 children with kwashiorkor and 6 adults with nutritional œdema.

TABLE I—FATTY INFILTRATION AND CHOLESTEROL IN LIVER BIOPSY SPECIMENS

Case no.	Age (yr.)	Sex	Fatty infiltration	Anisotropic material	Cholesterol content (% of weight of dry tissue)
Kwashiorkor:					
1	4	F	+ + +	+ + +	..
2	4	F	+ + + +	+ + + +	10·44
3	3	M	+ + + +	Nil	..
4	1½	F	+ + + +	+ +	..
5	7	M	+ +	Nil	3·250
6	1½	F	+ +	Nil	1·666
7	1	F	+ + + +	Nil	2·818
8	1¼	F	+ + + +	+ +	..
Nutritional œdema:					
9*	40	M	+ + +	+ + + +	..
10	38	M	+	Nil	5·333
11	35	M	+	Nil	9·00
12	30	M	+	Nil	1·692
13	55	M	+ + +	Nil	1·727

Normal value 0·24–0·388% of weight of fresh tissue (Bloor 1943, Ralli et al. 1941).

* Classical pellagra with œdema.

TABLE II—FATTY INFILTRATION AND CHOLESTEROL IN LIVERS AT NECROPSY

Case no.	Age (yr.)	Sex	Total lipids (% of weight of dry tissue)	Total cholesterol (% of weight of dry tissue)	Percentage of total cholesterol in total lipids	Fatty infiltration (histological)	Anisotropic material (histological)
14	3	M	13·4	2·079	15·5	+	Nil
15	3½	M	20·88	1·424	6·8	+ +	Nil
16	35	M	45·33	1·777	3·9	+ + + +	Nil
17	40	M	13·01	1·422	10·4	+	Nil

PRESENT OBSERVATIONS

Our attention was first drawn to the cholesterol component of the liver lipids in these conditions by the observation that, in some sections of liver biopsy specimens stained for fat with Sudan IV, a crystalline material in the form of flat plates with notched edges and needles was present inside the fat globules. The crystals stained poorly with Sudan IV. They were absent in sections from the same livers which were exposed to alcohol and xylene. The fact that they were doubly refractile under polarised light made us suspect that they might be cholesterol. The biopsy specimens, fixed in neutral formalin, were subjected to quantitative chemical estimation of cholesterol by the Liebermann-Burchard reaction. The results are given in table I. Because of the small size of the biopsy specimens it was impossible to estimate any lipid fraction other than total cholesterol. In a few cases coming to necropsy, however, the total lipids were also estimated; the results are given in table II. The severity of fatty infiltration of the livers was graded arbitrarily as 0 to + + + + on examination of Sudan-stained sections. The amount of anisotropic material in the sections was also graded in a similar manner on examination of the sections under polarised light. It will be seen from the tables that, in the livers in which chemical estimations were possible, there is moderate to considerable increase in the cholesterol content. Case 2, whose liver contained the greatest amount of anisotropic material (fig. 1), also showed the highest cholesterol value. Another liver biopsy specimen from the same case, after four weeks' treatment with skimmed-milk powder, showed almost complete disappearance of anisotropic material (fig. 2). The specimen also showed a striking reduction in the amount of sudanophilic material.

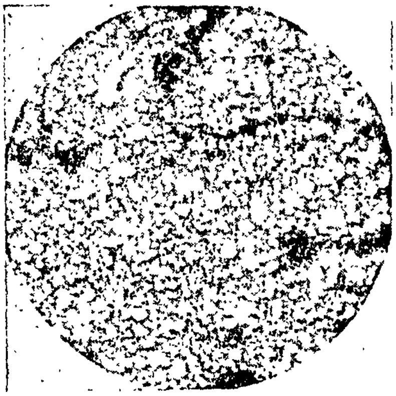

Fig. 1—Biopsy specimen of liver (case 2) under polarised light, showing large amounts of anisotropic material (× 70).

DISCUSSION

The pathogenesis of accumulation of cholesterol in the livers is not quite clear. The accumulation of cholesterol is accompanied in all cases by large amounts of Sudan-stained droplets, which are presumably neutral fat. This seems to resemble the accumulation of cholesterol in the "fat" fatty liver of choline deficiency in rats, in which the deficient formation of lecithin would be expected to lead to an accumulation of cholesteryl esters for lack of recipients for their fatty acids (Peters and Van Slyke 1946). Our observations, however, show that there is no direct correlation between the amount of cholesterol and the severity of fatty infiltration assessed histologically or chemically. They suggest that the accumulation of cholesterol is not merely incidental to the accumulation of neutral fat, and that a specific disturbance of cholesterol metabolism might be involved. It has been reported that the pancreatic factor, lipocaic, has a specific preventive effect on the deposition of cholesterol in the liver in animals (McHenry and Patterson 1944), and it is perhaps significant that extreme atrophy of pancreatic acini is characteristic of kwashiorkor (Waterlow 1948, Davies 1948). Our preliminary observations indicate that, on treatment with skimmed-milk powder, there is a regression of cholesterol together with neutral fat. The precise factors responsible for this effect are now being studied.

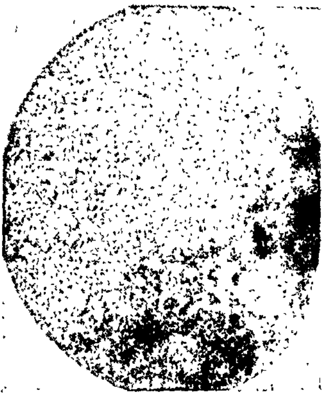

Fig. 2—Biopsy specimen of liver (case 2 after treatment) under polarised light, showing considerable decrease of anisotropic material (× 70).

SUMMARY

A considerable increase in the cholesterol content of livers was found in some cases of kwashiorkor and nutritional œdema in adults. The significance of this finding is discussed.

We wish to thank Sir Harold Himsworth for his most valuable comments, and our colleagues in the Nutrition Clinic for the supply of clinical material.

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"... Our bad habit of polluting the air with waste products of combustion and other chemical processes was formed long ago, but since the beginning of the industrial revolution a minor irritation has become a great social evil. In towns and industrial districts rain water loses its purity: ash and other solids fall continuously to the ground; the air contains a suspension of fine particles which penetrate indoors, to be deposited on walls, ceilings, curtains, and furniture; our clothing, our skins, and our lungs are contaminated; metals corrode, buildings decay, and textiles wear out; vegetation is stunted and blackened; sunlight is lost; germs multiply; our natural resistance to disease is lowered. In a hundred and one ways the miasma of atmospheric pollution is lowering our vitality and our enjoyment of life. . . . We cherish our freedom to do as we please in our homes, but just as we no longer throw rubbish into the street, we shall eventually cease to discharge smoke into the air."—A. R. MEETHAM, D.SC., *Atmospheric Pollution*. London: Pergamon Press, 1952; p. 5.

THE EFFECT OF CORTISONE ACETATE ON ADRENAL ASCORBIC-ACID DEPLETION FOLLOWING STRESS

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Sayers and Sayers (1947) showed that the depletion of adrenal ascorbic acid following various stresses could be abolished by prior administration of adrenal cortical extract. Of the crystalline steroids which they also tested, 17-hydroxy,11-dehydrocorticosterone (cortisone) and 17-hydroxycorticosterone were the most potent in this respect, followed in order by corticosterone, deoxycortone, and progesterone, the last exerting only a small effect. Gray and Munson (1951) obtained similar results with adrenal cortical extracts, but Fortier et al. (1951), using both free cortisone and cortisone acetate, could not substantiate the findings of Sayers and Sayers (1947).

In view of these conflicting reports, it seemed desirable to investigate the problem further in relation to cortisone acetate, and to determine if a relationship existed between dose and response.

METHOD

Male white Wistar rats were used, with an average weight of 150 g. (range 142–156 g.). Controls were killed by stunning followed by decapitation; both adrenals were then removed. Cortisone acetate (Merck) was centrifuged, washed free from suspending medium, and resuspended in physiological saline to the required concentration. In the first two experiments, the left adrenal was removed under ether anæsthesia two hours after the intraperitoneal injection of cortisone, and an hour later the rat was killed and the right adrenal removed. In the third experiment adrenocorticotropic hormone (A.C.T.H.) was administered intravenously two hours after the intraperitoneal injection of cortisone, and both adrenals were removed an hour after this. To minimise the stress of intraperitoneal injections of cortisone, saline rather than alcoholic preparations were preferred, administered in volumes of 0·2 ml. The adrenals were crushed with a glass rod in test-tubes each containing 2 ml. of 4% trichloracetic acid and a little sand. The rod and sides of the tube were washed with 3 ml. of trichloracetic acid, and about 75 mg. of acid-washed charcoal was added (it was found that large quantities of charcoal interfered with the recovery of ascorbic acid). After filtration the ascorbic-acid content of the filtrate was estimated by the method of Roe and Kuether (1943), with the following modifications:

TABLE I—EFFECT OF SALINE AND CORTISONE ON STRESS-INDUCED ASCORBIC-ACID DEPLETION

Experiment	No. of rats	Mean level of adrenal ascorbic acid (μg. per 100 mg.) ±S.E.		
		Left	Right	Difference
Controls ..	10	235 ±12	213 ±12	−22 ±13 (P> 0·1)
Saline	9	261 ±12	164 ±14	−97 ±12 (P < 0·01)
Cortisone ..	10	210 ±12	179 ±14	−31 ±14 (P> 0·05)
Comparison of means:				
Controls and saline ..		P> 0·1	—	P < 0·001
Saline and cortisone ..		P <0·01	—	P <0·01
Controls and cortisone		P> 0·1	—	P> 0·6

(1) The thiourea was made up in water instead of 50% ethanol. This prevents the turbidity (due probably to the formation of ethyl trichloracetate) which sometimes appears after the sulphuric acid is added.

(2) It was found simpler to mix the solutions of thiourea and 2 : 4-dinitrophenylhydrazine (1 : 5) before use than to add the reagents separately. This combined reagent keeps in the refrigerator for several weeks, but requires filtering before use.

(3) To 3 ml. of adrenal filtrate 1·5 ml. of colour reagent was added, and the tube was incubated at 70°C for 30 minutes. After cooling, 2 ml. of concentrated sulphuric acid was added. The colour intensity was determined with a Spekker absorptiometer using a 604 (Ilford) filter which transmits maximally at 520 mμ.

TABLE II—EFFECT OF CORTISONE AT DIFFERENT DOSE LEVELS ON STRESS-INDUCED ADRENAL ASCORBIC-ACID DEPLETION

Dose of cortisone (mg.)	No. of rats	Mean level of adrenal ascorbic acid (μg. per 100 mg.) ±S.E.		
		Left	Right	Difference
0	10	192 ±16	135 ±11	−57 ±13
2·5	10	181 ±9	153 ±7	−28 ±10
5·0	10	192 ±8	180 ±19	−12 ±18
10·0	9	185 ±14	175 ±13	−10 ±16
20·0	8	197 ±14	222 ±20	+25 ±14

Analysis of variance

Source of variance	Degrees of freedom	Sum of squares	Mean square	Variance ratio	P
Between doses:					
Due to regression ..	1	27,565	27,565	14·0	<0·001
Departure from regression ..	3	4084	1361	0·7	> 0·1
Within doses ..	42	82,849	1973	—	—
Total ..	46	114,498	2489	—	—

S.D. within doses = 44·4. b ±S.E. = 3·6 ±0·95.

RESULTS

Table I shows a comparison between a group of control rats, a group receiving saline and a group receiving cortisone. There was no significant difference between the ascorbic-acid concentrations of the left and right adrenals in the controls. After the injection of saline followed by left adrenalectomy there was a considerable fall in ascorbic-acid concentration in the right adrenal an hour later. This fall did not take place in the group pretreated with cortisone. There was, however, some difference between the mean initial levels of ascorbic acid, and the experiment was therefore repeated, the groups being stratified with respect to weight, and doses of 2·5, 5, 10, and 20 mg. of cortisone being used. The results are set out in table II. In this experiment there was no significant difference between the mean values for the left adrenal, and the inhibition of the stress response

TABLE III—COMPARISON OF EFFECTS OF A.C.T.H. AND SALINE (ADMINISTERED INTRAVENOUSLY UNDER ETHER ANÆSTHESIA) IN RATS PRETREATED WITH CORTISONE

Experiment*		No. of rats	Mean level of adrenal ascorbic acid† (μg. per 100 mg.) ±S.E.	Comparison of means
Pretreatment (intraperitoneal)	I.V. injection 2 hr. after pretreatment			
Saline	Saline	5	189 ±11	P <0·01
Cortisone 20 mg.	Saline	5	260 ±14	P <0·05
	A.C.T.H. 0·6 μg. in saline	5	211 ±12	

* Each injection was made up in a volume of 0·2 ml.
† In this experiment both adrenals were removed together an hour after the intravenous injection.

is clearly shown. It will also be seen that, over the dose range used, there was no evidence against a linear relationship between degree of inhibition and dose.

In accordance with the work of Sayers and Sayers (1947) we have also found that, in rats pretreated with cortisone, adrenal ascorbic-acid depletion still occurs after the administration of A.C.T.H. (see table III).

During the investigation, which extended from August, 1951, to May, 1952, the adrenal glands were found to be heavier in the winter. The cause of this is unexplained.

A few minutes after the injection of cortisone the rats became sleepy. This hypnotic effect has previously been noted (Selye and Stone 1944).

DISCUSSION

A notable feature of the results is the large dose of cortisone required to abolish the stress response. Sayers and Sayers (1947) found that 200 µg. per 100 g. of body-weight prevented the depletion of ascorbic acid that otherwise follows the administration of histamine (0·5 mg. per 100 g. of body-weight).

Further work will be required to establish the specificity of cortisone in this reaction, and to define the precise mechanisms involved. The fact that A.C.T.H. still produces a depletion of adrenal ascorbic acid in rats pretreated with cortisone suggests that cortisone acts not by neutralising A.C.T.H. in the peripheral blood or tissues, but by depressing the output of A.C.T.H. from the anterior lobe of the pituitary gland. It is not yet possible to state, however, to what extent the release of A.C.T.H. from the pituitary under physiological conditions depends on the level of circulating adrenal cortical steroids.

The method described might provide a basis for the assay of A.C.T.H., rats pretreated with cortisone being used instead of hypophysectomised rats.

SUMMARY

The depletion of adrenal ascorbic acid following unilateral *adrenalectomy* in rats can be inhibited by *prior administration* of cortisone intraperitoneally.

Over the dose range tested there was no evidence *against a linear relationship between degree of inhibition* and dose.

A.C.T.H. still causes depletion of adrenal ascorbic acid in rats pretreated with cortisone.

We are indebted to Prof. E. C. Dodds and Prof. A. Kekwick for their advice, and for affording facilities; Mrs. S. A. Simpson for invaluable help at all stages of the work; Dr. B. Clayton and Dr. I. C. Gilliland for helpful suggestions; Dr. P. Armitage for statistical aid; and Miss H. Grundy and Mr. S. Graves for technical assistance. Cortisone acetate (Merck) and A.C.T.H. (Armour) were generously provided through the Medical Research Council.

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New Inventions

IMPROVED ILIAC-CREST SUPPORTS

THE use of iliac-crest (pelvic) supports has been largely neglected by surgeons who use the Trendelenburg position. In place of iliac-crest supports they use shoulder-rests and flexion of the legs over the end of the operating-table. These are both bad—brachial palsy is likely from one[1] and calf and popliteal thrombosis from the other—and it is difficult to adjust the table "break" to coincide with the knee-joints.

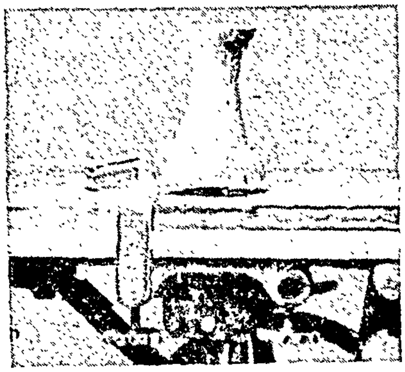

Fig. 1.

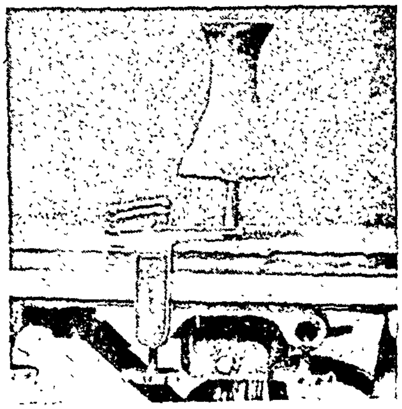

Fig. 2.

Ogier Ward[2] describes the use of his supports, but points out that it requires a little experience by a theatre technician to adjust them properly. In addition, they are of fixed height and may obstruct the surgeon. The rubber faces also tend to twist off and upset the mechanics of the supports.

The new supports described here are more efficient and easier to use because (1) the shape will fit any normal iliac crest; (2) the support rotates freely round a vertical axis and always presents a correct bearing surface for the iliac crest; and (3) the support can be raised or lowered to fit any iliac crest and keep out of the way of the surgeon (figs. 1 and 2).

These supports can be fitted to the standard Ogier Ward supports. In use they are largely self-adjusting, and their application is straightforward. They are initially applied to the waist of the patient and, as tilting takes place, the iliac crests move downwards into contact with them (fig. 3).

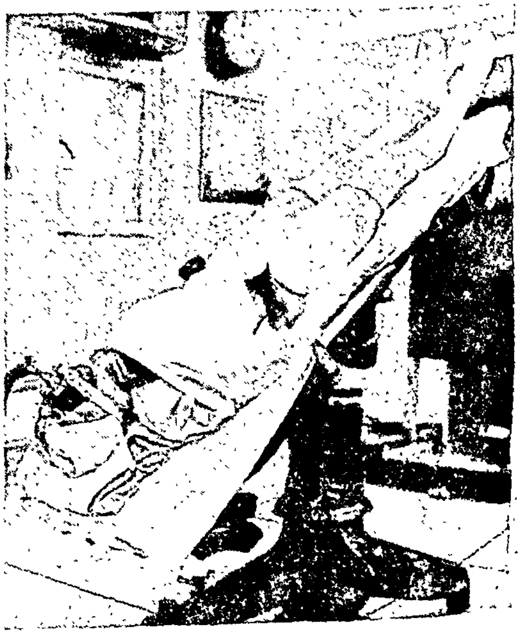

Fig. 3.

I wish to thank Dr. A. Danin for the photographs.

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[1] Ewing, M. R. *Lancet*, 1950, i, 99. Wood-Smith, F. G. *Brit. med. J.* 1952, i, 1115.
[2] Ogier Ward, R. *Lancet*, 1950, i, 423.

Reviews of Books

Medical History of the Second World War

Editor-in-Chief: Sir ARTHUR MACNALTY, F.R.C.P. Vol. I. *Medicine and Pathology.* Editor: V. ZACHARY COPE, M.D., F.R.C.S. London: H.M. Stationery Office. 1952. Pp. 565. 50*s.*

THIS is the first of eighteen volumes designed to record the history of military and civil medicine in the late war. (The whole will be but part of the Official History of the War, which judging by that of the war of 1914–18, is not likely to be finished for some time.) It is made up of signed contributions by many distinguished authors whose ability to make bare facts and sombre figures readable is apparent and welcome. Any doctor, however specialised his interests, can read most of this book with interest and benefit. That there is so little overlapping by the contributors is no doubt due to editorial skill; but the prospectus of the volumes now in preparation suggests that it will be hard to avoid this difficulty throughout.

The book begins with general reviews of the medical problems of the three Services and of the civil population in war. Each approaches the subject in an individual way, and each is admirable—an adjective which may also be applied to Desmond Curran's review of naval psychiatry. Some of the more specialised contributions reach a rare level: for example, L. W. Harrison on venereal disease, Macdonald Critchley on exposure after shipwreck, and A. A. Miles and R. E. O. Williams on airborne infections produce reviews of the first order, appraising the work of others from their extensive personal experience. At the same time, some balanced and informative chapters —e.g., on undulant fever, the serological typing of streptococci, and advances in hæmatology—seem out of place in this collection; for, though knowledge of these increased during the war, it did not increase as a result of the war. For an account of blood-transfusion we shall presumably have to wait for a later volume. A few authors give brief and tantalising notes on the medical experience of the enemy: these are of major interest and, because the information is hard to come by, might be extended in future volumes, or even be the subject of an additional volume.

It is a commonplace to say that in spite of the horrors of war we must be thankful for the benefits to medicine and science which derive from it. In this volume these seem less noteworthy than the mental attitude of almost every contributor. We entered war not only ignorant but recognising our ignorance and minded to learn; and every chapter records trial and error, patient observation, and determination to know the answer. A generation of doctors prepared to doubt and eager to seek is a great gain; and those who fear that the inquiring or statistical mind is linked with a heartless inhumanity will take pleasure in the kindly and personal sympathy with their patients which few of these Service doctors have been able to conceal.

Compared with the medical history of the previous great war, this book is better printed, better edited, less detailed, and less expansive; a better work for immediate reference, though possibly duller reading for the orderly officer on duty. The references are numerous, well chosen, and almost always accurately quoted.

Roentgen Manifestations of Pancreatic Disease

MAXWELL H. POPPEL, M.D., F.A.C.R., associate professor of clinical radiology, New York University. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 366. 77*s.* 6*d.*

THE pancreas is a so-called silent area for the radiologist, because its density is equal to that of surrounding tissues and there is no contrast medium which is selectively secreted or concentrated by it. It is therefore all the more surprising to read a book of some 400 pages on the X-ray manifestations of pancreatic disease and to find that most of it is excellent and little redundant.

The stimulus to X-ray investigation has, of course, been provoked by advances in surgical technique which permit removal of large areas of the pancreas with a small mortality-rate, and survival without chronic invalidism. Pancreatic calculi are easy to diagnose by radiography and pancreatic cysts are readily localised by their characteristic impression on adjacent viscera; but much new information has been obtained by study of the radiological relation of the pancreas to the duodenum and bile-ducts and by correlating apparently trivial deformities with disturbances of function known or suspected to be associated with pancreatic disease. Deformities of the duodenal loop due to carcinoma of the head of the pancreas should be as well known to the radiologist as the niche of a gastric ulcer; and good lateral views enable him to diagnose large tumours of the body of the pancreas and differentiate them from other retroperitoneal masses. Disturbed motility of the small intestine, and stasis in the bile-ducts, are pointers to pancreatic disease, and should soon become as significant as pylorospasm with peptic ulceration. More spectacular is the association between pancreatic fibrosis and chronic pulmonary fibrosis, an observation first made radiologically by Neuhauser. The possibility of a relation between psoriasis and pancreatic dysfunction is, although speculative, a remarkable example of potential advances. Doubtless the more general use of aortography with direct visualisation of the pancreatic arteries will solve many obscure problems.

The author presents all these facets in a most detailed and yet modest way. This is a very intelligent book, admirably combining radiology with anatomy, physiology, and pathology. Its illustrations are excellent.

New Outlook on Mental Diseases

F. A. PICKWORTH, M.B., B.SC., consultant pathologist, Group 6 Hospitals, Birmingham. Bristol: John Wright & Sons. 1951. Pp. 304. 60*s.*

THE learning, integrity, and sustained effort that have gone into this book enforce much respect: Dr. Pickworth has devoted his life to the studies and views here so elaborately presented. He has had the courage to leave the highroad of contemporary thought about the pathology of mental disease and pursue his original and unaccepted ideas devotedly. Only a reviewer converted to his beliefs could say that the outcome justified Dr. Pickworth's constancy. His thesis is that chronic infections produce a pathological condition in the cerebral blood-vessels leading to interference with the labile patterns of blood-flow in the brain upon which normal behaviour depends: and so mental disorder occurs. This he illustrates with much ingenuity, even going so far as to account for thought, judgment, and other mental functions in terms of cerebral vascular architecture and direction of blood-flow. It is easier to discern in Dr. Pickworth's book a dominant theme than a counterpoint of self-criticism interwoven with the argument: this deficiency gives the work a strong flavour of *idée fixe*, reinforced by the loose and at times rather inconsequent exposition. The strictly histological section of the book is exempt from any such objection; it bespeaks Dr. Pickworth's notable contribution to the morphological study of the capillaries and smaller blood-vessels of the brain.

An Introduction to Abdominal Diagnosis

A Handbook for Students and Practitioners. ALAN E. LEE, M.D. Melb., F.R.C.S., F.R.A.C.S., senior visiting surgeon, Brisbane Hospital, Brisbane. Sydney: Australasian Medical Publishing Co. 1951. Pp. 176. 32*s.* 6*d.*

THE author of this book laments " the lack of any real interest in the mechanism of symptom production " and has attempted to study the nature of abdominal symptoms and to enunciate an acceptable theory by which they may be related to their various causes. This laudable ambition he has gone a good way to fulfil. His criticisms are, however, more applicable to chronic than to acute abdominal disorders.

The difficulty lies in choosing between several possible explanations of symptoms. Mr. Lee draws upon many sources and gives a fair account of the various theories of abdominal pain. Upon his personal and definite opinions, however, he bases an explanation of certain visceroptotic syndromes which may not find general acceptance. Theories are useful stimulants but not always faithful guides. Nevertheless we agree with him that clinical science should be cultivated.

The value of ancillary aids, such as radiography, is perhaps not sufficiently emphasised in this book; so long as a proper perspective be observed, such aids should be used whenever possible.

The Great Medical Bibliographers

JOHN F. FULTON, professor of the history of medicine, Yale Medical School. Philadelphia: Pennsylvania University Press. London: Oxford University Press. 1951. Pp. 107. 32*s*.

Dr. Fulton here publishes three lectures which he admits "did not afford adequate opportunity to deal with the contributions of the great medical bibliographers in any detail." Though one may regret that they were not expanded before publication, the three short chapters are packed with useful information and make an excellent starting-point for more detailed study.

The story begins with Johann Tritheim, a Benedictine bishop who had become an abbot in 1483 at the age of 21. The three most remarkable bibliographers were Conrad Gesner (1516–65), Albrecht von Haller (1708–77) and John Shaw Billings (1838–1913), and they were all remarkable men. Gesner's publications on bibliography were a mere tool to his larger aspirations, which included a comprehensive Greek lexicon, a huge volume on botany, and translations of surgical and medical texts. Haller was an infant prodigy who made good. At the age of 8 he had written 2000 brief biographies of historic persons and at 10 he had compiled a Greek lexicon with supplements in Hebrew and Chaldee. A practising physician, he found time to write long and detailed bibliographies in his own hand. He also wrote widely on many aspects of medicine, surgery, anatomy, and physiology. When he broke his right wrist he learned within 24 hours to write with his left hand. There was no limit to his accomplishment. Billings, the greatest of them all, conceived the vast Army Medical Library in Washington, and its unrivalled Index Catalogue, while he was still a student.

The text is adorned with a few portraits and reproductions of the title-pages of the most important works mentioned.

Roentgen Diagnostics

5th ed. H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, E. UEHLINGER. Translated by JAMES T. CASE, M.D., D.M.R.E. London: Heinemann Medical Books. 1951. Pp. 868. £12 12*s*.

BEFORE the war this German textbook of radiology, edited by Schinz, Baensch, and Friedl, was a standard European work frequently consulted by the English-speaking world. Though it was printed and published in Germany, its principal authors and editors were Swiss. It increased in size and scope as radiology progressed, and by 1939 had reached a fourth edition. During the war the standing type was destroyed by bombing, some of the contributors died, and the editors were faced with the enormous task of collecting new writers and new material. The result is an outstanding work, largely compiled by Swiss and Swedish radiologists, who—since both countries were neutral during the war—have had the leisure and incentive denied to the combatants. It is no longer a textbook but rather an encyclopædia of radiology.

This is the first of five volumes of the English version of the *Lehrbuch der Röntgendiagnostik*.[1] About a third of it deals with general principles of radiation physics and radiological interpretation, and the rest describes fractures and inflammatory and congenital diseases of bone. The illustrations are both fine and abundant, and the bibliography is vast. The four volumes yet to appear are on the same scale. The detailed text correlates radiological appearances with pathology superbly. Although Schinz stresses the clinical side of the picture, this is not quite so well done, nor is differential diagnosis given adequate consideration in some sections. Some rather unwary statements creep in, such as "the prognosis is bad in Paget's disease" or "sarcoidosis may first manifest itself as a renal calculus"; but these are vagaries of the individual author. The vast amount of scientific material, so well compiled and documented, makes this a reference work without equal in any language.

The English translation, by Dr. James T. Case, whose personal contributions to radiology in America have earned him international recognition, is completely literal, with many rather long and involved Germanic sentences. It would be possible to shorten the text greatly without loss of detail and accuracy; but he is to be congratulated none the less on the care with which he has undertaken so exacting a task.

The Extra Pharmacopœia (Martindale).—Volume I of the 23rd edition of this book, which was the subject of an annotation last week, is published by the Pharmaceutical Press, 17, Bloomsbury Square, London, W.C.1. There are 1352 pages and the price is 55*s*.

Tropical Medicine (6th ed. London: J. & A. Churchill. 1952. Pp. 560. 40*s*.).—The last edition of this work came out in war-time, and suffered the inconveniences attendant on that state of affairs. Now Sir Leonard Rogers, F.R.S., and Sir John Megaw, calling Sir George McRobert to their round table, have been able to include both the war-time discoveries and others made since, and so to present a thoroughly up-to-date account of their subject. Having in mind the needs of medical students, and of those many doctors who must treat tropical diseases without the help of modern laboratories, they have described carefully the methods of diagnosis which, as they say, can be practised "with the help of a microscope and a few simple appliances." With the same practical intention they give plenty of space to the common tropical diseases.

Textbook of General Surgery (6th ed. New York: Appleton-Century-Crofts Inc. 1952. Pp. 1154. £6.).—This well-esteemed textbook by Prof. Warren H. Cole and Prof. Robert Elman has been submitted to excisions, resections, anastomoses, grafts, and various plastic operations which have removed any traces of advancing age. It now carries new sections on chemotherapy and vascular surgery; and the sections on massive upper gastro-intestinal hæmorrhage, on preoperative and postoperative care, and on burns, have been rewritten. No attempt is made to give details of operations, though they are described in principle; non-operative techniques are fully explained. The teaching in this book has always been founded on physiology and surgical pathology, to the great profit, no doubt, of students who can afford to use it.

Problems of Ageing (Cowdry) (3rd ed. Baltimore: Williams & Wilkins Company. London: Baillière, Tindall, & Cox. 1952. Pp. 1061. 114*s*.).—This revision of Cowdry's text by Mr. A. I. Lansing, PH.D., comes at an opportune time, when the basic biological and pathological problems of old age are attracting much attention from biologists and clinicians. The editor's task has been thoroughly done. Most of the previous studies have been retained and expanded, and he contributes a new opening chapter on the general physiology of the ageing process, including a survey of his own work on the cumulative age-factor in rotifers. The chapter on qualitative histological and histochemical change has been brought up to date, though the sparsity of new observations is a measure of the amount still to be done. The important new observations in the chemical pathology of arteriosclerosis made by Gofman's team, using the ultracentrifuge, and by Siperstein studying the synthesis of cholesterol in the arterial wall, as well as the pathology of arteriosclerotic processes are reviewed. There is some overlapping here between the contributors, but no real redundancy. Other chapters deal with the production of experimental hypertension, the pathology of ageing in special systems and sense organs, and the physiology of homœostasis, with a certain amount on the surgery, demography, and applied social psychology of the age process. The most serious omission is the lack of a special section on the pathology of joint diseases (the word "arthritis" does not appear in the index) whose clinical importance in geriatrics is at least equal to that of the arterosclerotic group of diseases, less dramatic though their effects may be.

Dr. Lansing, who has himself contributed a great deal to the store of suggestive observation on this problem within a very short time, speaks in his preface of the depressing lack of new work on gerontobiology, and rightly congratulates the sociologists and psychologists on their more militant approach (though his sociological contributors might perhaps have shown more awareness of work done outside the United States). Silences in research often precede a storm of fruitful activity, and we may hope that this is the case with the biology of ageing.

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[1] Reviewed in *The Lancet*, 1951, i, 154.

THE LANCET

LONDON: SATURDAY, OCT. 4, 1952

Cancer of the Lung

THE vital statistics of the world show few trends iore dramatic than the rise during the last thirty ears in the notified death-rate from cancer of the ing; and there is little doubt that the increase is oth real and numerically important. Of the several recipitating causes suggested—exposure to tar, xhaust fumes from motors, industrial haze, and moking—the last strikes closest to the heart. We an accept quite philosophically risks from tarring f the roads and industrial pollution of the atmosphere hich are universal and at present unavoidable; and ew of us are asked to inhale carcinogenic hydro-arbons at work; but our control of our personal moking habits may decide our own fate. This sense f personal decision gives a piquancy to the various eports on the relation between smoking and cancer f the lung, of which the latest is the article on p. 651 y Dr. McConnell, Dr. Gordon, and Dr. Thelwall Jones.

Their investigation follows the same pattern as earlier studies by Muller,[1] Wynder and Graham,[2] and Doll and Bradford Hill [3] in which the smoking histories of patients known to be suffering from cancer of the lung are compared with histories given by control subjects, usually patients with some other disease. The Liverpool workers have also made collateral comparisons between the two groups with respect to other aspects of the life-history which might be relevant—namely, place of residence (past and present) and nature of occupation. In neither of these particulars did the lung-cancer patients differ from their controls. But before the possibility of occupational hazard is dismissed, it should be noted that this method of approach does not permit of any calculation of the number of people "exposed to risk" in particular occupations, and that only broad occupational groupings can be employed. As a result the presence of excessive death-rates from cancer of the lung among small occupational groups may be obscured. On the other hand, the information on smoking habits has been carefully collected from patients whose diagnosis is not in doubt, and, though the number of such patients is relatively small and the control subjects were interviewed two years later, the results bear comparison with previous work. Even with as many as 100 patients, chance variations in the proportion of non-smokers may be considerable, so that one looks for similar trends rather than complete agreement between the data reported from Liverpool and, say, the results of Doll and Hill. This is particularly apposite when one is tempted to seize hopefully on the suggestion that perhaps only the smoking of more than 20 cigarettes a day is really dangerous, because there is no technically significant difference between the proportions of non-smokers in the cancer and control groups. As the authors imply, this technically insignificant difference may well result simply from the smallness of the series observed. From Doll and Hill's data on 709 cancer patients and the same number of controls, there emerges a consistent upward trend in the apparent risk of developing cancer of the lung as the number of cigarettes smoked increases from 1 a day onwards, and until more data accumulate it would be safer to accept their gloomier view.

In each of the four studies mentioned, the approach has been the traditional clinical one of comparing the frequency of some personal habit among a group of patients suffering from a certain disease with "normal" expectation; and nowadays it has become customary to base that "normal" expectation on the results of identical inquiries from carefully paired control groups not suffering from the disease. To this approach there are, unfortunately, possible methodological objections. Patients with symptoms referable to the respiratory system may be more likely to exaggerate their smoking history. Again, in the study of coronary thrombosis, for example, the finding that patients with that disease more frequently gave a history of heavy smoking than did healthy men of the same age does not necessarily mean that smoking is a cause of coronary disease. Indeed, a critic with psychosomatic leanings might suggest that the cardiac lesion and the smoking excess were both expressions of some more deep-seated psychological disharmony: in other words, their observed association in the same patient was coincidental rather than causal. Strictly speaking, the proof that smoking causes cancer of the lung in men could come only from a deliberate experiment in which young subjects were allocated at random to groups given cigarette rations ranging from 0 to 50 per day and followed up until death. Such experiments, however, are possible only on animals, and only a modified form of a "forward" investigation is practicable. Whether one smokes or not is largely a matter of personal choice, and that choice may be bound up with other factors—social, occupational, and economic—which may be related to one's predisposition to cancer of the lung. Self-selection thus may introduce a bias in the "forward" just as in the "backward" clinical type of survey. Some at least of the possible sources of bias may be taken into account by restricting comparisons between different types of smoker and non-smokers to members of the same social and occupational group; and in one of two current "forward" studies that is being done. Readers will know of Professor Bradford Hill's appeal to the profession to record our smoking histories so that they may be filed for future reference. The implications may not have been immediately obvious, but the scheme has a stark simplicity. We classify ourselves on the basis of our present and previous smoking habits *now*—i.e., when we are likely to be unbiased by respiratory symptoms. *Later*, one of our colleagues will certify the cause of our death and we

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1. Muller, F. H. *Z. Krebsforsch.* 1939, 49, 57.
2. Wynder, E. L., Graham, E. A. *J. Amer. med. Ass.* 1950, 143, 329.
3. Doll, R., Hill, A. B. *Brit. med. J.* 1950, ii, 739.

can then be added to the numerator of the death-rate whose denominator is the number of doctors of our age who share our smoking habits. In the fullness of time, a comparison between the lung-cancer death-rates in the various grades of smokers should give vital *evidence on the validity* of the present results of "historical" clinical studies.

A similar investigation is being made by the research staff of the American Cancer Society.[4] In view of the complications inevitable in trying to collect death certificates and other data from doctors in every State in the Union, the epidemiology panel of the society decided to exploit the enthusiasm for scientific and medical research which is the American's birthright. About 100,000 lay volunteers have been enlisted, and have been asked to complete a detailed questionary for not more than 10 of their friends over the age of fifty. Both present and past smoking habits are to be carefully recorded—the plutocrat who thinks in terms of x cigars per day, for example, is asked when he started, and how much and for how long he smoked the various forms of tobacco. At annual intervals thereafter, the lay worker is asked to report on the health of his "subjects," whether smokers or non-smokers. All eventualities have been foreseen. If (to use the phrase which is almost English in its under-statement) the research-worker is "not readily available," a substitute is nominated to carry on the yearly observation and report. It appears that non-smokers are commoner in the U.S.A. (roughly 10% of middle-aged men compared with our 5%). About half a million men are being observed, and it is estimated that, at current U.S. death-rates from cancer of the lung, four years must elapse before a comparison of the mortality experience of non-smokers and smokers of every degree will give a decisive answer to the question—is smoking conducive to cancer of the lung?

Both these "forward" studies have a wider interest from the methodological point of view, applying as they do essentially simple methods on a wide scale to the study of chronic disease. Their results will thus be awaited with quickened interest. Meanwhile, we can note some fresh evidence on the effect of atmosphere pollution on mortality from cancer of the lung. Some years ago Dr. PERCY STOCKS pointed out a broad association of rising cancer mortality with increased urbanisation,[5] and now, in an address to the National Smoke Abatement Society's annual conference, he has reported that the risk of dying from cancer of the lung in any area is closely related to the number of domestic chimneys (which are responsible for the large winter excess of arsenic and benzpyrene in the air), their concentration in the area, and the prevailing wind conditions. Large conurbations of more than 200,000 dwellings, like London, Manchester, and Merseyside, have lung-cancer death-ratios around 160, while Birmingham and Leeds ratios are 134 and 132 respectively, and Newcastle with its 87,000 houses has a ratio of 114. The effect of the prevailing wind has been highlighted by his showing that the black areas of high lung-cancer mortality in Finsbury, Shoreditch, Bethnal Green, Stepney, and Bermondsey coincide with the displacement by the wind of smoke from the congested heart of London. As STOCKS remarks, cancer may be defeated by the elimination of its precipitating factors rather than by any radical advance in treatment, and these studies should result in that precise identification which is the first step to removal.

Humidity and Infection

IN everyday life we are continually being reminded of the ways in which climate or weather may influence health and disease. The well-known difference between a "bracing" and a "relaxing" climate, the popular conviction that rheumatism is due to damp, and the evil consequences of sudden changes of *temperature—these examples are familiar.* Yet as a subject for serious investigation the effect of meteorological factors on body and mind is still generally neglected. Even the relation of weather to epidemics is not as well understood as one might suppose.

When he was studying smallpox in India, Sir LEONARD ROGERS [1, 2] showed that outbreaks which spread during dry weather came to a sudden end with the onset of the rains, and he established a correlation between low absolute humidity of the air and the incidence of the disease. In a paper which we publish this week Dr. B. B. WADDY reaches a similar conclusion about the behaviour of cerebrospinal fever in Africa. From their observations on previous epidemics he and others have suggested that this disease waxes when humidity is low and wanes when humidity rises; and the big epidemic on the Gold Coast in 1947–48 provided further evidence to the same effect. A fall in the average absolute humidity between November, 1947, and January, 1948, was associated with a steady increase in cases from 2 to 5 per week in November to the peak figure of 1711 in mid-March. On the other hand, a steady rise in absolute humidity, which started about mid-March and continued through April, was followed by a rapid decline in the number of cases during April and May. In fact the number of cases in any given week varied inversely with the absolute-humidity figures for the previous four weeks. From these facts about cerebrospinal fever, WADDY goes on to discuss two other respiratory infections in which there seems to be a similar relation to low absolute humidity—namely, lobar pneumonia [1, 2] and influenza.[3]

Recently SNOW [4] has investigated the connection between humidity and the incidence of poliomyelitis in Australia. The data here are somewhat confused: in some epidemics poliomyelitis behaved in the same way as the infections already mentioned, but in others the situation was reversed, the number of cases increasing as humidity rose. SNOW makes some interesting suggestions as to the ways in which humidity might influence the course of epidemics, and raises again the question of a direct effect on pathogenic micro-organisms. It may be recalled that EDWARD et al.[5] found that influenza virus suspended in the air survived much longer in a dry atmosphere

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4. Horn, D. *Cancer News.* February, 1952, p. 13.
5. Stocks, P. *Regional and Local Differences in Cancer Death Rates.* H.M. Stationery Office, 1947.

1. Rogers, L. *J. State Med.* 1925, **33**, 501.
2. Rogers, L. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1926, no. 106.
3. Ministry of Health. Report on the Pandemic of Influenza. H.M. Stationery Office, 1920; p. 160.
4. Snow, D. J. R. *Med. J. Aust.* 1952, ii, 17.
5. Edward, D. G. ff., Elford, W. J., Laidlaw, P. P. *J. Hyg., Camb.* 1943, **43**, 1.

than in a humid one; and Loosli et al.[6] reported similar results. Likewise Williamson and Gotaas[7] and De Ome[8] found that several species of pathogenic bacteria lived longer in low humidities than in high ones. On the other hand some workers have found exactly the opposite. Dunklin and Puck[9] reported that a saline suspension of pneumococci, dispersed in air, survived well enough at low and high relative humidities, but at about 50% relative humidity the organisms died rapidly. Payne,[10] studying the survival of intestinal organisms on the hand, found that the time during which living *Bacterium coli* could be recovered from the skin depended on the relative humidity of the air: the organisms seemed to be killed most rapidly at humidities of 40–50%, but they surived much longer at higher and perhaps at lower humidities. There need be no surprise, however, at this conflict of evidence. It is clear that the survival of micro-organisms in an artificial suspension in air depends on a delicate balance between physical conditions—between, for example, humidity, temperature, state of dispersion, and the nature of the suspending fluid. At two extremes of temperature we know how critical such conditions can be. For the destruction of bacteria, saturated steam is far more efficient than hot air; while at low temperatures modern methods of freeze-drying have shown that bacteria can survive for years provided the freezing and drying are done in just the right way. The influence of humidity on the survival of pathogenic micro-organisms in natural conditions must be an even more complicated affair; for here we have to reckon with the influence of humidity not only on the organisms themselves but on the host and on the host's defences against infection.

A digression into physics and physiology is necessary at this point to make the distinction between absolute and relative humidity on which Waddy's argument largely hangs. Absolute humidity is measured by the actual *amount* of water vapour in the atmosphere: relative humidity expresses the amount of water vapour present under any given conditions as a percentage of the amount necessary to saturate the atmosphere under those conditions. The absolute amount of water vapour in the air on a hot dry summer day may actually be much greater than the amount on a cold wet winter day. For example, at 71°F. with a relative humidity of only 60%, the absolute humidity is about 11 g. per c.m.: but at 34°F even 100% saturated air contains only about 5 g. of water per c.m. Thus the low absolute humidity said to favour cerebrospinal fever might equally well be associated with hot dry weather in Africa and with cold wet weather in Britain. In endeavouring to explain the effect of this low absolute humidity, Waddy points out that when air enters the lungs it has reached or nearly reached body-temperature and is very nearly saturated with water vapour: the absolute humidity of saturated air at that temperature is 43 g. per c.m. This means that, except in very hot and damp weather, air in its passage from nose or mouth to lungs must abstract considerable quantities of water from the surfaces of the respiratory tract; and the drying of the mucosa may be much greater in winter than in summer. The complementary process is the familiar one by which expired air condenses rapidly on a cold day. It is evident that every breath may involve the transference of large quantities of water from one phase to another, and, as Snow remarks, this may considerably influence the activities of the respiratory mucosa. The effect may perhaps be beneficial, by stimulating a flow of fresh mucus, or it may be harmful, by causing either excessive secretion or excessive dehydration.

There are of course other ways in which changes in humidity could promote or inhibit the spread of infection. Many micro-organisms survive for long periods in dust, and dry conditions may well favour their spread by this means. Humidity could also act more indirectly—e.g., by an effect on sanitation or on the breeding of flies, mosquitoes, and other insects, or by causing people to congregate indoors. It is interesting, however, to note that, apart from poliomyelitis, the infections in which there seems to be the closest association with changes in humidity belong to what is usually regarded as the airborne type of infection—smallpox, lobar pneumonia, cerebrospinal fever, and influenza. Though the relation between humidity and infection is evidently complex, it is also important; and its very complexity should offer a challenge to epidemiologists, meteorologists, and statisticians. A great many relevant facts are doubtless available to anyone who is prepared to look for them in the right places, as Dr. Waddy has done.

A Pause for Thought

Not so long ago brooms were made with little exertion by gipsies and other dilettanti characters, and sold to the housewife at the back door. Since the invention of different and more scientific tools for cleaning houses, however, this primitive transaction has been overlaid; and nowadays no sooner has an inventor enunciated a principle than designers apply it, improvers improve it, and machine-makers make—first the tools to make the machines to make the invention, then the machines, and finally the parts of the invention itself. These are assembled by assemblers, loaded into trains and lorries by porters, sold by salesmen, and delivered by vanmen and their satellite boys. In fact, agreeable as labour-saving devices often are they seem to make a lot of work. Something of the same sort is happening in medicine. A new advance, though it may save lives and shorten illness, often entails such making of equipment, extension of buildings, enlarging of staff, training of teams, and general reorganisation as must cause the single-handed Victorian doctor to turn eagerly in his grave. Yet, it seems, not one of these things is done "properly"—that is, as precisely and exquisitely as its proponents advocate. Every branch of medicine could absorb more men and money, till imagination pictures the entire nation dedicated to the study of a single patient.

Social medicine faces some special problems, for our proper and reasonable concern for the welfare of the disabled, the deficient, and the old is being expressed in a great expansion of services. Mr. John

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[6] Loosli, C. G., Lemon, H. M., Robertson, O. H., Appal. E. *Proc. Soc. exp. Biol., N.Y.* 1943, 53, 205.

[7] Williamson, A. E., Gotaas, H. B. *Industr. Med.* 1942, 3, 40.

[8] De Ome, K. B. *Amer. J. Hyg.* 1944, 40, 239.

[9] Dunklin, E. W., Puck, T. T. *J. exp. Med.* 1948, 87, 87.

[10] Payne, A. M. M. *Mon. Bull. Minist. Hlth Lab. Serv.* 1949, 8, 263.

A. OLIVER, PH.D., speaking at Belfast on Sept. 8 at the conference of the British Association for the Advancement of Science, protested that we have *launched our vast social provision* (he was referring particularly to our provision for the elderly) in a philosophic vacuum. We hardly know what we are doing or why we are doing it, much less where it is leading us.

The fact that we have an ageing population is now well known. A sample taken from the 1951 Census returns from Great Britain indicates that already nearly 1 in 7 of the population are of pensionable age. The killing diseases of infancy, youth, and middle age have been so far mastered that more people now survive into old age. But they survive in a world where houses are scarce and domestic servants rare; few of them, moreover, have more than two or three grown-up sons and daughters to rely on in need, and many of them have none. Their grandchildren, too, have acquired a scarcity value, and get more room in the house, and more of their parents' attention, than children got in the past. The mother of a young family, determined to give her children the best chance she can, and also doing—perhaps in crowded quarters—all the family housework, cooking, washing, and mending, may not have much time, either figuratively or in fact, for an elderly relative. These things, Dr. OLIVER thinks, are combining to weaken the sense of family responsibility for old people; and the law is encouraging this decline: for though each of us is legally responsible for maintaining himself, though a husband and wife are responsible for maintaining one another, and parents are responsible for maintaining their children, there is now no legal obligation on any of us to look after our elderly relatives. The wide range of family responsibilities laid on us by the old poor-law have melted from the statute-book. To this new freedom Dr. OLIVER finds people react, broadly speaking, in one of two ways. Either they rejoice in the opportunity to push their elderly relatives into the care of the public authorities, or else they murmur reflectively that there is something wrong with the law, and that families ought to be made to look after their old people.

At all events, either as a cause or a result, the rise in public responsibility has been associated with a decline in private responsibility. The discovery of many old people, sick or dying in conditions of extreme neglect, has shown us the need for more hospital beds for the elderly, more long-stay annexes, and more residential homes. But, as Dr. OLIVER pertinently asks, how many more? Dr. J. H. SHELDON[1] in his study of old people in Wolverhampton, in 1947, found that 98% of them were living at home, either alone or with relatives: only 2% were in hostels or public institutions. Moreover, more than half the widowers or widows living alone had children living close at hand. This does not suggest any serious decline in family feeling. On the other hand, 7·7% of old people were causing "great strain" on the younger generation, the words being used to imply "a mode of existence which deprived the individual of a normal life and turned her into a drudge." It is often argued that these 7·7% should be having care elsewhere than at home; and, if the 2% already receiving institutional care are added this means that such care would have to be available for some 10% of the elderly population. That would mean, according to Dr. OLIVER'S estimate, some 20,000 homes or hostels in Great Britain, with 20,000 matrons, 20,000 cooks, and so on—in all some 100,000 people employed to look after 10% of the elderly. Such a state of affairs is certainly conceivable, he said, but is it economically possible, or socially desirable? That members of the younger generation under strain ought to be relieved goes without saying; but can we not relieve them in ways which are less disruptive of the lives of old people, less damaging to the sense of family responsibility, and less extravagant in the use of woman-power and money? Dr. OLIVER believes that we can—by providing home helps, sitters-in, sitters-up, laundering, chiropody, holiday schemes, and other medical and social aids "to ensure that the well-meaning daughter does not waste the best years of her life at the beck and call of some self-centred old tyrant"; and by providing more houses, perhaps with a suitable room or self-contained annexe, so that parents with young children can look after their old people and still keep something of the freedom they need to rear their families. Moreover we should help old people to go on working as long as they want to, and are able; for they have special attributes which younger people lack, and interest in work helps them to keep well and survive. The place for the old person, he said, like the place of anybody else, is in his own home; and we should help him to stay there as long as possible. It is certainly the place where most old people want to be.

It can be argued, of course, that by the time these extra services are provided the monetary saving would not be great; and that more women are needed to look after single old people in their own homes than would be required to look after the same number grouped in hostels. But Dr. OLIVER was concerned only secondarily with the financial aspect. His chief point was that the progress made in social work and legislation in the last ten years had been "achieved without any real preparation in fundamental thinking." If it becomes the fashion to put old people into homes and hostels something harmful will have befallen us all. "In the last analysis the values are nearly always moral values, and moral values are what gives purpose to politics."

A New Blood-donor Service

THE Ministry of Health announces the formation of a panel of nearly 2000 blood donors whose red cells have been completely classified and who will be available to give blood for transfusions in which the subdivisions of the blood-groups must be taken into account. Several hundred distinct combinations of blood-groups are covered by the donors on the panel, which is the first of its kind in the world. The preliminary testing and selection of donors was made by the regional transfusion centres, and the Blood Group Reference Laboratory of the Medical Research Council then carried out the detailed testing and classification. When a patient requires blood precisely compatible with his own, it will now be possible to ask a regional transfusion centre to select a suitable donor from the panel, and the search, which is often urgent, will be much simplified.

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[1] The Social Medicine of Old Age. London: Published for the Nuffield Foundation by the Oxford University Press, 1948.

Annotations

THE MALNOURISHED MIND

STARVE a child of fats and sunlight and you create crippled dwarf. It seems feasible that a mind nourished n an unbalanced diet, and in a half light, may show omparable deformities. In his presidential address to he American Surgical Association this year, Dr. Daniel C. Elkin,[1] putting the case for the study of the humanities in the making of a doctor, asserted that we have emphasised the science courses for "premedical" tudents to the detriment of their education. He was peaking, of course, of America, but his arguments apply here aptly enough. He had been struck by the gnorance and the actual illiteracy of many doctors; and by the narrow and utilitarian outlook of students applying for places in medical schools. If these young people, most of whom have "taken science" in their last two years at school, are asked "why did you take these subjects," they often reply that they have been told by their advisers that this is the surest way to get into a medical school. He quoted Sir Richard Livingstone's opinion:

> "It is characteristic of today that, when we discuss which subjects should be studied, or which languages should be learnt, the first consideration is nearly always utility; we ask what is most useful for the machine, not what is most likely to make a good human being."

Some enlightened medical schools urge prospective students to acquire a liberal education, and declare that admissions committees will not be impressed by a history of two years of school science. But in actual fact, the candidate follows such advice at his peril[2]; for coming freshly to science in competition with those already grounded in it he is liable to flounder through his first year, fail in his 1st M.B., and so (in this country, at any rate) risk his place in the school, and with it his only chance of training as a doctor—a curious punishment for attempting to broaden his mind.

The question is not merely of literacy, or of acquiring the ability to carry on an educated conversation. It goes far deeper, Dr. Elkin believes; for beyond the content of the curriculum there are the values. The worth of a humane education—by which he clearly means education in history and letters rather than in dead languages—is to give the learner, he says, "a perception of the rôle of mankind as revealed in its history, its wisdom, its beauty; its ugliness, its growth, its regressions—in brief, its life." It is "a catalyst in the perception of the truth that 'shall make ye free.'" It would be wrong, of course, to suppose that this is the prerogative of the humanities alone. An understanding of the theory of evolution is also a catalyst in the perception of truth; and medical students are not the only young people nurtured on an unbalanced diet: the science-starved arts student can be as mentally rachitic as the scientific philistine. Dr. Elkin, however, was also concerned to remind us that the student who has learned science and nothing else is particularly vulnerable to the devices of unscrupulous seekers after power. The receptiveness of the mind depends much on the transformer, emotion; and while we have been ignoring this fundamental fact "the barbarians" have been learning to use it.

> ". . . the modern barbarians," he quotes Stanley Dorst as saying, "do not destroy science and technology, they do not wipe out the machine values, but convert them into terrible forces of evil and death so that those who would out-do their mad rush must out-do them in ruthlessness. What they do destroy with devastating thoroughness is liberal culture of the people. They destroy their roots in the past, their libraries, their free press, their religion, their belief in the essential dignity of man. In short —destroy the education which makes men free."

Facts, figures, techniques will change many times in a student's lifetime; values last; and the responsibility of teachers (in medicine, as in other subjects) is to teach the young to distinguish values—to demonstrate, as Dr. Elkin says, that there are other things than technique in surgery, science in medicine, and knowledge in life. "We have expected too much of science, and in so doing we have been trimming down those lamps of education which shed our best light."

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1. *Ann. Surg.* 1952, 136, 337.
2. *Lancet*, 1952, i, 602.

ABDOMINAL AORTOGRAPHY

THE progress in angiocardiography and cerebral angiography that has followed the introduction of new contrast media and apparatus has reawakened interest in translumbar aortography as a means of investigating abdominal disease. Its usefulness has already been established in certain renal conditions and in lesions of the abdominal aorta and its branches.

The pioneer work was done by Dos Santos as early as 1929.[1] The technique is relatively simple: with the patient prone, a 16 or 17 B.W.G. needle is inserted below the 12th rib, a hand's breadth to the left of the spine; it is then directed forwards, medially, and upwards, using the vertebral body as a guide, until it enters the aorta. In order to display the kidneys and the splenic and superior mesenteric vessels the needle must be at the level of D12: at the level of L2 only the inferior mesenteric artery and aortic bifurcation will be shown. 20 ml. of 70% diodone is injected rapidly either by hand or by some form of pressure apparatus. To get the best results from the examination, serial films should be taken during the next 10 seconds.[2] A more elaborate method described by Farinas[3] involves retrograde catheterisation via the femoral artery. The aorta and the renal and splenic vessels are seen most clearly in the first 2 seconds, while the density of the renal shadows increases for about 5 seconds. When a larger quantity of diodone (30 ml.) is used the portal vein may be seen in 7–10 seconds.[2] The abdominal aorta and the renal, splenic, and superior mesenteric vessels are clearly seen, and in most cases a well-defined outline of the cortex and medulla of the kidney is obtained. The spleen and wall of the gut also increase in density as the diodone accumulates in them.

Aortography can often decide, before operation, the nature of filling defects visible on intravenous or retrograde pyelograms. For instance, a cyst shows as a clear avascular area; and an abnormal circulation may be demonstrated when a neoplasm is present. Well-defined patterns are being recognised in polycystic disease and hydronephrosis.[4 5] Again, information may be gained about the origin and distribution of the renal arterial supply, and may help the surgeon in planning a local resection of a kidney. The size of the renal arteries and the depth and density of the cortex may give some assessment of renal function or indicate the degree of damage in a diseased kidney. In occlusive disease of the aorta and iliac arteries, the site and extent of the process can be determined and the anastomotic circulation outlined. Aortography has been little used in disease of the pelvic viscera, and it has so far been disappointing in demonstrating hyperplasia or tumour of the adrenal gland. However, Weyde[5] has noted changes of possible significance in two cases of early renal tuberculosis.

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1. Dos Santos, R., Lamas, A. C., Caldos, J. *Méd. contemp.* 1929, 47, 93.
2. Johnstone, A. S. *J. Fac. Radiol., Lond.* 1952, 3, 231.
3. Farinas, P. L. *Amer. J. Roentgenol.* 1941, 46, 641.
4. Weyde, R. *J. Oslo City Hosp.* 1952, 2, 3.
5. Weyde, R. *Brit. J. Radiol.* 1952, 25, 353.

The procedure seems to carry little risk; for there has been no fatality in the 3500 published cases, though thrombosis of the superior mesenteric artery has followed accidental direct injection. Local anæsthesia is usually adequate, but a small dose of thiopentone can be given to apprehensive patients. The injection of diodone is usually followed by a feeling of warmth. Accidental injection into the paravertebral tissues may cause intense local pain, but nothing worse, and the diodone is rapidly absorbed. The investigation should not be performed in patients with severe hepatic or cardiac disease or with nephritis. At present it seems likely that abdominal aortography will, because of its cost and complexity compared with other forms of investigation, be reserved for those cases of renal disease in which simpler investigations have failed to give a definite answer, but it may well prove of increasing value to the surgeon in his treatment of occlusive disease of the aortic and iliac arteries. Further research may extend its use to other viscera and show whether it can be applied to lesions of the portal system.

RUBBER HAZARDS FOR THE SKIN

DERMATITIS is well known as a hazard in the rubber industry; and in the U.S.A. it apparently involves some 3% of workers.[1] In addition, those who use rubber appliances of any sort are liable to be affected. Rubber is now used so extensively that dermatitis from this source may not be recognised unless the possibility is borne in mind. Thus, trouble may arise from such commonplace causes as rubber fittings on clothing, rubber gloves or sponges, or the more unusual eyelash curlers or "gay deceivers." Leider et al.[2] have analysed 125 cases of proven rubber sensitisation. Rubber sponges were the cause in 40, rubber gloves in 17, and rubber parts of garments in 25. Other causes mentioned by these and other workers include dress shields, condoms, rubber bands, kneeling-pads, finger-guards, bathing-caps, dental dams, goggles, bunion protectors, earphones, and stethoscope fittings. Eczematous sensitisation to adhesive dressings is sometimes due to rubber[3] and not to some component of the "spread."

Crude rubber is vulcanised with the aim of increasing its strength, elasticity, and resistance to temperature changes. With crude rubber sulphur is used; but purified rubber needs the addition of accelerators, which also reduce the amount of sulphur required. Modern accelerators are mostly organic compounds, such as hexamethylene-tetramine (a potent skin irritant), carbon disulphide, aliphatic amine addition products, substituted guanidines, and mercaptobenzothiazole. Many accelerators are rendered yet more effective by activators, such as metallic oxides and fatty acids. Finally there are anti-oxidants, age-resisters, or stabilisers, which retard the atmospheric oxidation that otherwise proceeds rapidly in raw or even vulcanised rubber.

Mallette and von Haam[4] have studied the skin-irritating and skin-sensitising properties of twelve compounds widely used in the industry. Skin tests showed that the compounds of all three groups—accelerators, activators, and anti-oxidants—were mild to severe irritants and that many, especially in the anti-oxidant group, were moderately sensitising. It is no easy matter to determine the exact cause of eruptions due to rubber, owing to its many varieties and the reticence of some manufacturers and firms using rubber materials. In a case of pruritus vulvæ from sensitisation to a condom Clarke[5] traced the cause to free alkali from potassium oleate used as a stabiliser. That sensitisation may arise from substances present in very small amounts is suggested by Bettley,[6] who has described the case of a patient who was sensitive to rubber containing benzthiazole. Solutions of this substance gave positive patch tests when diluted to 1 part in 10^{14}. This patient even reacted to indirect contacts—blankets on which rubber hot-water bottles had lain—and this was verified by patch tests with lint which had lain loose in a match-box with a piece of rubber for three days. According to Ellis and Siegel,[7] the accelerators in some rubbers are loosely incorporated and are "leeched" out by sweat, or if in excess they may "bloom" out spontaneously. Irritating or sensitising compounds may also be continually formed on the surface of certain "vapour-cured" rubbers. Blank and Miller[8] have found that the commonest cause of an allergic, eczematous, contact-type dermatitis of the feet is the anti-oxidant monobenzyl ether of hydroquinone, which is used in the rubber adhesive in the combined linings of shoes.

In addition to dermatitis, leucoderma may occur from exposure to rubber dust; here again the cause is the monobenzyl ether of hydroquinone, which presumably interferes with the oxidation of tyrosine to melanin. Zakon and Goldberg[9] noted 9 examples amongst 200 workers all similarly exposed, and concluded that other factors besides contact are needed to produce this disorder, one being an alkaline skin reaction and another the solution by sweat of anti-oxidant from rubber. Leucoderma may also arise among the users of rubber articles; Leider et al. have described leucoderma of the penis from the use of condoms, and leucoderma round the mouth from rubber sheeting used as a dental dam.

THE LOCK

AFTER 206 years as a centre for the treatment of venereal disease, the London Lock Hospital is to close on Oct. 31. Thus ends a famous descendant of the lazar-houses of the Middle Ages, which were diverted from the care of leprosy to that of syphilis when the latter disease swept Europe at the end of the 15th century.

William Bromfeild, surgeon to St. George's, founded the Lock in 1746 in Chapel Street, a stone's throw from his own hospital, because there was no other place for the treatment of venereal disease in the rapidly extending West End of London. For the first hundred years it was staffed largely by George's men. John Hunter walked its wards as a student, but he quarrelled so much with Bromfeild, Hawkins, and Gunning that he never got on the staff. Samuel Lane and Edward Cutler were both surgeons to the Lock, and each applied for appointment to the staff of St. George's. Lane was the proprietor of a successful private school of anatomy, the Grosvenor, where the George's students did their preliminary work, and it was thought he was sure of the post; but Cutler won. The disappointed Lane moved his school to Paddington and with his friend, William Coulson, there founded St. Mary's Hospital and its medical school. In the next hundred years three generations of Lanes served St. Mary's and the Lock—Samuel, James, and Ernest. Walter Coulson was also one of its surgeons, but there seems to have been some trouble there, for with his uncle William he founded a new hospital in Berners Street, which he called St. Peter's Hospital for Stone. Thus the Lock Hospital

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1. Schwartz, L., Tulipan, L., Peck, S. M. *Occupational Diseases of the Skin.* Philadelphia, 1947; p. 498.
2. Leider, M., Furman, D., Fisher, A. A. *Arch. Derm. Syph., Chicago,* 1952, 65, 587.
3. Schwartz, L., Peck, S. M. *Publ. Hlth Rep., Wash.* 1935, 50, 811.
4. Mallette, F. S., von Haam, E. *Arch. industr. Hyg.* 1952, 5, 311.
5. Clarke, G. H. V. *Brit. J. Derm.* 1948, 60, 57.
6. Bettley, F. R. *Proc. R. Soc. Med.* 1952, 45, 491.
7. Ellis, F. A., Siegel, J. M. *Arch. Derm. Syph., Chicago,* 1948, 58, 405.
8. Blank, I. H., Miller, O. G. *J. Amer. med. Ass.* 1952, 149, 1371.
9. Zakon, S. J., Goldberg, A. L. *Arch. Derm. Syph., Chicago,* 1951, 64, 441.

as responsible to some extent for the foundation of oth St. Peter's and St. Mary's.

Many distinguished men served the Lock, including eate (an early master of the College of Surgeons), Villiam Blair (the friend of Lettsom, whose portrait ppears in Medley's picture of the founders of the Iedical Society of London), Berkeley Hill, Alfred Cooper nd Jonathan Hutchinson the younger. Addison was ts most distinguished house-surgeon, and David Living-stone was probably its most famous postgraduate.

The records of the hospital from 1746 to 1952 are omplete, and they cover, as nothing else could, the istory of the treatment of venereal disease in England luring that time. On no account must they be lost, nd we hope they will be placed in the safe keeping of, say, one of the Royal Colleges, the Royal Society of Medicine, or the Medical Society of London.

VISCERAL ANALGESIA IN TABES

IT has been known for some time that tabes dorsalis may on rare occasions account for loss of painful visceral sensations and so mask abdominal catastrophes, though few examples have been published. Recently Grimble and Csonka[1] have described the case of a tabetic of 59 who seemingly died of heart-failure although at necropsy they found a large chronic gastric ulcer which had apparently perforated some three days previously. The abdomen had been distended and tympanitic during his last days, but he had no tenderness or pain and had been able to eat solid food an hour before he died. The pathological findings in the central nervous system were those of moderately severe tabes with posterior-column degeneration, conspicuous leptomeningeal thickening extending out to invest the posterior nerve-roots (which showed small areas of scarring), and moderate marginal demyelination of the entire cord. There were no local lesions in the brainstem.

In discussing their patient, Grimble and Csonka recall that Bockus[2] described three visceral pain mechanisms: (1) true visceral pain, which is produced for example by stretching the capsule of a solid organ, or by distension of a hollow viscus, and which is transmitted by afferent fibres along sympathetic pathways; (2) referred pain, the exact nature of which is still not understood; and (3) pain which Morley[3] has called the "peritoneo-cutaneous reflex," which has been transmitted from peritoneal nerve-endings via afferent somatic fibres, and which is felt in the corresponding segmental skin area over the abdomen, where it may be associated with muscular rigidity. They believe that in their patient not only were visceral pain impulses from the stomach via the splanchnic nerves interrupted, but other routes traversing somatic nerve-fibres were probably involved as well; for he had shown extensive hypalgesia over the whole trunk, and the peritonitis following perforation had been completely silent. They also infer that bladder afferents had also been interrupted because for some time he had had an insensitive bladder which often became distended without discomfort.

The subsequent course within the spinal cord of visceral pathways in man is to some extent still in dispute. Hyndman and Wolkin[4] concluded from their experience with anterior chordotomies that the spinothalamic tracts carried visceral pain sensation from every source: in this they disagreed with White[5] who stated that interruption of the spinothalamic tracts would not relieve the sensation of a distended colon or bladder. More recently, however, McMichael[6] reported the pathological findings in a patient with Erb's syphilitic spinal paralysis who had lost sensation of bladder fullness, and he concluded that the cord pathways for bladder afferents in man lay in the posterior and superficial regions of the lateral columns, where Barrington[7] had shown them to lie in cats. Strong support for this view was provided last year by Nathan and Marion Smith[8] from a detailed study based on 27 patients who had been subjected to unilateral or bilateral anterolateral chordotomies; they showed that the pathways subserving sensations of bladder fullness, as well as pain of urethral and ureteric origin, lie within the spinothalamic tract on the surface of the cord opposite the dorsal lateral process of the anterior horn of grey matter. It seems possible, therefore, that in Grimble and Csonka's case afferent fibres from the bladder were disrupted within the cord as indicated by the marginal demyelination found at necropsy. As they admit, their case has not added to our knowledge of the neuro-anatomy of visceral pain pathways, but their report is of value in that it draws attention to this interesting and potentially dangerous complication of tabes dorsalis.

A NEW MURMUR

MURMURS in the cardiovascular system are produced by turbulence in the blood-flow from narrowing or other irregularity in the blood passages. Vibrations are set up in the vessel walls, and the resulting sounds are conducted particularly well in the direction of the blood-flow.

A new physical sign of compression of the subclavian artery at the thoracic inlet has now been described by Edwards and Levine,[9] who find that a bruit is audible over the affected artery in the posterior cervical triangle. Sometimes this is heard with the patient in the resting position; but it is intensified—and may only be heard—when he tenses the scaleni by depressing the shoulder and bending the neck away from the affected side.[10] With this manœuvre Edwards and Levine find it easier to detect different degrees of the murmur than the accompanying variation in pulse-pressure. (This accords with general experience in feeling the pulse while listening to the diastolic range of sounds.) A microphone can be substituted for the stethoscope, and a permanent visual record obtained from a recording electrocardiograph, the other channels of which can be used for synchronising the tracings with those from heart leads.

Vascular symptoms in patients with cervical rib or scalenus syndrome seem usually to be due to compression of the subclavian artery, either by an aponeurotic band from a scalenus muscle or by the rib itself; but sometimes clavicular pressure may play a part. This was clearly shown by Eden.[11] In treatment scalenotomy has given place to formal dissection of the vasculonervous bundle in the affected region. Direct pinching of the subclavian artery is a more familiar feature than it was when Lewis and Pickering[12] described it in Trotter's patient with Raynaud's syndrome and a cervical rib. Diagnosis, however, is not always easy. The majority of patients have no cervical rib; and pain in the arm and Raynaud's phenomenon are often ascribed to causes other than compression of the bundle at the limb root. The simple auscultatory test described by Edwards and Levine may prove most useful in detecting such compression and in indicating the cases that require operation.

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Special Articles

CLIMATE AND RESPIRATORY INFECTIONS

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INFECTIONS acquired via the respiratory tract occur in epidemic form during the dry season in tropical Africa, and major epidemics, particularly of cerebrospinal *meningitis* (C.S.M.), *are confined to arid regions.* In temperate climates respiratory infections are at their height in late winter and spring. This contrast seems to have been accepted without explanation. Banks (1942), writing on C.S.M., said:

> "A fall in temperature or else a rise in humidity appear to start the upward trend of the disease, the maximal effect being apparent a month or so later. Exceptionally, as in the Sudan, the change to dry dusty weather is associated with the disease."

Experience, especially of C.S.M., in the Northern Territories of the Gold Coast has led me to speculate on this apparent discrepancy, and I propose to put forward evidence that the common factor is low absolute humidity (A.H.).* That low A.H. is an important factor in the epidemiology of lobar pneumonia and smallpox in a tropical climate has already been stated by Rogers (1925, 1926), but its significance appears to have escaped attention. In a temperate climate, such as that of England, A.H. is lowest in the winter and highest in the summer.

Many of the figures I shall use in this paper are not superlatively accurate, but they are accurate enough to serve as illustrations and no further apology will be made for them.

RESPIRATORY INFECTIONS IN TROPICAL AFRICA

In the countries bordering on the Sahara, lobar pneumonia becomes epidemic, to an unknown extent, every dry season, and smallpox epidemics, when they occur, do so during the dry season and fade out when rain begins to fall. The spectacular epidemics of C.S.M. in the Sudan, Nigeria, and the Gold Coast between 1930 and 1950 have received more attention than the other diseases. The rise and fall of C.S.M. in relation to the climate are much more clear cut than those of smallpox, and the epidemiology of smallpox is obscured by vaccination campaigns. I suspect that lobar pneumonia has a sharply defined epidemic season, but few figures have been collected. C.S.M., therefore, is the only example of tropical epidemiology that I shall discuss in any detail.

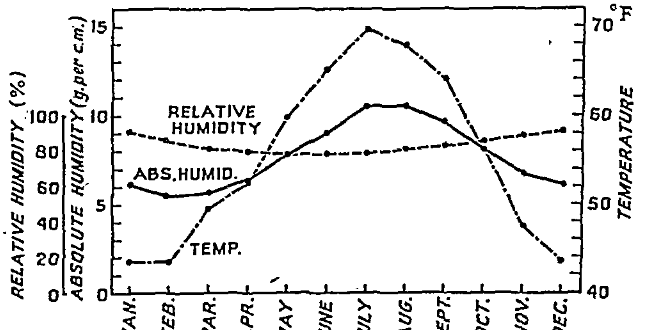

Fig. 1—Average temperature, relative humidity, and absolute humidity at Kew observatory.

C.S.M. is a disease of the dry season in dry places; epidemics are cut short with dramatic suddenness by wet weather and places with humid climates are free from serious epidemics. Usually an epidemic ends with the fall of rain, but there are records—e.g., in the Sudan—of an epidemic fading though no rain fell. Epidemics work round in cycles from the Sudan to Nigeria, on to the Gold Coast and back through the French territories to the Sudan.

The Lobi country in the western part of the Northern Territories of the Gold Coast suffered terribly in the early years of this century (Walton Claridge 1915) and again in the early 1920s. The Gold Coast became reinfected with a small outbreak in the north-east in 1939. The western side of the Northern Territories was again attacked in 1942, and in 1945 there was an epidemic of 9864 cases in a population of about 250,000 (Browne et al. 1947). In this area conditions of close crowding and bad ventilation could hardly be worse. The houses have no windows and only a small hole for a door. The occupants often sleep huddled close together for warmth.

TABLE I—TEMPERATURE AND HUMIDITY IN GOLD COAST EPIDEMIC OF CEREBROSPINAL MENINGITIS, 1947–48

Week ending		Average temperature (°F)	Average relative humidity (%)	Average absolute humidity		No. of cases of C.S.M.
				(gr. per c.ft.)	(g. per c.m.)	
Nov.	8 ..	71·5	89·0	7·4	17·0	3
,,	15 ..	67·0	62·5	4·5	10·3	1
,,	22 ..	70·0	47·5	3·7	8·5	1
,,	29 ..	70·0	44·0	3·5	8·0	2
Dec.	6 ..	66·5	46·5	3·3	7·6	2
,,	13 ..	71·0	61·0	5·0	11·4	5
,,	20 ..	67·5	34·5	2·5	5·7	11
,,	27 ..	69·0	31·0	2·4	5·5	8
Jan.	3 ..	68·5	23·0	1·9	4·35	11
,,	10 ..	66·0	21·5	1·5	3·45	36
,,	17 ..	67·0	20·0	1·45	3·32	46
,,	24 ..	67·5	20·5	1·5	3·45	28
,,	31 ..	71·0	14·5	1·2	2·75	80
Feb.	7 ..	68·0	18·0	1·3	2·98	182
,,	14 ..	73·0	23·0	2·05	4·7	502
,,	21 ..	74·5	26·0	2·3	5·3	803
,,	28 ..	75·0	19·5	1·8	4·1	874
March	6 ..	76·0	41·0	3·9	8·9	1492
,,	13 ..	73·0	38·0	3·3	7·6	1711
,,	20 ..	74·5	13·5	1·25	2·85	1349
,,	27 ..	74·0	37·5	3·4	7·8	731
April	3 ..	78·0	68·0	7·0	16·0	1213
,,	10 ..	80·5	65·5	7·2	16·5	737
,,	17 ..	75·5	83·5	7·8	17·9	585
,,	24 ..	77·5	83·0	8·5	19·5	256
May	1 ..	76·0	86·0	8·3	19·0	45
,,	8 ..	—	—	—	—	29
,,	15 ..	—	—	—	—	11
,,	22 ..	—	—	—	—	5
,,	29 ..	—	—	—	—	3

Temperature and humidity were measured at 6 A.M. There is negligible correlation between the number of cases and A.H. for the same week, but if the disease [illegible] with A.H. of the previous four weeks, th[illegible] is −0·33 (standard error 0·20) which is [illegible]

The figures of seasonal C.S.M. in the Sudan, Nigeria, and the Gold Coast indicate a degree of mass immunity following a major outbreak. In the western Northern Territories there were 853 cases in 1944; 9864 in 1945; and 52 in 1946. In Nigeria the number of cases reported in some of the big epidemics were only guesses, but the figures show the same fall after an outbreak. In the Sudan the disease did in fact die out in the area affected by the big epidemic of 1936 (Elliott 1947).

This trend—the building up from season to season until a really big epidemic occurs and then the sudden drop—is, I think, a fair indication that the carriers must greatly outnumber the cases, and that carrying the infection does confer some degree of immunity.

ATMOSPHERIC HUMIDITY AND C.S.M. IN THE TROPICS

It has been assumed that rain stops an epidemic by reducing dust-transmission; indeed, watercarts have been used in town streets in an effort to do this.

At the beginning of the dry season night temperatures are lower than at any other time of year. The population ongregates more closely at night, and this has been dvanced as the main cause of the seasonal variation of .S.M. But during the rains nights are quite cold enough o cause exactly the same crowded sleeping conditions; have studied the sleeping habits of people in the western Northern Territories and they are if anything worse in the rainy season when leaking rooms are abandoned and dry ones take an extra quota of humanity. Nevertheless, only sporadic cases of C.S.M. occur at this time.

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* Absolute humidity is measured by the actual amount of water vapour in the atmosphere (in grains per cubic foot or grammes per cubic metre).

The relation of C.S.M. to relative humidity (R.H.) † in tropical Africa has been discussed before.

Riding and Corkill (1932) showed that the incidence in Khartoum rose as humidity fell and vice versa. The association was graphically exact and rain was assumed to be the cause. Corkill (1939) convincingly discounts actual rain as the factor. He writes: "In the epidemic . . . the association was clear and constant," but he adds that subsequent epidemics have sometimes declined before R.H. started to rise, and he discarded the theory that variations in R.H. were the immediate cause.

White (1942) reported an epidemic in Tanganyika which began to decline when R.H. was still low. He commented on the outbreak of sore throats which always accompanies an epidemic, and remarked that it was probably caused by drying of the nasopharyngeal mucosa. The decline of this epidemic may be wholly or partly explained by its long duration and the relatively small number of cases (about 900). Steps to avoid overcrowding were taken and should have had some effect after the epidemic had reached its peak.

The Gold Coast epidemic of 1945 ended when patchy showers fell in only parts of the district; an association with low R.H. suggested itself to me at the time, but the only figures available are too inaccurate to reproduce. All that can be said is that the epidemic coincided with a typical dry season, the curve of humidity in the Northern Territories showing a rapid drop in December and a slower but steady rise towards the end of February. Unexpected showers make very little difference; the climate is dependent on wind from the Sahara.

The next major epidemic of C.S.M. was in the Northern Territories in 1947–48, and here I was able to obtain accurate figures of temperature and humidity. The figures were recorded at Tamale, more or less in the centre of the Northern Territories, where the climate is typical of the whole, though in the extreme north the dry period lasts slightly longer and is a little more severe.

Table I shows the weekly figures and the corresponding number of cases of C.S.M.

TABLE III—OUTDOOR AND INDOOR HUMIDITIES, ENGLAND, 1947—SPECIAL CASES

Conditions		Outdoors				Indoors			
		Dry bulb (°F)	Wet bulb (°F)	Relative humidity (%)	Absolute humidity (g. per c.m.)	Dry bulb (°F)	Wet bulb (°F)	Relative humidity (%)	Absolute humidity (g. per c.m.)
Army hut with 36 men in it; 2 iron stoves; poor ventilation (measurements at 3 different positions in hut)*	11.20 P.M.	42·0	41·5	97	6·65	60·5 61·0 60·5	55 54 54	71 64 66	9·25 8·60 8·72
	2.0 A.M.	38·0	38·0	100	6·08	56·5 56·0 56·0	51 51 51	70 72 72	8·17 8·26 8·26
Office with central heating and electric fire		42·5	35·5	47	3·67	61·0	47	31	4·13
Lecture-theatre with plenum and exhaust ventilation; humidifier not working ..		46·0	41·5	68	5·51	73·0	54	28	5·51
Lecture-room with central heating and double windows; poor ventilation; after a lecture		34·0	34·0	100	5·28	69·0	59	55	9·63
Overcrowded underground train.. ..		32·0	32·0	100	4·82	61·0	53	58	8·03
Underground bakehouse; baking not in progress		42·5	35·5	47	3·67	57·0	48	50	5·96

* Figures from Angus and Luxton (1947).

Overcrowding and badly ventilated sleeping accommodation have recently been somewhat discredited as causes of the spread of C.S.M. However, during the epidemic cycle in the Northern Territories, from 1945 to 1950, there was no confirmed case of C.S.M. in a European, only one case among hundreds of African nurses, and only one among the servants of Europeans—a young boy who slept in the town and not in the servants' quarters at his employer's house.

RESPIRATORY INFECTIONS IN TEMPERATE CLIMATES

A graph of the annual variations of temperature, absolute humidity, and relative humidity in England (measured at 1 P.M. at Kew observatory) shows that A.H. is at its lowest during the winter and highest in July and August, and that A.H. in a temperate climate bears a much closer relation to the temperature than to R.H. (fig. 1).

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† Relative humidity is expressed as the percentage of water vapour in the atmosphere as compared with the amount necessary to saturate it under the existing conditions.

TABLE II—COMPARISON OF OUTDOOR AND INDOOR HUMIDITIES IN ENGLAND, 1947

(Indoor readings taken in a living-room with an open coal fire)

Date	Barometric pressure (in. Hg)	Outdoors					Indoors			
			Dry bulb (°F)	Wet bulb (°F)	Relative humidity (%)	Absolute humidity (g. per c.m.)	Dry bulb (°F)	Wet bulb (°F)	Relative humidity (%)	Absolute humidity (g. per c.m.)
Feb. 6 ..	30·0	P.M.	32·0	31·5	95	4·59	51·5	45·0	59	5·73
„ 7 ..	29·6	A.M.		Not taken	—	—	47·0	41·5	62	5·05
	—	P.M.	29·0	28·0	88	3·67	49·0	43·0	61	5·51
„ 8 ..	29·5	A.M.	29·5	29·0	94	4·13	44·0	38·0	56	4·36
	—	P.M.	31·5	30·5	89	4·24	49·0	42·0	54	4·82
„ 9 ..	—	A.M.	31·0	31·0	100	4·59	45·5	39·5	57	4·59
	—	P.M.	35·0	35·0	100	5·50	50·5	44·5	62	5·73
„ 10 ..	29·6	A.M.	36·0	36·0	100	5·70	46·5	40·5	58	5·05
	—	P.M.	34·0	34·0	100	5·23	49·5	43·5	61	5·51
„ 11 ..	29·6	A.M.		Not taken	—	—	47·5	42·0	62	5·05
	—	P.M.	27·0	27·0	100	3·90	46·0	40·5	61	4·82
„ 12 ..	—	A.M.		Not taken	—	—	43·0	38·0	63	4·36
	—	P.M.	28·0	28·0	100	4·13	47·0	40·5	56	4·82
„ 13 ..	29·6	A.M.	29·0	29·0	100	4·24	45·0	39·0	57	4·36
	—	P.M.	31·0	30·5	94	4·36	47·0	41·0	59	5·05
„ 14 ..	—	A.M.		Not taken	—	—	44·0	39·0	63	4·59
	29·7	P.M.	34·0	33·5	95	4·82	48·5	42·5	61	5·28
„ 26 ..	—	P.M.	38·0	33·5	62	3·67	59·0	48·5	45	3·45*

* Heating by electric fire and paraffin stove instead of coal fire.

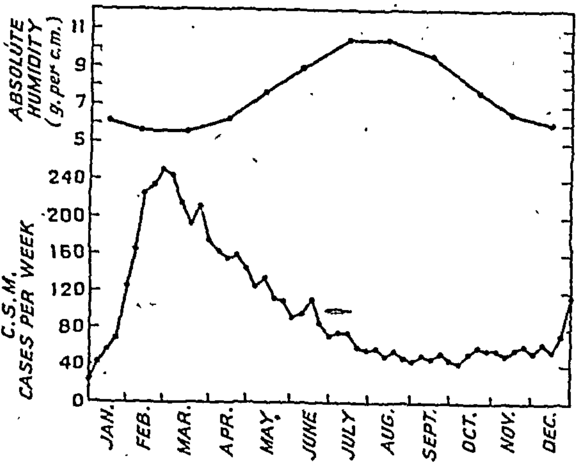

Fig. 2—Cerebrospinal meningitis in England and Wales (1940) related to average seasonal absolute humidity.

Most respiratory infections are probably acquired indoors in the ways delightfully recorded by Pickles (1939). I could not find any figures which compared the outdoor and indoor atmospheric conditions in England, and I therefore recorded some myself during the winter of 1946–47 (table II).

In a room without double glazing A.H. does not rise very much above that out of doors, and it is certainly not as high as the average summer A.H. The reason for this is fairly obvious; any excess water vapour promptly condenses on the windows and walls which are cooled from outside.

Mr. T. C. Angus, D.SC., of the London School of Hygiene, very kindly gave me figures recorded in a badly ventilated Army hut under conditions similar to those studied by Glover (1918). These figures and some further observations of my own are given in table III.

Changes in outdoor A.H. follow those indoors sufficiently closely to be used in studying the relation of A.H. to respiratory infections.

I have not studied the daily weather readings for the year 1940, but a graph of the C.S.M. epidemic of that year and of the average seasonal A.H. shows a fairly clear association (fig. 2).

I could find only one long series of observations on the carrier-rate of C.S.M. in England (Glover 1918). These figures were not taken regularly every week, and the 4-weekly averages which I have taken from Glover's graph are probably not exact. Table IV shows these averages and the corresponding Kew figures for temperature and humidity.

The coefficient of correlation for the carrier-rate and A.H. of the same 4-weekly periods is —0·65. That for carrier-rate and A.H. for the previous 4-weekly period is —0·73. The standard error is 0·29, so both the figures are significant. R.H. has no association with the carrier-rate.

TABLE IV—TEMPERATURE, RELATIVE AND ABSOLUTE HUMIDITY, AND MENINGOCOCCAL CARRIERS, SEPTEMBER, 1917, TO SEPTEMBER, 1918

(Glover (1918) defined the organisms as "gram-negative cocci morphologically indistinguishable from meningococci")

4-weekly period	Temperature (°F)	Average relative humidity (%)	Average absolute humidity (g. per c.m.)	Carriers (% of persons examined)
1	61·5	76·5	10·3	—
2	55·5	84·0	9·4	21
3	45·0	85·5	6·5	39
4	44·7	85·0	6·4	41
5	34·8	81·0	5·8	57
6	41·7	84·0	5·3	81
7	43·3	86·0	6·4	67
8	41·2	80·5	5·5	40
9	44·0	82·0	6·2	29
10	52·5	74·0	7·8	67
11	59·5	64·5	8·5	49
12	60·5	68·0	8·5	26
13	63·4	75·5	11·2	23
14	61·0	74·0	10·3	13

Glover associated overcrowded sleeping conditions with a high carrier-rate, as did Peters and Gunn (1929) and Whittingham et al. (1931). But the Medical Research Council (1918) cast some doubt on the relation of C.S.M. and bad ventilation per se.

I believe that the relation of carrier-rate, disease, and climate could be studied conclusively in countries close to the Sahara, if the necessary laboratory equipment were available.

INFLUENZA

The pandemic of influenza had three waves, two in 1918 and one in 1919.

The Ministry of Health (1920) quoted the report of the French Direction d'Hygiéne, which observed that the mortality in 1918 was low during a remarkably dry and cold spell in France from May to June. It then went up slowly, and came down again when the weather became warmer and unusually heavy rain fell. It rose again towards the end of a dry August. September and October had 6 weeks of drought with temperatures below normal; this was a peak period for deaths from influenza. In November temperatures became normal again and abundant rain fell; the death-rate decreased. Another cold spell followed and a second mortality peak occurred.

TABLE V—INFLUENZA, TEMPERATURE, AND ABSOLUTE HUMIDITY, LONDON, 1918 TO 1919

Week of year (1918)	Temperature (°F)	Absolute humidity (g. per c.m.)	Influenza deaths	Week of year (1918)	Temperature (°F)	Absolute humidity (g. per c.m.)	Influenza deaths
18	51·6	7·45	3	45	44·4	6·9	2433
19	50·2	7·5	7	46	36·1	4·8	1665
20	62·1	9·7	6	47	38·7	6·0	1178
21	61·5	9·4	6	48	44·6	7·1	912
22	61·0	8·6	5	49	49·1	8·5	660
23	58·3	7·5	5	50	51·6	8·9	322
24	58·3	8·1	5	51	40·7	5·7	186
25	57·4	8·5	10	52	47·0	7·6	95
26	59·9	8·5	67	(1919)			
27	63·5	8·9	218	1	39·0	5·65	65
28	59·4	10·3	287	2	39·9	5·85	68
29	65·7	11·2	192	3	40·3	5·95	43
30	61·5	10·8	86	4	33·8	4·6	33
31	63·7	11·9	38	5	32·2	4·1	58
32	62·8	10·5	21	6	30·4	3·3	100
33	63·9	9·85	20	7	33·1	4·75	273
34	64·2	11·9	12	8	42·4	6·35	653
35	56·7	8·7	12	9	40·5	5·4	808
36	59·2	10·3	12	10	43·9	6·75	597
37	57·7	9·7	14	11	42·4	5·7	435
38	54·4	8·6	9	12	36·9	4·65	230
39	51·3	7·1	17	13	36·9	4·1	125
40	59·4	10·3	17	14	42·1	5·7	91
41	50·8	8·25	80	15	48·0	7·15	105
42	47·9	7·8	330	16	48·7	6·35	71
43	47·9	8·0	1256	17	44·8	5·5	43
44	51·5	8·25	2458	18	50·0	7·6	44

Low A.H. is an adequate measure of coldness and dryness, so recourse has again been made to contemporary weather readings. At the time of the pandemic waves, A.H. was lower than average. Table V gives the climate figures for London only, but the Ministry of Health (1920) state that the London weather was typical of that for the whole British Isles.

The three waves of influenza began respectively in the fifth, fifth, and seventh weeks after a pronounced decline in A.H. The waves passed their peaks and declined five, six, and three weeks after A.H. began to rise again. The Ministry of Health report says:

> "These results suffice to establish a *prima facie* case in favour of the view that an unseasonable deviation of weather towards the side of coldness played some part in the mortality of the epidemics. They not less clearly testify against any claim that weather conditions rank among the primary factors of epidemic prevalences."

There could be no fairer summing-up. None the less the connection does exist.

LOBAR PNEUMONIA

The report also analyses the weekly incidence of lobar neumonia in relation to the temperature of the previous reek for the years 1850–89 and 1903–14. The coefficients f correlation are as follows :

First quarter, 1850–89	.. ..	−0·371
Fourth ,, ,,	.. ..	−0·686
,, ,, 1903–14	.. ..	−0·707

(The standard errors are 0·046, 0·046, and 0·087.)

In view of the connection I have indicated between he temperature and A.H. in temperate climates, and etween lobar pneumonia and the dry season in tropical Africa, the statement of Rogers (1925, 1926) that lobar pneumonia and low A.H. are closely correlated is confirmed.

CRITICAL ABSOLUTE HUMIDITY

Rogers gives a critical figure of 0·7 in. Hg (the equivalent of 17·2 g. per c.m.) as a critical figure for A.H., above which smallpox dies out. This figure is seldom if ever reached in England, but it may correspond to a critical figure for the Northern Territories of the Gold Coast.

If there is a critical value for C.S.M. the English and Gold Coast figures suggest that it may be in the region of 10 g. per c.m.

AIRBORNE ORGANISMS AND ABSOLUTE HUMIDITY

Robertson (1943) mentions high humidity as being rapidly fatal to organisms. Loosli et al. (1943) investigated the viability of an influenza virus in various atmospheric conditions, and found that the infectivity of the virus declined much more rapidly at high R.H. Similar results were obtained by De Ome (1944) for *Salmonella pullorum*. De Ome found that increase of temperature also increased the rate of loss of viability, and that the combined effect of increasing the temperature and R.H. appeared to be cumulative. This combined effect amounts to an increase of A.H.

The meningococcus is said to be an exceedingly sensitive organism, highly susceptible to drying or cooling. A leading article in THE LANCET (1931) stated that the organism dies out rapidly below a temperature of 71°F. But such a temperature is very seldom reached in English homes during the winter, and anything approaching it is considered much too stuffy ; yet C.S.M. is a winter disease. I know of no explanation for this discrepancy.

PHYSIOLOGICAL EFFECTS OF LOW ABSOLUTE HUMIDITY ON THE RESPIRATORY TRACT

Epidemics of C.S.M. are accompanied by outbreaks of sore throats. It may be that the meningococcus carrier suffers directly from his infection, but the effects of low A.H. on the respiratory tract are worth considering.

When air enters the alveoli of the lungs it has reached body-temperature and is saturated with water vapour. Its A.H. is therefore 43 g. per c.m.—a constant whatever the external atmospheric conditions. The figure is correspondingly raised by a fever. The extra moisture supplied to the air on its way to the lungs comes from the upper respiratory tract, with the nasopharynx contributing the major share. The amount of extra water vapour required depends, not on the R.H., but entirely on the difference between the external A.H. and the constant humidity of the alveolar air.

From this point of view the air of a temperate winter is far from moist ; it dries the nasopharyngeal mucosa much more than summer air, and so corresponds to the air of the tropical dry season. It is possible that the vitality and resistance to infection of the upper respiratory tract are lowered by this drying action, particularly after a rapid fall in A.H., before physiological adjustment has been made.

Thus, in conditions of low A.H. certain airborne organisms have been proved to live longer, and the upper respiratory tract has to supply more moisture to saturate the tidal air. These facts are in accordance with the epidemiology of C.S.M. in both temperate and tropical climates, and of influenza and lobar pneumonia in the instances I have given. If, as I have tried to show, airborne infections are related to low absolute humidity, such infections could possibly be reduced by humidifying the indoor air, particularly in crowded places. It may be useless to attempt this in the absence of double glazing, but the subject would bear investigation.

SUMMARY

I have tried to show that low absolute humidity is an important factor in the spread of airborne diseases.

The evidence is based on a study of outbreaks of cerebrospinal meningitis in the Gold Coast and their relation to climatic conditions. An analysis of an epidemic of the disease in England and Wales and of the influenza pandemic also supports the proposition. Cold dry weather seems to favour the spread of airborne infection in this country.

The infectivity of certain airborne organisms is increased in air of low absolute humidity. Such air also dries the nasopharyngeal mucosa more rapidly and may thereby lower its resistance.

As a preventive measure the humidity of the air in crowded places might be increased where practicable.

I gratefully acknowledge figures obtained from the published records of the Meteorological Office and the Office of the Registrar-General, and from the annual reports of the medical services of Nigeria, the Gold Coast, and the Sudan. I am indebted to Dr. R. L. Cheverton, director of medical services, Gold Coast, for permission to publish the paper, and to Dr. G. A. Knowleden for correcting my results of coefficients of correlation.

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DARENTH PARK HOSPITAL

The Care of Mental Defectives

FOUNDED in 1878 as a school for imbecile children, Darenth Hospital has become one of our largest centres for adult mental defectives of all types. It stands in some 168 acres, of which 126 acres are its own farmlands, on a high ridge above Dartford in Kent—an airy site with a magnificent outlook—and houses at present some 1800 defectives, about 700 of them women, and the rest men. It is capable of taking 1443 men and 956 women, but some wards are empty because of lack of staff.

Mr. J. Tizard and Mr. N. O'Connor, who have been studying, in Darenth and other hospitals, the employability of defectives, estimate[1] that more than half the adult cases in such hospitals are high-grade patients ; and that a large proportion of these are young trainable adults and adolescents who may eventually be discharged from the provisions of the Mental Deficiency

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[1] See *Lancet*, Sept. 27, 1952, p. 621.

Acts. This being so, it is timely to review what has already been achieved, and is being achieved, at Darenth; for defectives are not less individualistic than the rest of us—rather the reverse, in fact—and attempts to train them for industry will hardly be fully successful unless they are preceded or accompanied by sound social training, such as Darenth tries to give.

The aim has always been, as Dr. J. K. Collier Laing, the physician-superintendent, points out in his annual report for 1951, to return the patient, after training, to the outside world, able as far as possible to fend for himself. Discharges in 1950 and 1951 (apart from transfers to other hospitals) amounted to about a third of the new admissions—of which there were 145 in 1950 and 111 in 1951. In addition, over 300 patients were out on weekly parole in 1951, and an average of 192 were on daily licence.

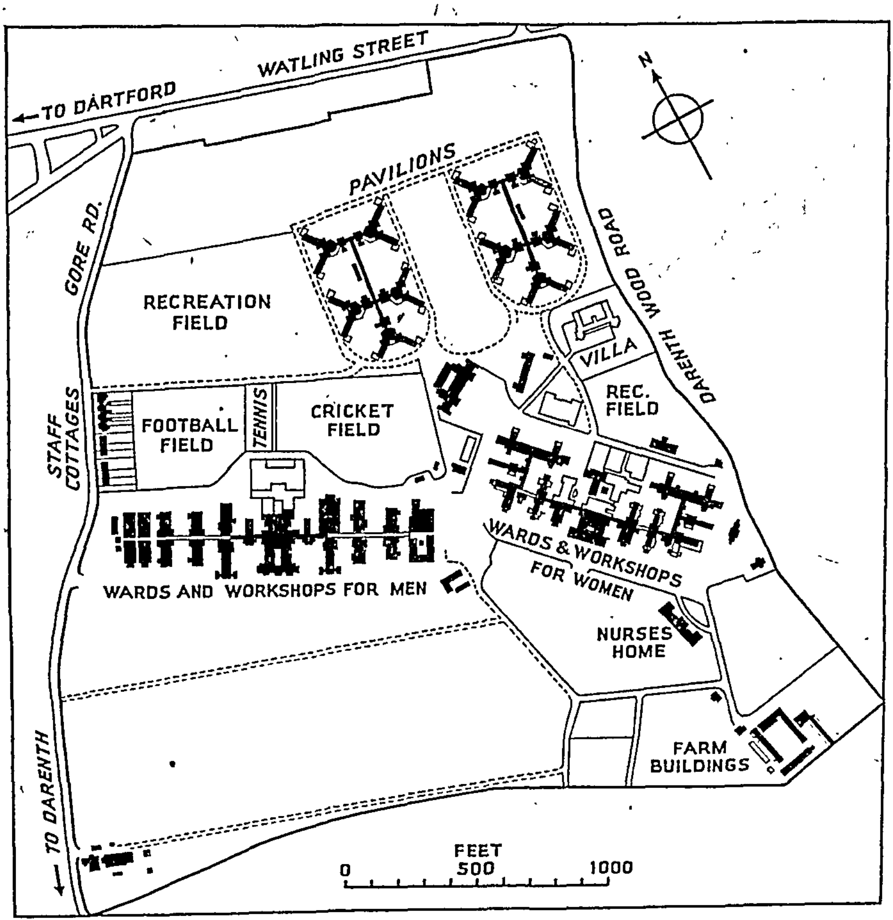
It is thus clear that a very large proportion of Darenth patients live many years or even the whole of their lives in the colony; and it is therefore important to know what opportunities they have to contribute to their own community as well as to the community outside the hospital.

FARMING AND MAINTENANCE

The hospital consists of several large blocks, as the plan shows, set in gardens and farmland. Most of the patients live in open wards, with dormitories attached. Between and round the wards are gardens well stocked with flowers; and these are maintained by a small staff of trained gardeners supported by male patients. It is the experience of the head gardener that most of these patients are able to understand simple lessons on gardening, and that they make very keen workers. Such lessons are given in a classroom on wet days, as well as by practical demonstration in the open. Patients are very decided in their tastes; if they like working in a glass-house, that is what they like, and they will not take readily to other kinds of gardening. If they like open-air gardening, there again they make their choice once and for all. Some of them go out on licence as under-gardeners, and very reliable ones they make.

The chief farm superintendent, who has charge of the hospital acres and herds, also directs farming at the neighbouring hospitals of Stone Lodge (161 acres), Joyce Green (546 acres), and Mabledon Park (20 acres). Smaller acreages of arable land and rough grazing at the Southern Hospital and elsewhere are also under his care. Tuberculin-tested attested cattle herds are kept on all the main farms except Mabledon Park, where pedigree pigs are raised; and large numbers of pigs are bred on the other farms as well. Poultry is mainly concentrated at Stone Lodge and Joyce Green. The annual milk-supply is some 74,000–80,000 gallons, and in 1951 over 165,000 eggs were distributed. Poultry and meat were supplied to the hospitals in the group, and pork was sufficiently plentiful to be supplied to other hospitals as well. The farms also raise all kinds of feeding-stuffs for the stock (amounting last year to 1632 tons) and provide vegetables and fruit for other hospitals as well as those in the group. The work is thus considerable, and provides occupation for many patients in the medium and higher grades of intelligence. They often seem to take naturally to agricultural work, and to be happy in it.

Hospital maintenance provides work for many others. Thus there are bricklayers and painters among the patients, working under skilled craftsmen. These keep the buildings decorated and in repair, besides helping with any new building which is going on. In the carpenter's shop patients help to cut the timber needed by the builders and to make all the wooden fittings used in the hospital, such as stools, benches, and the like. The tinsmith's shop turns out new kettles, coal-scuttles, and dustpans, as well as a great supply of tins and other household articles. There is a mattress-making shop, where hospital mattresses are repaired and pillows made; and on occasion new mattresses are completed. Each stage in the process has to be prepared and presented so that mentally defective workers can understand and master it. The same applies to the upholsterer's shop, where hospital furniture is repaired and re-covered with professional skill and finish—the craftmaster breaking down the various stages in the process so that they become comprehensible to the men working under him. Some parts of it, such as the cutting-out, he must necessarily keep in his own hands, to prevent waste; but nearly all the work can be, and is, done by patients.



The tailor's shop is mostly engaged on repairs, for the men's clothes are bought in bulk from outfitters, and the women make their own dresses. Nevertheless in 1951 this department of Darenth made 12 tweed suits as well as 158 shirts and various coats and pairs of trousers, and was responsible for the repair of nearly 6000 garments and much other work. The matmaking department completed over 200 mats, and repaired as many more; but matmaking goes on all over the hospital, for even disabled patients who cannot leave their ward can enjoy this kind of straightforward handiwork. The same applies to brushmaking, basketwork and which are pursued in several parts of the hospital as well as in their official departments. The shoemaker's department, in

951, turned out 6 pairs of orthopædic boots needed by atients, besides repairing well over 8000 boots and shoes.

The women patients, who cannot very easily be allowed o work alongside the men, are normally employed in the undry (which is very popular), or on needlework. ome hundreds of them have become skilled machinists. hey do all the needlework for the hospital, making resses for themselves and the nursing staff, as well as urtains, bed-linen, rugs, towels, pinafores, underlinen, ight clothes, and anything else which is needed. They ork willingly and happily, but—as always happens ith mental defectives—with plenty of outspoken comment. A thousand nightshirts for another hospital, for nstance, had proved rather a tedious assignment: they were all ready to try something else.

OUTSIDE WORK

Sometimes the output is greater than is needed for ospital maintenance, and sometimes outside orders are illed. Brooms and brushes are always made in excess of the hospital's need, and are sold outside. Unfortunately the market for hand-made brushes has lately allen off. The bookbinding and printing shop is engaged almost entirely on outside work. Much of the bookbinding and printing for the hospitals of the region is done there—a very large assignment—and in addition writing-paper and postcards are cut, and pasteboard folders and envelopes made. Darenth, it seems, bound the file copies of THE LANCET till the pressure of other work made this impossible. In 1951 well over 3000 books were bound there, and more than 500,000 forms printed. Even in a ward of disabled men, some of them blind, handicrafts are pursued with keen interest and pleasure. Some of the best basketwork in the hospital is done here, as well as rugmaking, carpentry, assembly of table-lamps, and other small manageable jobs: even the blind patients knit. The products are sold. In this ward, patients are given plenty of encouragement, but there are no fixed working times; the patients please themselves about how much they do, and they do a good deal.

During the study made by the Medical Research Council team, various other outside commitments were undertaken. Selected groups of patients now help to complete and pack the cardboard containers used by confectionery firms, or file the rough edges from plastic wireless parts. They are well paid for this work, and are allowed to have 5–10*s.* weekly—the exact amount depending on their performance—as pocket-money. The rest of their money is banked for them, and by applying to the matron or chief male nurse they can withdraw sums to spend on clothes, presents, or holidays, or to send home. The prestige of sending home money is, of course, very good for them; but Dr. Laing finds he sometimes has to defend them from rapacious relatives, who, once they find these patients can earn decent wages, do not hesitate to bleed them. In addition to those working in hospital there are, of course, all those working outside on licence—in factories, on building sites, and elsewhere.

LIFE IN DARENTH

The dayrooms of the wards are furnished with comfortable chairs, small tables, hand-made rugs, flowers, and—in the women's wards especially—embroidered tablecloths and cushions. The atmosphere is happy, and the social side well developed. Film shows are given twice a week in one of the three halls, and are also taken on a mobile set to the ward for disabled patients. There are dances weekly, concert parties at Christmas, summer coach-outings (mixed parties where the men escort the women, and all behave with great propriety), a horticultural fête, and a very lively club called the Good Intentions, run by the patients, of which the founder members were all delinquents. This club meets weekly and now accepts those with good records as well as those who have lived down a dubious past; and the waiting-list for membership is long. The spirit in the workshops is cheerful, and the patients enjoy their meals.

Darenth, in fact, is a town in itself, providing work in most of the ordinary trades. Moreover, it is a town with a good community spirit and plenty of social life, and patients who leave often revisit it affectionately for years afterwards. Mental defectives are not necessarily at their happiest when living at large in the community; some of them, at least, are relieved of much anxiety, and of a sense of inferiority, by living in the company of their peers. Some, certainly, are capable of marrying and making good parents, if not very bright ones; but for most of them a single life is desirable. The weight of responsibility which the sex instinct imposes is hard for some of them to bear without the support of an ordered life and friendly discipline. Mentally defective girls, especially, are liable to be exploited when they are not supervised.

All these factors have to be taken into consideration when preparing a patient for a post in industry, or for any other life outside the hospital. Many defectives can be trained to do a straightforward, or even quite a complicated, job as well as the next man or woman; but that may not be all that is needed to fit them for life in the outside world. The main achievement of Darenth is probably the steadying influence which life in ordered friendly surroundings exerts even on disturbed patients. Darenth patients out on licence working with normal men, though they are sometimes teased a little at the outset, are soon accepted and championed by their fellow-workers; and this suggests that they have learned to show their reliable and likeable qualities, even in the face of some prejudice. Since defectives are very sensitive to criticism, this is surely a tribute to their training.

Public Health

The Society of Preventive Medicine

THE new president of the Society of Medical Officers of Health is Dr. Andrew Topping, dean of the London School of Hygiene and Tropical Medicine, and he was installed on Sept. 18 by his predecessor, Dr. W. G. Clark.

In his presidential address, Dr. Topping said that the society would celebrate its centenary in four years. In the first sixty years of its life its members had been engaged in the practice of old-time preventive medicine—improvement of water-supplies, sanitation, and the control of infectious diseases. In the years just before and just after the first world war the changes brought about by the development of local authorities' and personal health services, provision of hospitals, clinics, and dispensaries led to the society gaining many members who were not medical officers of health—a source of criticism of the society's organisation when he joined nearly thirty years ago. It was highly important that more of the junior medical officers should be able to attend meetings, and there was now to be a change in the name of the society which should encourage eligible non-members to join. It was to be called the Society of Preventive Medicine.

As (strangely enough) the first Aberdonian among the 72 presidents, he would deal first with the finance of health and disease. For generations they had been preaching that prevention of disease largely by removing the conditions which conduced to it was not only the logical approach but was also much less expensive than curative efforts. With each succeeding year the costs of curative medicine had been soaring and there seemed to be no limit. Patients suffering from avoidable or easily curable illnesses were encouraged to go to the hospital and the specialist.

Dr. Topping quoted Dr. Hugh Paul's illustration of the cost of curing one blue baby "which would never be a normal child" and of the much better use to which that money could be put in saving the lives of many children by preventive measures and improvement in environment and working conditions. The money spent on tuberculosis sanatoria might be much more effectively used in educating the people in prevention of the disease. Then, regarding prematurity, he was convinced that a large proportion was due to inadequate antenatal care or unwillingness to follow instructions. The modern prematurity unit was most expensive: the right thing to do was to educate the public and so stop the large number of cases. Referring to Bradford Hill and Doll's study of the relation between cigarette-smoking and lung cancer, he said that the publicity had been negligible; it was easier to order another deep therapy unit at colossal cost. The financial position of the country might cause a swing towards prevention as the cheaper expedient, but it would be a pity if this were forced on us by economic necessity rather than by conviction.

The teaching of preventive medicine needed much improvement, particularly at undergraduate level. Little more than lip service was paid to it by some clinical teachers. The teaching of preventive medicine should be done in the ward or (as in the Edinburgh experiment) in the homes of the patients. Habits, environment, occupation, and population trends were most important to the medical student if he was to help the public to understand how to prevent ill health.

As to the tropical countries and the backward countries of Europe, efforts at improving health were foredoomed to failure until these peoples could get improvement in their general economics and agriculture. In many tropical areas there might be lessening of malaria, great improvement in the water-supply, and so on, but for two months of the year there was practically no food. Was it wise to try to reduce infant mortality if one could not at the same time ensure food for the children saved? As a member of a Rockefeller Foundation team in Southern Italy, a pastoral and agricultural area, he had seen children actually starving; there the greatest need was drinking-water, seed, and fertilisers.

It was time, Dr. Topping said, that we pulled out heads out of the sand and faced the difficulty of family spacing. We should aim at improving the quality rather than quantity of our children. Equally obvious was the tendency for the most irresponsible and those in the lowest strata of our population to produce large numbers of children, while higher grades, irrespective of religion, were limiting their families. This general problem was enhanced by the reduction in the infant mortality-rate, the increased expectation of life, and the production by the chemists and biochemists of more and more life-saving drugs. The latter would doubtless before long produce a drug to delay cardiovascular degeneration or even prevent its occurrence. Also it was certain that the cause of cancer would be pinpointed. The biggest world problem facing us was not disease—great enough though this was—and it was not denigration of the preventive services: it was the inevitable consequence of the reduction in infantile and child mortality coupled with the effect on the expectation of life of the new life-saving and life-prolonging drugs.

Blindness in Scotland

There were 9119 blind people in Scotland on March 31, 1952—an increase of 226 over last year's total. In an analysis of this figure the Department of Health for Scotland says that, though the number of blind children has been falling for many years, it has now shown a slight increase. 20 children under the age of 5 were newly registered as blind in the year up to March 31 last—roughly double the average for recent years. An increase in the number of cases of retrolental fibroplasia was partly responsible.

Notification of Puerperal Pyrexia

In his report for 1951 Dr. I. Gordon, medical officer of health for Ilford, says that for some time he has written to doctors in his area who have notified a case of puerperal pyrexia and asked them for the cause of the illness. The regulations do not require the cause to be stated on the form, and Dr. Gordon had been wondering what exactly was being notified.

Of 65 cases notified in Ilford since Aug. 1, 1951, answers have been given for 62; and in 50 of these "the fever was quite unconnected with any infection of the birth passages." In 34 instances the fever was attributed to some disturbance of lactation. Dr. Gordon continues:

> "Who are notifying the cases? In Ilford 63% of births occur in hospital, but 89% of notifications came from the hospitals. Although complicated cases tend to be admitted to institutions, the causes of this fever are so trivial that they might well occur in domiciliary practice. The conclusion we have come to is that the busy family doctor, appreciating the triviality of this notification, neglects to fill in yet another form, whereas the hospital doctor, more bound by rules, and with the help of the temperature chart, does so.
>
> We may assume then that, at any rate in Ilford, notification of puerperal pyrexia has little relationship to infection of the birth passages, as intended, but tends to be merely an indication of minor breast troubles in maternity wards. This is a form . . . that can be easily dispensed with."

W.H.O. Committee on Influenza

At its first session in Geneva last month this committee suggested that the World Health Organisation could help to make information about future influenza epidemics more widely and more rapidly known; for the only prospect of using vaccines effectively seems to lie in identification of the strain of virus at a very early stage in the outbreak. The committee also advised that centres be established to give instruction in laboratory techniques, that the number of research laboratories be increased, and that research publications be made more widely available.

Report on Leprosy

A World Health Organisation report[1] says that estimates of the world's leper population vary from 2 to 7 million. The difficulties of early diagnosis and the inadequate medical services in the most heavily infected areas make it hard to give more accurate figures. The disease is commonest in Asia where there are roughly a million lepers in both India and China. The few endemic foci in Europe are mostly found in the Mediterranean countries, particularly in Spain, Portugal, and Greece. The report comments on the great progress achieved in freeing the leper from the added misfortune of being an outcast; many sufferers are now able to lead a more or less normal life.

New Regulations for Air Travel

After Oct. 1 a person arriving by air in this and other countries which have accepted the provisions of the new *International Sanitary Regulations* will no longer be required to make a personal declaration of origin and health.[2] If such a person is later found or suspected to be suffering from a dangerous infectious disease it may be necessary to trace contacts from the same aircraft. The Ministry of Health has therefore asked medical officers of health to notify such cases direct to the Ministry, so that arrangements may be made to trace contacts through the press and the B.B.C.

Resumption of Slum Clearance

Mr. Harold Macmillan, Minister of Housing and Local Government, speaking at Plymouth on Sept. 24, said:

> "We are hearing a great deal just now about houses which, it is said, are being left unoccupied, or even falling down through lack of repairs. It is said that all the ground we are gaining by building new houses we are losing because an equal number are falling down through decay.
>
> "We must remember that a great many houses ought to be pulled down. Before the war over 60,000 a year were being demolished under slum-clearance schemes. The tragedy today is that people still have to live in houses which would have been pulled down but for the second world war. Nearly 13 years have passed. It is time to take up this work again. It is absolutely vital that local authorities in this country should begin now to consider a resumption of slum clearance. It is a natural function for them—indeed, it is one of their most important—and only they can do it.
>
> "I am often reminded that good agricultural land is being sterilised through building in wrong places. Surely there is no better way of preventing the waste of agricultural land than by using again valuable housing sites which already exist inside our cities and towns. We must build more and more new houses because the waiting lists are still long, but where we can, let us build on sites that are ready-made. Let us start to pull down the worn-out houses and to fill up the toothless gaps in our cities and towns."

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[1] *Epidem. vit. Stat. Rep.* 1952, 5, no. 6.

[2] See *Lancet*, Aug. 23, 1952, p. 391.

In England Now

Running Commentary by Peripatetic Correspondents

WE are told by the pundits that should we be unlucky ough to meet, in a business way, a bullet, a bomb, a bus, the first reaction to the impact will be one of tense surprise. This will be followed by a period of ock and diminished consciousness. The pain, we are sured, will come later.

I was reminded of this sequence of events when I amined for the first time the school bills evoked by nding two children to boarding-school. I have survived e first stage and am now well into the second. Here y mind dwells with irritating persistence on the lidity of the argument which permits the Inland evenue to abstract the part of one's earnings intended r the education of one's own children in order to lucate other people's, leaving little option but the ate schools where there seems to be no room.

My mind wanders round and round this point, but in e great Omar's words comes out "by that same door herein I went." Clearly salaries are not based on ildren's school bills but on some beatific state of lf-sufficiency where "a jug of wine, a loaf of bread d thou" should be the sum total of our worldly eeds. And, as usual, the pundits are wrong: the rocess has been very painful right from the start and ems likely to persist for a long time.

* * *

Two conversations with toddlers have made me realise hat different things the word "hospital" means to the nall child. One bright little chap with mild cœliac isease was strutting about in a man's white pyjama cket which reached to the floor. He hadn't seen me, ough he had heard I was coming. At Sister's suggestion asked him who he was. "I'm Dr. Blank" was the reply, entioning my name. I learned later that he had a tethoscope hidden away, and with this and his white oat he did ward rounds with the other children. Hospital" to him meant fun and games. When I eached home, a small boy of about 3 suddenly appeared n the drive and said he wanted to "look." It appeared hat it was my car he wished to see. After careful nspection his nannie came to say it was tea-time. Have you had your tea?" he said. "Yes" said I. "Where did you have it?" he asked. "Oh, I had my tea t the hospital," I replied. He looked puzzled and rightened and eyed me carefully. "Haven't you been ery well?" he said.

* * *

The appearance of a new edition of Martindale's *Extra Pharmacopœia* reminds me that its extraordinary omprehensiveness has made it the basis of a party game mong pharmacists on their festive occasions. Marks re awarded to competitors who can enumerate the onstituents of Mother's mixture (not to be confused with Mother's ruin, which is not indexed), with a bonus or those who know that Mother's mixture originated n University College Hospital—the very fountainhead of Clinical Science. The sophisticated will know, of course, that Trooper's ointment is a trifle demodé. and that Tuba root is designed for the discomfiture of *Musca domestica*, and not for eradicating troublesome musicians. High marks are doubtless gained by competitors who refuse to be trapped into equating Arlacels, Crills, Spans, and Tweens, recognising (from their familiarity with Martindale) that these are *not* parts of a tentative scheme for an international system of weights and measures, but simply non-ionic complex esters or ether esters derived from the hexahydric alcohol, sorbitol.

* * *

I suppose that I have known mon cher ami français for some ten years or more. During that time our lengthier conversations seem always to have centred around one topic—the sweet reasonableness of the French language when compared with the hideous complexities of the English. The conversations usually take the form of long, and often rather lame, explanations from me on our apparent perversity in employing several words where the French employ only one. The frequent defeats I suffer in debate have in no way diminished my smug superiority in being part-owner of such a difficult language.

I had the misfortune last week to cut my finger and for a time flaunted a bandage. My friend was concerned: "What is the matter? Tu as mal au doigt?" "Just a cut: not very sore," I replied. His expression changed from sympathy to suspicion. "In French," he remarked firmly, "we use only one word 'mal,' we say 'mal de tête,' 'mal d'estomac,' 'mal au doigt.' Why do you use many words such as sore, pain, ache?" "Different qualities of sensation," I explained airily. "No-one would dream of saying I have tooth pain, always toothache. I should say that an ache is dull, rather persistent, doesn't obtrude into consciousness so much." I was disturbed by a brief memory of a molar some years ago for which this description was about as apposite as Pussy for a Bengal tiger, but I carried on. "The expression 'pain' is, on the other hand, reserved for a more severe, sharper sensation." I felt rather proud of this spontaneous explanation which my friend dutifully accepted. At least he accepted it until that unfortunate morning when my wife greeted us at breakfast with: "Goodness, my shoulder does ache. The pain kept me awake for hours."

* * *

Pigheaded? Well, perhaps I am,
But I'll no ventriculogram.
I do not care
—I may be dull—
For all that air
Inside my skull.
Gosh, how I'd like to swipe
That scientific type,
So ignorant and smug,
Who cheerfully injects,
Regardless of its side-effects,
The latest wonder drug.
Confound his knavish pricks
He'll play no monkey tricks
On me. Neither at this, or any other juncture
Will I submit to sternal,
Iliac, lumbar, or any other infernal
Puncture.
Once and for all, old cock,
You can keep your stellate ganglion block.
No matter how pained you look or how surprised
I'll not be catheterised;
Nor have you the remotest hope
Of passing that sigmoidoscope.
Lastly, I will grant you a biopsy
Neither of skin nor gland.
And kindly understand
I here and now refuse autopsy.

* * *

Religion has gained another victory over Science in our family. On Sunday evening I was told, with the assurance of the young: "You know, mummy, you were wrong when you told us about babies growing in tummies. Really God makes them out of dust."

* * *

Under the present set-up medical officers of health seem to be looked upon as survivals who have outlived their time. More popular in the public, as well as the Ministerial, view are those rare fellows—Physicians, Pathologists, Pædiatricians, Psychiatrists—in fact, anyone whose designation begins with the magical letter P. I realise, of course, that we medical officers of health have the D.P.H., but the P, sandwiched away in a qualification, has lost its power, and until we have got a new name we shall never attain any respect from our medical colleagues, our employing authorities, or the public. P must come into this; P is absolutely essential; P is the transformer: P is the touchstone—without which public regard can never come to us. And I think the way is easy and the outcome bright. Let us only make more astute use of our training and experience as experts in hygiene. As specialists in Psanitary Pscience we shall surely deserve well of our P-loving Public.

* * *

Advertisement for rheumatism cure in the Underground: "I have only taken two bottles and after months of agony I am almost well again."

Letters to the Editor

THE R.M.B.F

SIR,—I shall be grateful if you will give space for an appeal to provide Christmas gifts for the beneficiaries of the Royal Medical Benevolent Fund.

Gifts at Christmas time have a special value and significance, for they make the recipients feel that they are not forgotten and are being given personal help and sympathy.

I hope that subscribers to the Royal Medical Benevolent Fund will spare a little more to help colleagues and their relatives who have fallen on hard times, and that members of the medical profession who do not subscribe to the Fund will do so without delay. Owing to the increased cost of living, as shown by the higher prices of food, fuel, and other necessities, the need for support is greater than ever. Donations and subscriptions should be sent to the secretary of the Royal Medical Benevolent Fund at the address given below, and marked Christmas Gifts.

Royal Medical Benevolent Fund,
1, Balliol House, Manor Fields,
Putney, London, S.W.15.

WEBB-JOHNSON
President.

BUTAZOLIDINE

SIR,—We have read with interest the comments of Dr. Dudley Hart and Dr. A. M. Johnson on the toxic effects of butazolidine (Sept. 20). While we are in agreement with their note of caution about the use of any new drug, we feel that they have been singularly unfortunate in their experiences.

We hope to publish shortly our further observations on butazolidine therapy, but we can mention now that in over 280 cases we have been impressed by the lack of toxic side-effects.

Since using enteric-coated pills we have noticed no gastro-intestinal upset of any kind.

Three patients have developed rashes. Two of these were shown to be due to causes other than butazolidine (in one case an enema and in the other phenobarbitone). Further doses of butazolidine in these two cases produced no eruption. The third patient, definitely sensitive to butazolidine, was also sensitive to a number of other drugs—e.g., morphine, codeine, and iodoform.

Two cases of œdema of the ankles have been seen: one cleared up completely although the drug was continued; the other promptly subsided when the butazolidine was withdrawn.

Two patients have shown transient slight albuminuria which disappeared spontaneously, although the drug was not stopped.

We now use small maintenance doses instead of continued full dosage, and this may be of importance in the avoidance of side-effects.

Glasgow Royal Infirmary.

R. A. PEEBLES BROWN
J. P. CURRIE.

SIR,—We have used butazolidine in 50 cases of rheumatoid arthritis, with symptomatic relief of varying degree in all but 2 patients; 2 other patients relapsed to their former state after a few days though they were still receiving the drug. Despite its efficacy, the toxic effects of butazolidine have been so frequent, and in 2 cases so severe, that we no longer regard its routine use as justifiable. Complications included 5 cases of maculopapular eruptions, 3 of generalised œdema, and numerous instances of œdema of the feet and ankles. 2 patients, in particular, gave grounds for serious concern.

1. A patient treated with butazolidine developed a maculopapular rash followed by fever and purpura. At the height of her illness various neurological disturbances appeared, including paralysis of the left leg with an extensor plantar response, and incontinence, from which she has made only a slow, and so far incomplete, recovery. These features were regarded as the outcome of a hæmorrhagic myelitis.

2. Another woman developed dryness of the mouth, with enlargement of the parotid and submandibular salivary glands, and was found to have complete agranulocytosis.

In the second case urgent admission to hospital was necessary for blood-transfusion and chemotherapy, and in both these patients the ultimate outcome is still uncertain at the time of writing.

Most of our patients have been given butazolidine in a dosage of 400 mg. per 24 hours; a few have had 800 mg., but none have had more than this. Toxic effects have occurred at both dosage levels. If our cases are grouped with those recently reported by others, it is seen that these complications may be expected in about a fifth of all cases treated, and they include, in addition to the examples already mentioned, gastritis, melæna, and hæmatemesis. It is to be feared that some such disasters are inevitable if this drug is used enthusiastically and extensively without the strictest control.

Brook General Hospital,
London, S.E.18.

GEOFFREY E. LOXTON
DAVID LE VAY
PETER WILSON.

SUCCINYLCHOLINE

SIR,—Recent letters in your columns have dealt with prolonged apnœa after the administration of succinylcholine, and they seem to contradict our assertion[1] that the pseudocholinesterase level of the serum determines the extent and duration of response to the drug. One of them [2] has already been answered,[3] and it was pointed out that, even with a normal pseudocholinesterase level, neostigmine will prolong the response to succinylcholine because it inhibits the enzyme.

Dr. Durrans's careful observations on thiopentone (Sept. 13) are of considerable interest, but we cannot accept his implication that thiopentone and hyperventilation are the real causes of prolonged apnœa after succinylcholine. In collaboration with Mr. L. W. Hall, B.SC., M.R.C.V.S., of the Royal Veterinary College, we have established that raising the pseudocholinesterase levels of the plasma of animals under treatment shortens the duration of apnœa after succinylcholine.

Further, one of us (P. W. S. G.) was given 10 mg. of succinylcholine chloride intravenously without previous thiopentone or any premedication. He was thus able to assess consciously its effects. The depolarising reaction in this instance was most unpleasant; there were spasms of muscle groups, arching of the spine, inability to lift the head, spasm of the pharyngeal constrictors, and an apnœa lasting 40 seconds. The pseudocholinesterase level of the serum was 82 units (the level is defined as 1 unit when 1 ml. of serum liberates 1 µl. of CO_2 per minute from an acetylcholine-bicarbonate buffer solution). We then raised his pseudocholinesterase level to 122 units by intravenous administration, and 10 mg. of succinylcholine chloride was again injected without thiopentone or premedication. This time there was virtually no depolarisation, and it was possible to raise the head, lift the eyelids, and breathe freely. The only subjective experience was a transitory sense of heaviness. We feel that these observations confirm our findings that the response to succinylcholine depends on the level of [illegible] in the plasma.

Dr. Reid and [illegible] 27) measured whole blood cholinesterases in five patients who had responded to succinylcholine with an apnœa of only 5 minutes; the values varied from 113 to 125 "cholinesterase numbers," determined by the method of Aldridge and Davies.[4] In two patients in whom apnœa lasted for

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1. Evans, F. T., Gray, P. W. S., Lehmann, H., Silk, E. *Lancet*, 1952, i, 1229.
2. Mackay, M. L. *Ibid*, July 19, 1952, p. 145.
3. Lehmann, H. *Ibid*, July 26, 1952, p. 199.
4. Aldridge, W. N., Davies, D. R. *Brit. med. J.* 1952, i, 915.

5 minutes the values were 91 and 94 respectively the normal range is 80 to 129). Thus they found only n insignificant difference in enzyme levels. We suggest hat the failure to obtain bigger differences was due o the fact that they measured the cholinesterase activity f the whole blood. The determination of whole-blood holinesterases was designed to discover early stages of nsecticide poisoning. The relevant insecticides lower he activity of both the pseudocholinesterase of the plasma and the true acetylcholinesterase of the red cells. The conditions encountered in clinical practice, he chief of which is liver disease, affect the pseudocholinesterase of the plasma only, and the true acetylcholinesterase in the red cells remains unaffected. Thus the measurement of whole-blood cholinesterases is as unsuitable in this instance as a determination of whole-blood potassium for the measurement of changes in the plasma-potassium concentration. In our cases, to which several more have been added since the publication of our paper, the true acetylcholinesterase was normal throughout, but the pseudocholinesterase of the serum was materially lowered—a fact which would not have been obvious had we performed our estimations on whole blood.

We feel therefore that there is no reason for altering the view that the response to succinylcholine is dependent on the level of pseudocholinesterase in the plasma.

F. T. EVANS
P. W. S. GRAY
H. LEHMANN
E. SILK.

St. Bartholomew's Hospital,
London, E.C.1.

INTERNAL MEDICINE AND INTERNIST

SIR,—The very successful second International Congress of Internal Medicine (the Congress of Internists) lately held in London has raised the question of the significance of the terms "internal medicine" and "internist"—terms in general use on the Continent and in America, but less familiar in this country where they are regrettably confused with the designations "general medicine" and "general physician."

In fact, during these recent years internal medicine has developed as a specialty in its own right, its development being based on the new physiological knowledge of the functions of regulation and integration of the living being. This development is also due to a reaction against the intensive analytical spirit fostered by other specialties, a spirit not always conducive to effective treatment.

As Sir Russell Brain, president of the congress, has said, the various specialists today consider the whole man by departing from their special angle, whereas the internist first considers the whole man and proceeds later to the detailed examination of special parts. Actually the procedure of internal medicine—as applied by the typical Continental professor of clinical medicine—is more complex, because we cannot know the whole without knowing the parts, and we cannot know the parts without knowing the whole. The internist, using intuitive artistic powers, at first obtains a conception of the patient as a whole. He then proceeds to a detailed examination of the parts, using the precise rational scientific method. In the course of this analytical exploration some facts emerge which modify the conception of the whole patient, and this initiates further researches, and so on, until the precise conception of the whole individual patient is reached. The internist, in fact, passes dialectically—to use the term applied by Plato to the supreme method of knowledge—from the whole to the parts and from the parts to the whole, with the object of a superior synthesis, which is the real diagnosis.

It is obvious that in his detailed exploration of parts the internist may need the help of other specialists, in the same way as other specialists, including surgeons, may need the help of the comprehensive intellect of the internist. The difficult problems of medical practice can only be approached through team-work. A sharp division between medical specialists is impossible. There are specialists—for example, neurologists and cardiologists—who more and more adopt the internist point of view, and there are internists who lean in their studies towards a special aspect, particularly that relating to metabolism, endocrinology, and psychosomatics. At all events, the rise of the internist is an interesting factor in our stirring intellectual times.

London, W.1.
A. P. CAWADIAS.

RENAL FUNCTION

SIR,—Your annotation of Sept. 6 on Diurnal Excretory Rhythm deals with a physiological phenomenon which cannot be explained in terms of the biochemical concepts generally accepted today. Previously I have argued strongly against the current biochemical interpretation of anuria, and I believe that current explanations of renal function may prove equally unreliable.

As evidence of the postulated mechanism of sodium transport, too much significance has been attached to the recovery of a hypotonic urine (on only two occasions definitely, I believe) from the proximal tubule by the method of microdissection (Walker et al.[1]). Platt[2] has recently thrown doubt on the figure of an 80% obligatory reabsorption of water and electrolyte from the proximal tubule; and the independent observations of his team,[3] of Brodsky and Rapoport,[4] and of Wirz, strongly suggest that a mechanism exists by which water, electrolyte, and possibly other dissolved substances are secreted into the distal tubule. We can in fact no longer follow complacently the prevailing school of thought on the function of the proximal and distal tubules. This school emphasises tubular function, under hormonal control, as dominant in urine production, and tacitly assumes the paramount importance of the suprarenal and pituitary—to the exclusion of the glomerular mechanism in this connection. But two facts militate strongly againt this view. The first is that glomerular filtration can be shown, in certain circumstances, to play the leading part in urine formation.

In support of this I would cite Bykov's[5] experiments on his conditioned dogs subsequently hypophysectomised, in which reduction in urine volume could have been caused by diminution in glomerular filtration-rate alone.

Lauson,[6] by injection of albumin into a nephrotic patient caused a rise of water and salt excretion—too immediate a rise to be ascribed to any cause other than the increase in glomerular filtration-rate which accompanied it.

Shannon[7] has shown that, in the dog with diabetes insipidus, dehydration reduces the glomerular filtration-rate and with it the amount of water excreted.

Secondly, the hypothesis of maximal tubular transport has been seriously challenged. For example, Black, Platt, and Stanbury[8] have shown that hyperventilation, or previous low-sodium diets, effects sodium excretion in a way which is incompatible with the postulated tubular maximum.

The shortcomings of the prevailing ideas are evident, as I have said, when we try to explain the diurnal rhythm, wherein the change from lying down to standing up provokes a 10% reduction in the glomerular filtration-rate but withal a 70% drop in salt and water excretion. As the rhythm, in health, affects the output of both water and sodium chloride, it must, *if hormonal,* reflect suprarenal function alone. But Professor Borst[9] has produced unchallengeable evidence that, without variation in the glomerular filtration-rate, this rhythm occurs also in Addison's disease, where suprarenal function is in abeyance. Hence it cannot be a hormone effect.

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[1] Walker, A. M., Bott, P. A., Oliver, J., MacDowell, M. C. *Amer. J. Physiol.* 1941, 134, 580.

[2] Platt, R. *Brit. med. J.* 1952, i, 1313, 1372.

[3] Platt, R. *Ibid*, reference to work to be published with Roscoe.

[4] Brodsky, W. A., Rapoport, S. *J. clin. Invest.* 1951, 30, 282.

[5] Bykov, K. M. The Cortex and the Internal Organs. Translated from the Russian. 1948.

[6] Lauson, H. D. Renal Function: Transactions of the Second Josiah Macy Conference. New York, 1950; p. 49.

[7] Shannon, J. A. *J. exp. Med.* 1942, 76, 371.

[8] Black, D. A. K., Platt, R., Stanbury, S. W. *Clin. Sci.* 1950, 9, 205.

The corollary of this finding is to be found in certain of Harvey L. White's[10] animal experiments. By explanting the bladder trigone he was able to get samples of urine from the two kidneys under varying conditions, and he found that a certain degree of constriction of the renal artery on one side did not reveal its presence when inulin and *p*-aminohippurate (P.A.H.) clearance determinations were made a few days later. On the other hand, the sodium and water output on that side was reduced by half. This reduction could not be ascribed to a circulating hormone, for the opposite kidney's excretion was increased by a similar amount; so we are left to conclude that the change must have been largely intrarenal and related either (1) to the renal blood-supply, (2) to the load delivered to the tubules, or (3) to some of the blood being presented for clearance to nephrons other than those in the cortex. Of these three possibilities, the last is most likely because of the inappreciable change in the filtration-rate. It has been established that stimulation of the renal pedicle experimentally will cause partial or total diversion of the intrarenal blood route. There are no experiments so far, that I know of, that have tested the possibility that juxtamedullary nephron activity is associated with cortical activity in physiological conditions of diuresis or in experiments such as this. Their collaboration may affect clearances of inulin and P.A.H. in much less degree and much later than water and electrolyte excretion.

In pathological states the Trueta or Oxford mechanism operates differently. The cortical blood-flow is diverted, in stages, to the juxtamedullary area. Clearance figures —especially if the extraction ratio of P.A.H. is integrated[11] —could support the thesis that moderate stages of the "shunt" take place in moderate hypertension, while more advanced (and acute) degrees of shunt are associated with acute glomerulonephritis and with toxæmia.

In conclusion, may I express my belief that the current conceptions of renal function, and their general acceptance, are preventing progress? They have discouraged, and are still discouraging, research into the function of a major mass of renal tissue—the juxtamedullary nephron apparatus—whose place in the renal scheme they have altogether failed to explain.

London, W.1. JOHN SOPHIAN.

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[9] Borst, J. G. G. Second International Conference of Medicine. London, 1952. Also lecture to the Renal Association, Sept. 19, 1952.

[10] White, H. L. Renal Function: Transactions of the Second Josiah Macy Conference. New York, 1950; p. 128.

[11] Sophian, G. J. *Ciba Symposium on the Circulation,* 1951 (in the press).

A CHEAP SURGEONS' CAP

SIR,—Thirty-five years ago Sir Holburt Waring insisted to his housemen, dressers, and nurses that no hair should be visible inside the theatre; cannot dandruff fall from the eyebrows? To the survivors, the fisherman's jersey bonnet described by Mr. Howkins in your last issue can appear as a mere gesture.

In the interests of economy, a grocer's paper bag would offer more complete covering.

Sherborne, Dorset. JOHN WHITTINGDALE.

THE SPRUE SYNDROME

SIR,—Your representative who reported last week (p. 624) on the discussions that took place after the main papers at the Second International Congress of Internal Medicine, is to be congratulated on being able to summarise the many facts which each speaker attempted to crowd into the five minutes allocated to him. There is, however, one error which I think I should point out. I see that I am quoted as having said that a patient with sprue who did not respond to folic acid improved rapidly when he was given penicillin injections in addition. In fact, I think it more likely that the response was to vitamin B_{12}. The case has been reported (*Brit. J. Nutrit.* 1952, 6, 320). I apologise for taking up space with this letter, but the problem of the effect of antibiotics in megaloblastic anæmia is a complex one, and I do not wish to add further to the confusion.

Department of Medicine,
University of Edinburgh. RONALD H. GIRDWOOD.

CLINICAL STUDY OF ADRENOCHROME

SIR,—Adrenochrome, the red oxidation product of adrenaline, has wide therapeutic possibilities. While in some parts of the world a good deal of work is being done on the physiology, pharmacology, and clinical applications of adrenochrome, elsewhere it has elicited little interest beyond the study of its rôle in the chemistry of melanin formation.[1] [2] Clinically its use as an oxidation catalyst to maintain the efficiency of diabetic labourers in Germany during the late war is well known.[3–5] Adrenochrome and its derivatives, such as the -monoxime, -monosemicarbazone, and -monophenyl-hydrazone, are also known to be powerful hæmostatic agents.[6–8]

The physiological properties of adrenochrome are almost the same as those of adrenaline, except that it has not the same cardiovascular action; for in hypertensive animals it is a hypotensive agent. This leads one to believe that the effects of adrenaline, apart from its sympathomimetic and hyperglycæmic actions which are immediate and short-lived, must be due to the action of the adrenochrome produced in vivo. It has even been suggested that adrenochrome is the real metabolically active material of the adrenal medulla.[9]

To gain a clearer idea of the rôle of adrenochrome as an A.C.T.H. stimulator, the urinary 17-ketosteroid excretion and urinary uric-acid/creatinine ratio were estimated in two people who received injections of adrenochrome 1 mg. once a day.

While there was a slight rise in urinary uric-acid/creatinin ratio, the rise in urinary 17-ketosteroids was neither pronounced nor constant; and in one case (V. S.) there was eve a fall of 20%. This was thought to be due to the transien nature of the A.C.T.H.-cortisone *stimulation,* the effects o which were probably nullified in the course of the next twenty four hours. Hence repeated stimulation was *tried* by givin 1·5 mg. of adrenochrome every five hours for four injections and urine was collected for twenty-four hours from the first injection. There was a definite rise, *not only* in the urinary uric-acid/creatinine ratio, but also in the total 17-ketosteroid excretion (2–3 times the normal value).

These findings, and the fact that eosinopenia and lymphopenia were produced by adrenochrome, show that it has a stimulant effect on the pituitary-adrenal axis; and it can reasonably be expected to benefit conditions where A.C.T.H. and cortisone are known to help. Unlike

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1. Beer, R. J. S., Clarke, K., Khorana, H. G., Robertson, A. *J. chem. Soc.* 1948, 2223.
2. Harley-Mason, J. *Ibid,* 1950, 1276.
3. Greiff, C., Stocklein, J. *Med. Klin.* 1943, 39, 603.
4. Greiff, C., Stocklein, J. *Chem. Zentr.* 1943, ii, 2209.
5. *J. sci. industr. Res. (India),* 1945, 4, 259.
6. Derouaux, G. *C.R. Soc. Biol., Paris,* 1939, 131, 830; *Arch. int. pharmacodyn.* 1941, 66, 202; *Ibid,* 1943, 69, 142.
7. Roskam, J. *Arch. int. pharmacodyn.* 1945, 71, 389.
8. Roskam, J., Derouaux, G., Meys, L., Swalue, L. *C.R. Soc. Biol., Paris,* 1944, 138, 875.
9. *Ann. Rev. Physiol.* 1949. p. 69.

drenaline, it does not have any undesirable cardiac ffects, and this makes it more safe for clinical trial as ' poor man's cortisone." Further work is in progress.

Madras. V. SRINIVASAN.

ANTITHYROID ACTION OF P.A.S.

SIR,—We read with interest Dr. Librach's letter of Sept. 13. In a recent paper[1] we have shown that patients treated with salicylates have much higher blood-cholesterol levels than they had before treatment, and in most cases figures similar to those obtained in hypothyroidism are reached. These changes are similar to those found in patients treated with A.C.T.H. and cortisone.[2,3] Wolfson et al.[4] thought the rise was due to the development of hypothyroidism; they demonstrated that both A.C.T.H. and cortisone lower the plasma-bound-iodine level and decrease the radioactive-iodine uptake of the thyroid. To this phenomenon they gave the name corticogenic hypothyroidism.

The clinical and pathological changes during treatment with salicylates are similar to those found during hormone therapy, and we think that the probable reason for the rise in serum-cholesterol levels is the production of a corticogenic hypothyroidism. All the instances found by Dr. Librach during treatment with *p*-aminosalicylic acid can, we think, be explained on a similar basis.

Hackney Hospital,
London, E.9.

L. BERNSTOCK
A. FREEDMAN.

CALCIFEROL IN PULMONARY TUBERCULOSIS

SIR,—Dr. Jackson (June 7) claimed to have conducted a controlled trial of combined calciferol and chemotherapy. I pointed out (July 26) that his six weeks' observation was of limited significance. He agreed (August 9) "for the sake of completeness, it would have been better had a longer course been given." Having admitted the incompleteness of his own observations, his suggestion that I produce what he claimed but failed to produce—an adequate controlled trial—is somewhat irrelevant.

Attention in pulmonary tuberculosis today is rightly centred on the major advances in the fields of chemotherapy and surgery. The basic problem of resistance to the tubercle bacillus remains, however. The purpose of my publication was to present a hypothesis, supported by suggestive clinical observations, bearing on the effect of calciferol on the cellular response of the host. Calciferol remains the only known substance without antibacterial action which accelerates the healing process of a tuberculous lesion. Its action in lupus is unquestioned, and I still claim to have produced suggestive evidence that its action on pulmonary lesions is essentially of the same kind. Its mode of action is surely a subject worthy of experimental and clinical study.

New Delhi, India. J. FIELDING.

"EUGENICS: GALTON AND AFTER"

SIR,—Your review of Sept. 13 does not, I think, do full justice to this important and extremely interesting book by Dr. C. P. Blacker. You say that it would be a mistake to regard the book as a detached and academic survey: "It is written from a personal standpoint which many do not share." In my view, it would be difficult to find a book dealing with such controversial subjects as the measurement of intelligence, birth control, and the Lysenko controversy—to mention only three—written in a more objective manner. I do not know what the personal standpoint is to which you refer, but I would suggest that when a reviewer uses such an expression in criticising a book, he should, if he is fair, indicate the nature of the bias which he believes to exist.

University of Sheffield. JOHN PEMBERTON.

FILARIASIS IN SOUTH SEA ISLANDS

SIR,—You have been so kind as to give an annotation (Sept. 20) to our recent work on filariasis in Fiji, and we are grateful for your remarks on the claims of the non-periodic Pacific variety of Wuchereria to specific rank.

You did not, however, refer to the work of Prof. J. J. C. Buckley, which forms an addendum to our report, in which he has pointed out differences in the morphological features of this Pacific filaria—for instance, the smaller size, and distinctions in the outline of the head and formation of the tail of the female (lack of terminal bulbous swelling) which differentiate the Pacific filaria from *W. bancrofti*. This, if confirmed, should form the basis of a new species—*W. pacifica*. We are emboldened in making this claim by the consideration that the adult of *W. malayi*, another distinct human filaria, which is universally accepted as a valid species, differs in only very minor, and as yet unconfirmed, details from the type species—*W. bancrofti*.

London, W.1.

PHILIP MANSON-BAHR
W. JOHN MUGGLETON.

THERMOMETERS

SIR,—I am surprised that in your annotation of Sept. 13 you condone the placing of clinical thermometers in patients' mouths. Thermometers used exclusively in the axilla do not need to be washed, and the danger of their acting as fomites is slight. Furthermore, the risk of personal injury should they break is less than in the mouth.

My custom is to leave the thermometer in the axilla for at least five and often ten minutes. No time is lost by doing this, as I insert the instrument at once on meeting the patient if it seems likely that the temperature should be taken. In infants and small children I use the groin. During nearly nine years of practice, not one patient has crushed a thermometer.

You go on to discuss the designation of the different types of clinical thermometer in relation to their speeds of registering. I agree with your remarks, but not with the suggestion by the Association of Scientific Workers that there should be only one standard clinical thermometer. May I suggest that there is not really any difficulty in designating the third ("slow") type of thermometer? As far as the purchasing public is concerned, there could be "rapid thermometers," "medium thermometers," and "thermometers."

Uarán Mór,
Gaillimh, Ireland.

SEAGHÁN UA CONCHUBHAIR.

POLIOMYELITIS AND SANITATION ON TRAINS

SIR,—The disposal of human excreta on long-distance trains by discharging it on the line is an offence to all principles of hygiene and decency; yet this system obtains everywhere, even on Pullman coaches, and we are still adjured not to use the lavatories when in a station. I was "privileged" recently to view the undercarriage of an excursion coach before cleaning—a sight even more disgusting than it was Augean. Passenger-carrying aircraft have to provide internal sewage disposal, so why not the railways?

It may be far-fetched to suggest that the present system—or lack of system—plays a part in the dissemination of poliomyelitis; but in our present state of knowledge, the only known factor, aside from personal contact, is

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1. Bach, F., Freedman, A., Bernstock, L. *Brit. med. J.* Sept. 13, 1952, p. 582.
2. Adlersberg, D., Schaefer, L., Drachman, S. R. *J. Amer. med. Ass.* 1950, 144, 909.
3. Conn, J. W., Vogel, W. C., Louis, L. H., Fajans, S. S. *J. Lab. clin. Med.* 1950, 35, 504.
4. Wolfson, W. Q., Beierwaltes, W. H., Robinson, W. D., Duff, I. F., Jones, J. R., Knorpp, C. T., Siemienski, J. S., Eya, M. Proceedings of 2nd Clinical A.C.T.H. Conference. London, 1951.

Notes and News

THE MINISTER ON THE SERVICE

SPEAKING at Taunton on Sept. 27, Mr. Iain Macleod confessed to an unusual ambition.[1] He would like to be the first Minister of Health to pass no legislation about health. There has been, he believes, too much legislation and too many instructions issued from his Ministry about the health service. "It is about time," he added "we stopped issuing paper and made the instructions work. I want to try to re-create local interest in the hospital and, above everything, to get a complete partnership between voluntary effort and the State. I want to make it fun for people to serve. I want people to work in the Health Service, from the Minister down to the hospital stoker, because they want to be of service to the poor and crippled people of this country. I have set out deliberately to earn, and then to claim, the support of all the health professions in that idea."

MEDICAL RESEARCH COUNCIL OF IRELAND

IN its report for 1950 the Medical Research Council of Ireland describes further trials of the tuberculostatic compounds, B53 and B283.[2] An immediate conversion-rate of 50% has been achieved with B283 in a small series of cases of renal tuberculosis which had failed to respond to streptomycin. The results with pulmonary tuberculosis were not so encouraging, but most of the patients treated with B283 had chronic disease which had not improved with streptomycin and *p*-aminosalicylic acid, and the merits of the drug cannot be properly assessed until it has been tried in a greater number of early acute cases. The national tuberculosis survey, undertaken by the council at the request of the minister for health, has been using its mass-radiography unit to study the incidence of the disease among people in particular occupations. The cortisone clinical subcommittee has directed work on the use of cortisone in rheumatoid arthritis, rheumatic fever, rheumatic carditis, asthma, allergy, blood dyscrasias, Addison's disease, and Simmonds's disease; and a large number of ophthalmological conditions have been treated with cortisone. Particular attention has been given to the effect of cortisone on anuria. Clinical trials of terramycin are also in progress. Some interesting work at the Rotunda Hospital suggests that unsuspected deep thrombosis may be a commoner cause of varicose veins in pregnancy than is generally believed. Some of the other subjects under investigation last year in Eire were the urinary excretion of steroids in pregnancy; the effect of artificially raising the blood-urea levels of patients with peptic ulcer; and the types of influenza virus isolated in the severe epidemic of early 1951.

THE SMOKE NUISANCE

IN his presidential address to the annual conference of the National Smoke Abatement Society, held at Portsmouth from Sept. 24 to 26, Prof. F. E. TYLECOTE, F.R.C.P., spoke of the great damage done to vegetation and property and health by sulphur gases emitted from chimneys. A yearly emission of $2^1/_2$ million tons of sulphur meant "the huge figure of £62,500,000 per annum lost in the air." Mr. E. E. WILKINS, PH.D., reviewed the work of the Fuel Research Board, including tests of a plant for recovering sulphur in the form of ammonium sulphate and elemental sulphur. The only method of recovery hitherto used on a large scale had, he said, been relatively costly because of the enormous volume of gases to be treated and because the resulting product, calcium sulphate, is in a form of no commercial value. If the outstanding technical problems could be solved, the ammonia process was likely to be considerably less expensive than existing processes.

Dr. PERCY STOCKS, whose address is mentioned in a leading article on p. 667, pointed out that the burning of domestic coal yields a cancer-producing substance, benzpyrene. "The statistical facts we have extracted so far fit in rather well with the hypothesis that atmospheric pollution by domestic smoke is an important factor in the genesis of lung cancer, and that tobacco-smoking is superimposed on it as another important factor."

Dr. J. L. BURN, M.O.H. for Salford, said that industrial chimneys were proving less troublesome as time went on, and the chief difficulty today was domestic smoke: it caused at least half the total pollution and an even higher proportion of the worst pollutants such as sulphur and the tarry products which do significant damage to health. The method of creating smokeless zones was a progressive and positive policy, adaptable and flexible to meet the varying need of different areas: "let us demand more experimental areas where the smokeless zone principle can be demonstrated in varying conditions and circumstances, where details of the advantages and difficulties can be revealed. From the experience gained, a decision may be taken as to the wisdom of expanding the zones and in what areas new zones may be established." Having referred to the existing smokeless zones in Manchester and Coventry, and to the rejection by the Minister of Housing and Local Government of Salford's own more ambitious scheme for smokeless zones, Dr. Burn concluded by saying that all concerned in this great problem will have to show more fighting spirit in order to achieve the cleaner atmosphere they desire.

Mr. W. L. MATHER remarked that coal is one of the few commodities which escape taxation, and that "a tax on raw coal would certainly make industry burn it efficiently or not at all." Dr. W. R. MARTINE, administrative M.O.H. for Birmingham, advocated some form of financial incentive for those who play their part in eliminating smoke pollution. This might be provided by a rates rebate or exemption from increased rating, or by income-tax allowance in respect of expenditure on conversion of premises to smokeless heating.

CORNEAL GRAFTING

THE Corneal Grafting Act, which received the Royal Assent in June, came into operation on Sept. 26. Anyone who wishes may now arrange for his eyes to be used after death for this purpose by making a simple signed statement or a request in the presence of two witnesses. Where no express request has been made, some hospitals associated with centres where corneal grafting is done, if they are satisfied that there is no objection on the part of the patient before his death or his relatives afterwards, may authorise the removal of the eyes. Hospitals known to be doing this work include

Moorfields, Westminster and Central Eye Hospital, London; Queen Victoria Hospital, East Grinstead, Sussex; St. Thomas' Hospital, Lond [illegible] ...ited Sheffield Hospitals; Odst [illegible] ...ord Hospitals; Royal Berkshire [illegible] Bristol Ho... pitals; United [illegible] ...m Hospitals; Birmingham an [illegible] ...hampton and Midland Counties Eye Infirmary; Coventry and Warwickshire Hospital; United Manchester Hospitals; and United Liverpool Hospitals.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS

AT the annual dinner of the college, held in London on Sept. 26, the guests were so numerous and varied that Mr IAIN MACLEOD, the Minister of Health, was hard put to it to find anything they had in common beyond the fact of birth. Speaking of the retirement from the presidential chair of Dame Hilda Lloyd—"a splendid surgeon, a magnificent president"—and the succession of Mr. A. A. Gemmell of Liverpool, he pointed out that provincial presidents of the college have so far outnumbered London presidents by 5 to 1. The college, like Parliament, could go to the country for inspiration, but with the difference that it could hope to get it. Mr. C. D. KENNEDY, who later proposed the toast of The Guests, saw them particularly (among other things) as the rare, the common, and the weeds. When he came to enumerate them, however, he left the impression that everything in the garden was rare. Dame HILDA LLOYD welcomed her successor and spoke of the successful tour of Mr. G. F. Gibberd as the first Sims-Black travelling fellow. The Princess Royal's acceptance of an honorary fellowship, she said, would further grace the college, which already has the Queen and the Queen Mother among its fellows. Miss FLORENCE HORSBRUGH and Sir RUSSELL BRAIN responded. Sir Russell remarked that the guests were very happy to be able to leave the obstetrics to their hosts, and to come to dinner knowing they would have nothing to deliver but a speech.

EUROPEAN HEALTH COMMUNITY

IT is reported[1] that the French government is to submit in October to the committee of ministers of the Council of Europe a proposal to set up a supranational health community. The general aim of the community would be to remove economic and political obstacles to the free interchange of knowledge and materials. Its particular tasks might, for instance, include community research programme; the elimination of trade barriers to the interchange of pharmaceutical raw materials; community sanatoria in the Alpine areas of France and Italy; and common action against epidemics. Common rules for vaccination would be implemented and uniform regulations made for the use of some drugs, water control, food inspection, and child care. The rôle of the proposed community would be complementary to that of the World Health Organisation. In the opinion of M. Ribeyre, the French minister of health, a community of States of comparable development, such as those of Western Europe, could be granted more authority over its members than they would yield to one encompassing the whole globe.

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[1] *Manchester Guardian*, Sept. 29, 1952.

[2] See *Lancet*, 1952, i, 499.

[1] *New York Times*, Sept. 25, 1952

BRITISH SURGEONS IN INDIA AND CEYLON

Two surgical teams recently left this country for India and Ceylon under the technical coöperation scheme of the Colombo Plan. The equipment which both teams have taken with them is also being provided as a part of Britain's contribution to the scheme.

At the request of the Government of India, Mr. Robert Roaf, F.R.C.S., lately orthopædic surgeon to Liverpool Royal Infirmary, will set up an orthopædic department at the Irwin Hospital, New Delhi, and undertake clinical teaching there. He will be assisted by two physiotherapists, and it is hoped that a prosthetic technician will join the team soon. They will spend two years in India.

Last winter Mr. Donald Barlow, F.R.C.S., surgeon to the London Chest Hospital, went to Ceylon to advise the government on the control and treatment of tuberculosis and chest diseases. One of the results of his visit was the formation of a thoracic-surgery unit at Colombo General Hospital, and a British surgical team will now carry on his work. The team is led by Mr. R. Abbey Smith, F.R.C.S.E., thoracic surgeon to the Warwick group of hospitals, and his medical colleagues are Dr. Laurence Mountford, anæsthetist at the London Chest Hospital, and Dr. J. R. Edsall, who will act as registrar. They will be accompanied by a nursing sister and a physiotherapist. The team will be in Colombo for six months.

THE SAFE HEARTH

THE idea that unguarded fires are dangerous is at last beginning to gain ground among the general population; and this means that more people will be buying guards. The pity is that they may buy quite useless guards. With this in mind, the recently formed Birmingham Burning Accidents Prevention Committee asked the makers of guards to submit to them guards of all types. The manufacturers coöperated willingly, and the committee classified the guards according to the degree of safety achieved. They have now published a thoroughly useful leaflet, "Advice on Fireguards" which clearly illustrates suitable and efficient guards for a reflector type of electric fire, a wall electric fire, a portable reflector type of gas-fire, an upright type of electric fire, and an open grate. The manufacturers will probably welcome this guidance as much as anybody else, for it must be dispiriting to turn out guards which are useless for their purpose. It would be an excellent thing if copies of this leaflet could be distributed by welfare centres and health visitors to mothers of families. The Birmingham City Council, with much public spirit, has paid the initial cost of printing, and is selling the leaflets at the low rate of 30s. for 1000 copies. Inquiries should go direct to the Town Clerk, the Town Hall, Birmingham, and should be marked "Burning Accidents Prevention Committee."

A CHIEF IN SPITE OF HIMSELF

As a title, "Father of Crocodiles" does not suggest to the Western mind many of the domestic virtues—nothing, in fact of the warmth, self-abnegation, and sincerity of the best fathers. But different folk have different views; and when certain natives of Bechuanaland, serving with the British Army, and far from home in the Lebanon, wished to honour their Greek medical officer, Dr. George Spanopoulo, by making him their chief, that is the title they gave him. In a naïve but charming little book[1] Dr. Spanopoulo tells how he first met his future subjects when he was posted to the village of Lobatzi, near Mafeking, and what delightful people he found them. He was on equally good terms with the English officers in the mess, though he thought them shy of showing their feelings—for example, when he happened to kiss one of them goodbye. His own cheerful enthusiasm, as well perhaps as what he describes disarmingly as "the excited gestures so typical of my race," must have won him many friends, and certainly gained him the devotion of his Bechuanaland patients. He describes affectionately their loyalty, honesty, and simplicity, their passion for castor-oil, and the solemnities with which they initiated him into his new rank. "From now on, Sir," the interpreter told him impressively, "you are our respectable chief so far from our native land. You will have all our respect and love." Not every doctor has such a tribute paid him.

CANADIAN SURGICAL TEXTBOOK

AT a dinner held in Montreal on Sept. 12, with Dr. Gavin Miller in the chair, copies of the first Canadian surgical textbook were on view. Edited by Dr. H. F. Moseley, assistant professor of surgery at McGill University, the *Textbook of Surgery of the Royal Victoria Hospital, Montreal*, contains contributions from many members of the staff, and the line drawings are by Miss H. McArthur of the department of medical illustrations. Copies were presented to Dr. Gavin Miller, to whom the book is dedicated, to the Principal of McGill University, and to others who had contributed to its publication. Speakers described it as a piece of teamwork animated by loyalty to Dr. Miller as head of the department of surgery at the hospital.

University of Durham

On Sept. 27 the degree of M.B. was conferred on K. S. Dawes.

Royal College of Physicians of London

Lord Moran will deliver the Harveian Oration on Oct. 17, at 3 P.M., at the college, Pall Mall East, London, S.W.1. The oration is entitled Into the Past.

Royal College of Surgeons of England

The Thomas Vicary lecture will be given by Mr. V. Zachary Cope at 5 P.M. on Oct. 30 at the college, Lincoln's Inn Fields, London, W.C.2. The subject of the lecture is William Cheselden and the Separation of the Barbers from the Surgeons.

Royal College of Obstetricians and Gynæcologists

On Sept. 27 the Princess Royal visited the college to receive the honorary fellowship. She was presented to the fellows by Prof. Andrew Claye and Miss Gertrude Dearnley and admitted by Dame Hilda Lloyd, the president. In her reply the Princess said that, though the college was still young, the value of its contribution to medical and surgical science could not be estimated. The specialist knowledge it had placed at the disposal of doctors and midwives thoughout the world enabled them to give to expectant mothers confidence and a feeling of happy security at a time when they were most needed. The careful teaching of mothercraft, too, she was sure, would show its influence by ensuring a generation of healthy, contented babies.

On Sept. 26 the following were admitted to the membership:

Lily Arratoon, Janki Devi Arora, J. L. M. Bean, Anil Chandra Bhoumik, A. D. H. Browne, G. H. Burgess, G. G. Champion, Sivaccolunthu Chinnatamby, G. R. Clare, J. F. Correy, N. K. Crooke, G. E. Cummins, A. M. Dawson, R. D. De Vere, D. T. Dodds, C. P. Douglas, Robert Dowie, Sunit Kumar Dutt, Joseph Firth, Aileen C. Foley, M. S. Forrest, W. T. Fullerton, R. L. Gadd, D. F. P. Gordon, W. J. Gordon, J. J. Handler, Alexander Hunter, Daphne M. E. Kayton, R. D. Macbeth, I. A. McDonald, Margaret W. Macgregor, T. M. McNie, A. G. Mathew, T. P. Magee, P. R. Myerscough, E. P. D. O'Neill, J. G. O'Sullivan, Marjorie M. Paterson, Alexander Persey, G. W. Prueter, Delmont Puflett, Marie Quadros, M. B. Quane, Bibhuti Bhusan Rakshit, Harry Rees, Monica M. A. Reford, C. A. Simmons, E. L. Trott, Mary E. Walker, R. A. Warren, H. B. Watson, J. A. Williams.

Dr. Earl T. Engle, director of laboratories of gynecological pathology and endocrinology, Columbia University, New York, will deliver the Anglo-American lecture for 1952 on Thursday, Oct. 9, at 5 P.M. He is to speak on Trends and Needs in Fertility Research.

Medical Society of London

This society's programme for the first half of the coming session opens at 8.30 P.M. on Oct. 13 with the presidential address by Dr. Cuthbert Dukes. He has called his address Your Good Health. Four discussions have also been arranged for 8.30 P.M. on the following dates: Perils of Blood-transfusion (Oct. 27), Acute Intestinal Obstruction (Nov. 10), Bronchitis (Nov. 24), and Results of Injury to the Pelvic Diaphragm in Women (Dec. 8).

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[1] Rabaguena, the Father of Crocodiles. Nicosia, Cyprus: Zavallis Press. 1952. Pp. 46.

International Hæmophilia Society

A meeting of this society will be held at St. Pancras Town Hall, Euston Road, London, N.W.1, at 2 P.M. on Sunday, Oct. 5.

London Marriage Guidance Council

A course of five lectures for postgraduate students will be given on Wednesdays at 6.30 P.M. at 78, Duke Street, London, W.1, starting on Oct. 29. Further details may be had from the secretary of the council at that address.

Abortion Law Reform Association

The annual meeting of the association is to be held on Wednesday, Oct. 15, at 6.30 P.M., in the Conway Hall, Red Lion Square, London, W.C.1, when there is to be a discussion on the Prospects of a Parliamentary Private Member's Bill.

Casualties Union

This union is holding its tenth annual competition at 2.30 P.M. on Oct. 5 at Finsbury Borough Council Building Site, Holford Square, London, W.C.1. The competition, which is open to first-aid teams throughout the country will involve accident situations which might occur during large-scale building operations. The address of the hon. secretary of the union is 29, Whyteleafe Hill, Whyteleafe Surrey.

Midland Medical Society

The annual meeting of this society will be held at the Birmingham Medical Institute, 154, Great Charles Street, Birmingham, on Oct. 8 at 8.15 P.M. After the meeting Mr. K. O. Parsons, the retiring president, will give his valedictory address, on the Rewards and Penalties of Partial Gastrectomy for Peptic Ulcer.

The annual dinner will be held on Oct. 22 at the Midland Hotel, New Street, Birmingham, when Sir Allen Daley will give an address on American Medicine Today.

The Professional Nurses and Midwives Conference

The Duchess of Gloucester is to open this conference which is to be held at Seymour Hall, Seymour Place, London, W.1, from Oct. 13 to 17, under the presidency of Lord Webb-Johnson. Dame Hilda Lloyd will deliver the Blackham lecture, and other medical speakers will include Mr. Patrick Clarkson, Mr. N. R. Barrett, Dr. Paul Wood, Prof. D. R. MacCalman, Dr. Wilfrid Sheldon, Mr. D. H. MacLeod, Mr. Myles Formby, and Air Marshal Sir Harold Whittingham. Further particulars may be had from the secretary, Mrs. R. J. Blackham, 1, Garden Court, The Temple, London, E.C.4.

Ministry of Health

Sir Percy Barter, C.B., the chairman of the Board of Control, retired on Sept. 30 after 42 years' service. The Minister of Health has appointed Mr. I. F. Armer, C.B., M.C., deputy secretary of the Ministry, to take over the duties of chairman in addition to his present office. The central administration of the mental health services, other than the work of the Board of Control, will in future be included in the administration of the National Health Service generally.

The Minister also announces that a new division of the Ministry is being created to deal with all questions of remuneration in the health services and with related matters, including questions of staff complements and gradings. Mr. J. P. Dodds, at present under-secretary for finance and accountant-general in the Ministry, will be the under-secretary in charge of this division. He will be succeeded by Mr. A. S. Marre as under-secretary for finance and accountant-general.

Births, Marriages, and Deaths

BIRTHS

CARTER.—On Sept. 17, to Peggy (née Hope), wife of Dr. C. O. Carter—a daughter.

DUNKERTON.—On Sept. 25, at the Louise Margaret Hospital, Aldershot, to Mary (née Cattell), wife of Lieut.-Colonel G. H. H. Dunkerton, R.A.M.C.—a daughter.

HAYWARD.—On Sept. 21, at St. Bartholomew's Hospital, London, to Mary Anna, wife of Dr. Graham Hayward—a son.

PAYNE.—On Sept. 26, at Uplands, Hythe, to Helen (née Mitchell), wife of Dr. Dudley Payne—a son.

RODERICK.—On Sept. 22, 1952, at Princess Beatrice Hospital, London, S.W.5, to Désirée, wife of Dr. John Roderick—a daughter.

THOMPSON.—On Sept. 23, at Gravesend Hospital, to Betty (née Southwood), wife of Dr. Peter Thompson—a daughter.

DEATHS

LAWRIE.—On Sept. 25, John Lawrie, M.B. Edin., 10, Eglinton Crescent, Edinburgh, formerly of Woking, Surrey.

MERRICK.—On Sept. 26, at Kingston Hospital, Horace Townsend Newman Merrick, M.B. Belf., aged 87.

STRETTON.—On Sept. 27, John Weston Stretton, B.CHIR. Camb., F.R.C.S., of Lea Grange, Kidderminster, aged 64.

Diary of the Week

OCT. 5 TO 11

Monday, 6th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5.15 P.M. Mr. Charles Gray: Lumbar Backache.
6.30 P.M. Mr. H. Osmond-Clarke: Major Dislocations.
UNIVERSITY COLLEGE, Gower Street, W.C.1
5.30 P.M. Prof. E. R. Loew (Boston): *Properties of Adr* Blocking Drugs.

Tuesday, 7th

ROYAL COLLEGE OF SURGEONS
5.15 P.M. Mr. Hedley Atkins: Innocent Tumours of Breast.
6.30 P.M. Mr. A. J. Gardham: Right-ilia-fossa Tumours.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C. Prof. J. Z. Young, F.R.S.: Influence of Language Medicine.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Stre W.C.2
5.30 P.M. Prof. W. J. Hamilton: Comparative Anatomy of Skin.
CHADWICK LECTURE
5.30 P.M. (26, Portland Place, W.1.) Dr. H. E. Magee: Fo as a Health Factor.

Wednesday, 8th

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. J. C. Anderson: Hydronephrosis.
6.15 P.M. Mr. J. C. Goligher: Sphincter-saving Resections the Treatm [illegible] e Rectum.
ROYAL SOCIETY OF [illegible] Street, W.1
4.30 P.M. *Section* [illegible] Dr. Donald Wils Spinal Osteoporosis.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. C. W. McKenny: X-ray Technique.
MIDLAND MEDICAL SOCIETY
8.15 P.M. (154, Great Charles Street, Birmingham.) Mr. K. Parsons: Rewards and Penalties of Partial Gastrecto for Peptic Ulcer.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (University of Manchester.) *Section of Patholo* Dr. R. M. Fulton: The Heart in Chronic Pulmonary Disea
UNIVERSITY OF GLASGOW
8 P.M. (Department of Ophthalmology.) Dr. F. W. Campbell Twilight Myopia.

Thursday, 9th

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 58, Quee Anne Street, W.1
5 P.M. Dr. Earl T. Engle (New York): Trends and Needs Fertility Research. (Anglo-American lecture.)
ROYAL COLLEGE OF SURGEONS
5 P.M. Prof. Everett I. Evans (Virginia): *Management of th* Severely Burned Patient.
6.15 P.M. Mr. R. S. Handley: Secondary Deposits in Mamma Carcinoma.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Prof. A. Bradford Hill, D.SC.: The Statistical Approac
ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Ophthalmology.* Dr. N. Ambache: Physiolog and Pharmacology of the Autonomic Ganglia to the Ey Dr. C. H. Smith: Ocular Actinomycosis.
LONDON HOSPITAL MEDICAL COLLEGE, Whitechapel, E.1
4.15 P.M. Prof. S. P. Bedson, F.R.S.: Twenty-five years Virus Research. (Schorstein lecture.)
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corne S.W.1
5 P.M. Dr. Denis Williams: *Neurology lecture-demonstratio*
FACULTY OF HOMŒOPATHY, Royal London Homœopathic Hospita Great Ormond Street, W.C.1
5 P.M. Dr. W. Ritchie McCrae: Electro-physical Phenomena.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Superficial Mycotic Infections.
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. L. R. Twentyman Aims and Origins in Medicine.

Friday, 10th

ROYAL COLLEGE OF SURGEONS
5.15 P.M. Mr. R. C. Brock: Surgery of Valvular Stenosis.
6.30 P.M. Mr. G. Qvist: Surgery of Tuberculosis.
ALEX SIMPSON S[illegible]
5 P.M. (The [illegible] dren, Great *Ormond Stree* W.C.1.) [illegible]: Affections of the Skeleto in Children.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Brian Russell: Pyococcal Infections.

Saturday, 11th

SOUTH EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY
11 A.M. (Preston Hall, near Maidstone.) Mr. A. T. Fripp Joint Tuberculosis.

Thirty-two social workers from all over the world are no attending a two-week course, arranged by the British Counci Twenty-two of the members are holders of United Nations fellow ships or scholarships, and six are *Fulbright* fellows from th United States. The course will introduce them to Britain's soci services before they proceed to studies on their particular subject which include probation work, marriage guidance, reablement, an *public health.*

P.P.S.

PNEUMA, PSYCHE, AND SOMA *

GEORGE DAY
M.D. Camb.
PHYSICIAN, MUNDESLEY SANATORIUM, NORFOLK

HE problem as to why people get ill is only equalled the problem as to why people keep well. If we knew answer to either of these questions we might know w to prevent people from getting ill.

When I was a medical student, good health seemed to the normal state: you were born in good health, and u remained, so to speak, static, in that condition until nething went wrong with your works; and then you re ill. Given time, of course, your works would wear t in any case; and then you died. There was a lot of owledge as to how the works went wrong. Our teachers owed us how to locate the faulty part. This was called a liagnosis." Our textbooks devoted separate chapters sections to each organ and detailed all the different ings that could go wrong with it. For treatment, seases fell into two categories. You either went to a ysician and he would give you something, or you went a surgeon and he would take something away.

There was an intermediate, rather unsatisfactory type patient and he was sent to the electrical department for ysiotherapy. This, I felt was rather like popping a mperamental alarum clock into the oven: it was nazing how often it did the trick. All this worked cely as far as it went; but the reasons given as to why e works went wrong in the first place never seemed nvincing or conclusive.

Why did some people keep well while others got ill? nd how could one prevent the latter from getting ill?

THE CAR, THE ROAD, AND THE DRIVER

Mechanismic somatic medicine did not tell us why eople got ill, nor how they could be prevented from tting ill. Every layman is acquainted with well-ithenticated stories of presumably healthy primitive en turning their faces to the wall and dying for no scertainable organic cause, but just because a spell ad been put on them. Every general practitioner is ruck at some time or another by the way Darby will llow his Joan to the churchyard before the leaves have rned. People behave as no machine has ever behaved.

And so one grew dissatisfied with this mechanismic pproach and shifted insensibly towards the biological pproach. The organism's environment was now taken r more into account, and the concept was widened to clude both the machine and the road it was travelling. t once new light was thrown on the business of keeping ell. Good health became equated with Adjustment to nvironment. Failure to adjust spelled disease. The aintenance of good health ceased to be a dull static ondition and became an exciting dynamic process—as ighly skilled and as dangerous as tight-rope walking. ne was struck with admiration by the way in which one ealt with all the dangers that beset one every moment f one's life. More and more blame was thrown on the nvironment for being so adverse: especially by the acteriologists who were—and still are—discovering nore and more noxious micro-organisms to account for nore and more illnesses. But the question remained nanswered—why did one person remain well while nother got ill, granted that, as far as one could see, hey both enjoyed the same environment?

Then immunology and allergy were discovered. Some eople had more than others. The acid test was that hose who escaped illness must have the higher immunity, and vice versa. People who avoided an illness in January but succumbed to it in February showed seasonal fluctuations in their immunity; and this became linked with vitamin deficiency (which is always a safe bet), hormonic imbalance (which is coming up nicely), and other good scientific dodges. Even so, we did not seem to have got to the root of the problem.

And then came psychosomatic medicine. Now one must be very careful what one says about psychosomatic medicine, but may I try to tell you what I mean by the psychosomatic approach to medicine? You will have to forgive me for quoting myself:

> "It is easier to give a concept of the term 'psychosomatic' than actually to pin it down by a definition. My own tentative conception is that it is analogous to the term 'electromagnetic.' As you will remember well from your 1st M.B. days: in an electromagnetic system it is impossible to alter the flow of electricity without altering the magnetic field. Conversely any variation in the magnetic field is at once reflected in the electrical potential. The two are as inseparable as the heads and tails on a coin, being merely different observable aspects of the same phenomenon. In the same way every alteration in the psyche affects the soma, and vice versa, because (and this is the important and difficult thing to grasp) they are different but interdependent aspects of the same thing: a living individual."

I wrote that five years ago in response to a challenge to define the term, and in the hope that it would be knocked down, and something better and more intelligible reared in its place. But my Aunt Sally still grins back at me unscathed, so I must stick to her.

I will not attempt to define soma, the body, except to remind you that it is alive and so must not be confused with the things you once dissected; and that it manages to keep alive by diligently performing all sorts of complicated chemical processes which are outside our knowledge and control. Indeed it seems so determined to keep alive, so cunning at overcoming obstacles against its survival, so clever at repairing itself when damaged, and so ruthless when reproducing its kind, that it may well have a mind of its own, of which we are quite oblivious. At least it must be granted Schopenhauer's will-to-live.

The psyche, I would diffidently remind you, embraces more than the conscious mental processes: those processes concerned with remembering and forgetting, the evaluation of facts and the arrival at decisions. It includes also the emotions: those dynamic forces which move you to action, or move you to laughter or tears. Sometimes these emotions pop up quite uninvited into the field of consciousness, but more often they remain the back-room-boys—or rather the boilerhouse-boys of the psyche. Often too they seem to derive their force and direction from the somatic "will-to-live."

In my definition of "psychosomatic" I went on to say:

> "The phrase psychosomatic medicine suggests investigating the patient as a whole, accepting the idea that in every condition of life both psyche and soma are affected, and (in practice) treating whichever is handier. . . . There is nothing new in this. But with the advent of every new specific drug, serum, vaccine and operation, the emphasis is shifting more and more towards soma and farther from psyche. General medicine (and surgery in particular) is concerning itself increasingly with ridding a patient of the physical handicap of his illness and getting him back to work. Sometimes this is rather like performing highly skilled running repairs on the car when really it may be the driver who needs attention. Such treatment does not make the patient whole. It is no cure. Psychosomatic medicine, studying the patient as a whole, would seek to make it unnecessary for him to break down."

The concept you see, has widened still further, and our analogy now includes the machine, the road, and the driver. And of course the driver must take his share of the responsibility when things go wrong. Moreover his personality and habits are likely to predetermine the

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* From the Hunterian Oration delivered to the Hunterian Society on Feb. 25, 1952.

sort of things that are going to go wrong. The chap who drives on his brakes is going to wear out his brake-linings and his tyres. Different horrors await the fools who Never Change Down; who fail to replenish with oil and water; who drive with a load on their minds or a load on their knees, or who attenuate their contact with the reality situation with analgesic liquor. And of course it is true that, drive as carefully and as soberly as you will, no man can escape the fortuitous puncture and its possibly dire consequences.

Similarly, the psychosomatic approach suggests that *Every Man in His Humour*, be it "choler, melancholy, phlegm, or blood," is subject to the appropriate disease; for a humour

> "Doth so possess a man that it doth draw
> All his affects, his spirits, and his powers,
> In their confluctions, all to run one way."

Or in more modern parlance, certain personality types are associated with each psychosomatic affection. Thus there is the asthmatic personality type, the hyperpietic type, the mucous colitis type, the menstrual-disorder type, the arthritic type. Nowadays even our blotting-pads familiarise us with the unhappy facial characteristics of those who tend towards peptic ulceration. An element of predestiny is beginning to creep in. Free choice of ailments is becoming a mockery. And is it entirely true to say that, live he as carefully and as soberly as he will, no man can escape the fortuitous accident and its possibly dire consequences? Are accidents fortuitous, befalling the just and the unjust like rain? No. Certain individuals appear to be more accident-prone than occasion or statistical probabilities would warrant. As a class these individuals are not clumsier or more careless than their fellows. It seems as if every now and then they were assailed by a need to go and hurt themselves.

It may sound fanciful, but I believe that this is a commoner experience than is generally recognised. I fancy many of us can recollect that mood of savage disappointment which is so apt to lead to self-mutilation. When, for example, one is badgered away from the fireside to undertake some long-promised household job of carpentry—a job which in happier moments one would do with zest and no little skill—that is the time the screwdriver slips and lacerates the fingers or the hammer smashes the thumb. It is as if the body rebelled saying, "That'll larn you to try and make me do things I don't want to do." The ostentatious handkerchief wrapped round the thumb mutely relays this message to our Beloved Badgerer-in-Chief as, "Now see what you've made me do." And if only it evoked a low moan, not of sympathy or pity, but of apology and contrition, the situation we feel might be rounded off nicely. But that is conjecture: no man is in a position to say for certain.

GRODDECK'S APPROACH

At this point it is timely to turn to Groddeck and his philosophy. For Groddeck was the father, or perhaps the grandfather, or at any rate the Jolly Uncle, of the modern psychosomatic approach. At the beginning of this century Georg Groddeck, himself a doctor's son, was a physician practising at Baden, who only undertook chronic cases of which his colleagues had despaired. These he treated with bed rest, lots of water inside and out, and strenuous personally conducted massage. During the massage sessions his patients relaxed and talked freely about themselves; and Groddeck listened. It was only after he had cured many incurables and won considerable fame that he discovered that the massage part was not really necessary, except as a means to get the patient talking freely. He listened to his patients, and from what they told him in words and from their response to his ministrations he evolved a psychology similar to that of Freud, except that Groddeck's concept embraced all illnesses, organic as well as the psychoneuroses.

Groddeck's teaching was: "Life is lived by the It." The It was, to him, an entirely unconscious part of the psyche, bursting with energy, and possessing a sort of mind of its own, an entirely irrational, amoral, and primitive mind which was apt to direct this energy to suit its own requirements regardless of consequences. Just like Harpo Marx. The reactions of Harpo are It-directed without any appreciable inhibition or control—apart from the Hayes Office. He will, for instance, chase every pretty blonde he sees, and, if possible, tear all her clothes off. This, by Groddeck's reckoning, is exactly the sort of thing our It—at any rate the male It—would like to do. But our Ego is strong enough, usually, to repress the impulse:

> "Thus conscience doth make cowards of us all....
> And enterprises of great pith and moment
> With this regard their currents turn awry
> And lose the name of action."

Instead of action we may enjoy the idea as a brief day-dream. Or we may be so strongly inhibited that even this satisfaction is denied us because the impulse is never allowed to reach our consciousness, even as an idea.

There is always a confused sort of logic shaping Harpo's activities: the logic of punning, leading, via displacement, towards symbolism. When warned that a document lacks a seal, he triumphantly deposits a live sea-lion upon it. Asked for a secret agent's record, he slaps down a gramophone disc. He dresses in the stage costumes of an operatic tenor and is perplexed and dismayed to find he is still dumb, because the tenor, when he dons these same clothes, sings and sings as if nothing could stop him.

Groddeck's It shows the same paronomasia. The stomach is the one organ which can reject what it does not like: so vomiting is seized by the It as a symbol of rejection, and is called into play whenever anything offends the It—an obnoxious smell, the sight of blood, irritating substances in or around the brain, even fertilised ova establishing themselves in the uterine mucosa. Fainting, that mock-death, is enacted when consciousness of the reality situation becomes intolerable. On an equally superficial level this histrionic symbolism shows itself again and again in conversion-hysteria. The young soldier who has accidentally shot his mate will regain consciousness with a paralysed right hand. His right hand has offended him and he has symbolically cut it off. Spasmodic torticollis is developed by the unhappy Peeping Tom, who wants to look and dare not.

Not all the It's objectives are amoral, antisocial, or destructive. Sometimes our Ego is in complete harmony with our It and then we are 100% happy and efficient. Thus do we enjoy our simpler pleasures: resting when tired, eating when hungry, drinking when thirsty (or even when not), taking violent exercise when restless. Yes, and writing love-letters or the Brandenburg Concertos, painting the *Last Judgment* or the town red, planning 40,000-ton liners or booby-traps for our sisters. For on these occasions we are successfully humbugging the It with counterfeit currency: performing acts of creation symbolising the primal creative act which is the It's deepest craving. At other times, when the It is tugging at the leash in the opposite direction, we are neither completely happy nor efficient. It is then that accidents happen to us, we hurt ourselves or develop trivial ailments. If we fail utterly to come to terms with our It, our It is apt to take charge and play merry hell with us; and it is then that we get really ill. Groddeck warns us that the It always gets what it wants, either actually or in symbolic form. Illnesses and accidents are thus to be regarded—according to Groddeck—as purposefully fulfilling the needs and desires of the It ey may thus be a means for the It to avoid unpleasant ties, to achieve irresponsibility, laziness, and regression a childlike state of dependence upon others. We can y love, attention, and importance by being ill: we arned this in our cots. Illnesses curb our activities. ey break the monotony of life. They punish us.

Patients are seldom free from deep guilt feelings though they have forgotten what they feel guilty out. Why else should they ask: "Why should this ppen to me? What have I done to deserve this?" metimes it is asked with jocular plaintiveness, but more ten it is put seriously, and they proceed to extol their mewhat negatively virtuous lives exactly like the harisee at prayer. Occasionally this recital sounds a tle tinged with regret, as much as to say: "Had I nown this was coming to me in any case, I might not ave been such a good boy."

In all organic diseases, in all accidents, Groddeck ught the same sort of symbolism as is manifest in ysteria. He was always seeking to understand the organ-jargon" of the body, and thus to discover what e It was trying to convey by its charades.

Such was Groddeck's concept. Such was the basis of is therapy. And he was a great healer—not of psychoeuroses and conversion hysterias, but of patients ffering from honest-to-God Conjoint-type organic isabilities. He asked: Why did this patient take ill hen he did? What sort of an individual was he before e took ill? How had life been treating him in the ast? How had he been treating life? What has been eading up to his illness? What has precipitated it? nd why did he take ill how he did? What purpose oes this illness serve? Of what is it symbolic? What s the It trying to tell him?

Instead of prescribing something like a physician, or ubtracting something like a surgeon, he held, as it ere, a mirror up to his patients' nature and made them ee what had previously been concealed from them. His concept, moreover, did furnish a reason, albeit a antastic reason, why people get ill; and taught a rule of ife for the avoidance of illness—namely, "Come to terms ith your It."

But we cannot go all the way with Groddeck. Sometimes we can glimpse the It at work in other people—hen their asthma, their peptic ulcer, or their migraine lay up at what seems to all onlookers to be exactly the ppropriate moment, although never, of course, to the ictim himself. But we cannot stomach the idea that we urselves are puppets, activated by anything so rresponsible, so bafflingly impish and mischievous, as the Harpo-It.

As to listening to one's own It—why, surely the next step would be frank schizophrenia?

The British concept of psychosomatic medicine, in comparison with Groddeck's, is as stolid and respectable as the *Forsyte Saga;* and I am at a loss to know why it meets with such angry or derisive resistance. Of all the many ills that flesh is heir to, Halliday has listed a mere handful—some thirty-odd—as being psychosomatic affections. These, he has shown, possess ætiological features in common: chiefly that these diseases are chronic and given to remissions and recrudescences, and that their onset, remissions, and recrudescences are often determined by emotional experiences; that a particular personality type tends to be associated with each particular disorder; and—his greatest contribution—that the incidence-rate of these diseases in a community is affected by changes in the community's psychosocial setting.

In practice what it boils down to is the investigation of the patient's personality type and his history of precipitating emotional traumata. And most workers find that this is quite time-consuming enough.

But let us not mistake concepts for the truth. With our limited perceptions we can never apprehend the truth about anything. Sitting as we are with our backs to the light, each of us has to interpret the shadow-play on the wall and the echoes of the cosmos according to his experience. Each of us has to select from the cosmic Rorschach blot those details which seem significant, and which allow themselves to be organised into an intelligible system.

The simple concept of a half-crown as an embossed disc of silvery metal is easy to grasp and handle. When it turns into a dust storm of atoms with vast interstellar spaces, or a dance of protons, neutrons, and electrons, or a phenomenon of ineffable wave motion, it becomes unwieldy. We cannot grasp it in the same way. We do not want to grasp it in the same way because it has somehow ceased to be a half-crown, although it may be nearer the truth.

Of necessity we must be prepared to deal with concepts of varying complexity and as mutually contradictory as those of energised particles and wave motion appear to be. Naturally enough we select the simplest that satisfies our immediate needs. In medicine the mechanismic approach suffices when feeding the myxœdematous with thyroid or when whipping out the angry appendix; the biological approach is desirable when dealing with an epidemic of paratyphoid fever; and the psychosomatic approach justifies its vast time expenditure in those chronic diseases whose course is so often influenced by emotional factors.

THE TUBERCULOUS PERSONALITY

When we examine pulmonary tuberculosis in the light of psychosomatic medicine what do we find? Halliday does not recognise it as a psychosomatic affection, and it certainly does not fulfil his sevenfold criteria. Emotional traumata within the 18–24 months preceding the onset of the disease is to be found in many patients. But in enough to make it statistically significant? It is impossible to say. The disease, too, is phasic—it can play cat and mouse with its victim. The course of the illness is definitely affected by changes in the inner emotional environment. But what about the particularity of the personality type?

About four years ago I was determined to find out. By means of the Rorschach projection test administered to 400 consecutive patients admitted to the sanatorium, I tried to ascertain what peculiar personality traits, if any, these tuberculous patients might show in common. At the same time Wittkower was trying to do much the same thing with other groups of patients along different lines. I am sure he would forgive me if I state quite baldly that we both failed to arrive at any conclusions. Tuberculosis did not appear to be the prerogative or predilection of any specific personality type as revealed by psychological testing.

More recently I have set to work from the opposite direction. There were, I reflected, among my friends and acquaintances those who could not conceivably develop tuberculosis—or, if they did, could not possibly die of the disease or allow it to become chronic. They would make a good recovery, and the whole business would merely have been an episode—a few months' stepping aside from the hurly-burly—in their normal span of life. I compared notes with physicians at other sanatoria and found them in agreement with me. So we made lists of these immunes and it became an intensely interesting study, especially when we widened the field to include well-known characters in fact or fiction.

The real giants—the Beethovens, Shakespeares, da Vincis, Ghandis, Schweitzers of this world—are obviously immunes. Of other familiar characters we agreed that Hamlet might have developed tuberculosis—probably the long-drawn-out five-act variety; but not Fortinbras. Richard II yes, Bolingbroke, no. Falstaff in his prime, emphatically no: after his fall—well, possibly. Most of

Dickens's heroes and all his heroines might have fallen into an interesting decline, but most of his comic characters were immunes. Even durance in the Fleet could bring no harm to Mr. Pickwick and Sam Weller, but Mr. Jingle and Job Trotter I feel had a very narrow squeak. Aunt Betsy Trotwood, Mr. F's Aunt, Elizabeth Bennet, Mrs. Proudie, Lady Bracknell, Uncle Toby were all 100% immunes. They might get chills, rheumatism, gout—but not pulmonary tuberculosis. Most of the nice engaging failures in Barrie's plays could have had more than a touch of phthisis, but none of his horrid pitiable successful tycoons could possibly qualify.

Let me go to the other extreme and give you an account of one Tompkinson, a real patient with a borrowed name.

Tompkinson was a farm labourer, but his heart was not in the job. He was left a little money and bought a dreary little haberdashery shop with it, and got married. The shop failed and Tompkinson developed pulmonary tuberculosis. His more successful brother came to his aid, and Tompkinson came under our care. He was not—physically speaking—a very advanced case. He was not ill-nourished: his wife had looked after him well. He was not burning with resentment or frustration, for he seemed to accept his life-long failure quite unemotionally—almost apathetically—as the sort of thing that should be expected to happen to him. With P.A.S. and streptomycin—those therapeutic big brothers—fighting his battles for him his downhill course was delayed; but it was evident from the day of his admission that he could never recover. This death sentence could not be substantiated by his X-ray appearances, sedimentation-rate, [illegible] or assessable data. Not even [illegible]-hand, could the final outcome be so definitely foretold; for we know of those who can pick themselves up from the deepest slough and fight their way out of the toughest spot. One look at the man, a bare five minutes in his company, were as conclusive as a blown fuse.

For my part I found him a most awkward customer. I failed utterly to develop any sort of rapport with him. Now it was clear that he did not know me one-tenth well enough to dislike me with any conviction, so I assumed—quite rightly I later learned from his wife—that he was identifying me with his elder brother, whose bounty had got him under treatment earlier than would otherwise have been possible. Poor Tompkinson had never learned to accept charity. He hated being under any obligation and he hated his benefactors. He also had a sad, forgiving smile which I found intensely irritating. In short, we were not cut out for each other. Post—and, I hasten to add, not propter—hoc, his condition deteriorated patently, he packed up and went home, and died a few months later.

What can it be, I ask, that my immunes have in common, which some others have not got enough of, and in which friend Tompkinson was so sadly lacking? Vitality? Courage? Plenty of tuberculous patients have them in abundance. Indomitability? Steadfastness of purpose? We are getting warmer. I suggest that it is Pneuma, the neglected third party in the Greek triad. Pneuma, the spirit of life which is indomitable, which through faith urges towards a goal not impossible of attainment, and so is triumphant. My immunes, like Prince Hal, were "as full of spirit as a May morning."

It used to be said that tuberculosis was caused by frustration. But that cock will not fight. Tuberculosis is on the decline; frustration, I am told on all hands, is increasing. Frustration can no more cause the disease than can the ubiquitous tubercle bacillus. They can only cause the disease when on one plane the spirit is not strong enough to rise above the frustration, and on another when the body's resistance is not great enough to overcome the invader. This spirit of life must surely inspire every cell in the body: like an allergy. As Dr. Alfred Torrie, paraphrasing St. Paul, has put it: "The body is the temple of the Spirit. The mind is its channel."

There must be a goal and the goal must be possible of attainment. Let me give a thumbnail sketch of a case to illustrate this point.

A young girl, an economics student at a provincial university, developed tuberculosis. She came of an academically brilliant family: father one of the important back-room advisers to the country; elder brother and sister both easy double firsts. The cause of the young girl's breakdown was alleged to be overwork. It was quite true: she had been overworking. But with complete rest, pneumothorax treatment, and antibiotics she did not make the expected progress. Weeks and months went by. She seemed eager to get back to the university, but her return did not seem to get any nearer. Then she divulged that she had found it excessively difficult to keep up with those whom she regarded as her peers. So she was subjected to a battery of intelligence tests, and these showed what she had suspected but had always refused to face. She had not a first-class intelligence; she was a sound second-class, but she had not got the equipment to compete with the rest of the family. This came as a great relief, and her recovery dated from this reorientation. On discharge she took up shorthand and typing, and was gold medallist for the year. She then got a good responsible job in a municipal office. In her spare time she amuses herself with free-lance journalism. Her original goal was impossible of attainment—and her spirit failed her.

There is a case on record where a life was threatened with a railway share, but who has ever before heard of one being saved by an intelligence test?

It is surely failure of the Pneuma which causes the spellbound native to be literally scared to death. On losing his life-partner Darby loses heart and dies. Falstaff, after his renunciation, becomes discouraged and gives up the ghost.

PNEUMA, PSYCHE, AND SOMA

In Greek ideology, Pneuma, the spirit, is something separate and distinct from Psyche, the mind, and this would excuse us for not discovering it in our psychological tests. . . . And so now we arrive at the concept of an indivisible triad of body, mind, and spirit—Pneuma, Psyche, and Soma, "P.P.S." This approach to medicine might, I humbly suggest, be revived after centuries of desuetude. Elsewhere I have likened body and mind to two horses in double harness, sometimes in opposition, sometimes in harmony, interdependent in that if one be lamed the other must suffer disability. Now we have installed a driver of the chariot—Pneuma, the spirit which urges the whole unit forwards, guiding it to the light. If the Pneuma fail at his job, all will soon head for disaster—or come to a standstill.

Plato had this all worked out in 434 B.C. Let me refresh your memory of the *Phaedo*:

> "Let the figure be composite—a pair of winged horses and a charioteer. The human charioteer drives his in a pair and one of them is noble and of noble breed; and the other is ignoble and of ignoble breed, and the driving of them of necessity gives a great deal of trouble to him. . . . The right hand horse is upright and cleanly made, he is a lover of honour and modesty and temperance. The left hand horse, heedless of the pricks and of the blows of the whip, plunges and runs away giving all manner of trouble to his companion and the charioteer whom he forces to approach the beloved and to remember the joys of love."

Now is not that our Harpo again? Groddeck's It! Socrates called him the Appetites. Perhaps we should call him "body mind" in our modern parlance?

It is odd how we have neglected the spirit all these years. Presumably when medicine was divorced from the Church the apothecary-surgeon seized upon the treatment of the body and the mind; while the parson was left with the cure of souls, and he was never called in to see the case until his rivals had failed. And by always being put in to bat last on a very poor wicket, his powers have naturally dwindled. Then, too, that ridiculous controversy of Science versus Religion did not help. Like any sincere argument by the tone-deaf that music did not exist; it was invalidated from the start.

But at the back of my mind I still have Tompkinson on my conscience. Even if all this high-falutin' rigmarole be true, how is it going to help him? Can the Church lp him? Well, in the first place he may not like rsons any more than some people like doctors; and en not all parsons are alike in their outlook. Some em to be abandoning the spiritual discipline for the ore exciting playing-fields of psycho-analysis. If they n combine the two without losing their bearings I am uite sure they can be great healers. I once tried to llaborate with a young padre over a patient. I said, This man looks to me like a very unhappy man who is lost his faith in everything." The young padre id, "He looks to me like a manic-depressive." I alised that we were both trying to pass the buck.

Tompkinson was lacking in Spirit? Can Spirit be nparted where it is lacking, fortified where it is weak? f course it can. In battle a wavering line of troops, in e darkest days of the war a whole nation, can be llied and inspired by the voice of a great leader. Once velve dispirited villagers slunk into a room and were ansformed into the stuff martyrs are made of.

A PLACE IN THE COMMUNITY

The basic trouble with Tompkinson was that he was n "isolate," and I feel that his only hope might lie in eing initiated into a group. It would not matter much hat the group was, be it a bench of bishops, Masonic, r even the Brick Lane branch of the United Grand unction Ebenezer Temperance Association, so long as was a group of appropriate size where his absence or ailure to participate made a difference to everyone else n the group—in fact, to the group as a whole.

While I was in general practice I was involved each winter in producing Gilbert and Sullivan operas in one village and in training a madrigal society in another village. The participants in these different groups never got ill—during the season of activity at any rate. Absenteeism from rehearsals was exceptional even in the 1929 and 1932 epidemics of influenza when I was visiting more than half the cottages in the neighbourhood. We never postponed a show. We never played an understudy—in fact we never bothered to rehearse understudies. At that time I claimed that singing was prophylactic, but I am drawn to the conclusion that any group of people happily engaged in some purposeful creative activity maintain a high average of health. As any Service medical officer can confirm, the morale of a unit can be measured by the smallness of its sick parades. Out East it was the browned-off troops who suffered from desert sores—not the crack regiments in the line, who were making history.

Have we now at last a hint as to how to prevent people from getting ill?

Every sanatorium physician can see group therapy taking place before his very eyes without any intervention on his part. The more a patient identifies himself with the sanatorium group—without surrendering his individuality—the more strength does he derive from it. The problem of indolent tuberculosis has engaged my close attention for some years—the patient who hangs fire for months and months without responding at all encouragingly to all the many treatments that are tried. The vast majority do eventually get well. There is a sort of crisis, maybe without benefit of temperature variation, a turning-point, after which the progress seems just as assured as the stagnation had been previously. After this turning-point nothing can stop them getting well, it seems. Before then it is quite certain that any importunate interference would be met with disaster. I think we all have to confess about some of our major mishaps: "I operated before the patient was ready to get well."

This turning-point, I am convinced, is often brought about by the sanatorium setting and rarely by the medical attendants. But the sanatorium group could not touch Tompkinson. He did not give it a chance. Supposing he had, of his own volition, decided to make a pilgrimage to Lourdes? That in itself would have been a miracle. The miracle of Lourdes, it must be emphasised, is not the complete cure of bodily ailments: this has only happened to 200 patients of the 68 million who have been reported on—a matter of 0·003%. The miracle of Lourdes is the change in the personality of the many who make the pilgrimage. They come back with a changed attitude towards their illness or their incapacitation—an attitude of active acceptance, with an eagerness to help others achieve the same happiness. They have triumphed over their disease. But I have a strong suspicion that this miracle begins the moment the patient decides to set out. A patient sets out to see his doctor in hope maybe, but driven by fear; a pilgrimage is an act of faith, with hope, but with no such compulsion of fear. But is this journey really necessary?

You will be asking, Does this fellow advocate yet another branch of medicine—Pneumo Psycho Somatic Medicine—with textbooks and glossy-covered monthly journals of its own, subscription 20 dollars a year; a further chair with professor on its seat; a further three-month course for the medical student with a question in the conjoint finals? I am not advocating anything. I am merely suggesting that sometimes (when we have the time) it might pay us to look at an all too familiar patient with a new approach—no, not a new approach, a very, very old approach—and ask ourselves: "What is his (or her) spiritual strength and whence is it derived? Is he a church-goer? Has he friends, real friends? Is he an integral part of any community? What is he living for?" It might also be worth while to consult with the parson about difficult, disappointing cases. Perhaps he can approach the patient individually on a religious level where we would feel a bit shamefaced and out of our depth. Perhaps he has some group-activity into which the patient might be fitted. For Mr. and Mrs. Parson between them have their Bible study classes, their discussion groups, their sewing-parties, mothers' unions, boys' clubs, girls' clubs, guilds—some such little gatherings—most days of the week; and they are thus already performing yeoman service in keeping people well and happy. If all these activities suddenly ceased, and there were nothing to take their place, our waiting-rooms would assuredly become even more crowded.

PROLONGATION OF ACTION OF HYPOTENSIVE DRUGS

USE OF POLYVINYLPYRROLIDONE AND DEXTRANS TO LENGTHEN EFFECTS OF HEXAMETHONIUM AND HEXAMETHYLENE BIS-ETHYLDIMETHYLAMMONIUM

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BESIDES reducing the number of subcutaneous injections, a method of prolonging the period of action of a hypotensive agent and lessening fluctuation of the blood-pressure would probably be advantageous in various ways. If the fall in blood-pressure lasted longer, the mechanical load on the circulatory system would be less, and more relief might be afforded to the 10% of hypertensive patients whose headaches are at present insufficiently relieved.

In about 1 in 4 or 5 patients the blood-pressure may be well controlled with hexamethonium bromide (H.M.B.) by mouth (Kilpatrick and Smirk 1952), often with a smoother and longer action than can be obtained with injections of simple aqueous solutions of H.M.B. or its homologues. In about 1 in 3 or 4 patients veratrum alkaloids by mouth can be used successfully to obtain a good control over blood-pressure (Smirk and Chapman 1952).

In most patients, however, the best control over blood-pressure has involved subcutaneous injections of simple aqueous solutions of H.M.B., usually thrice daily. With injections of simple aqueous solutions the blood-pressure unfortunately fluctuates widely, rising in the interval between injections, though seldom to the original hypertensive level. Not only is this less satisfactory from the standpoint of the patient but also, without detailed observation (involving in practice the help of trained technicians), it is difficult to adjust the dose in terms of the effect on blood-pressure.

METHODS

The following methods have been used in the Dunedin Hospital in attempts to spread out the action of H.M.B.:

(1) Adrenaline hydrochloride, or the longer-acting adrenaline mucate, has been added to the H.M.B. injection in a concentration of 1/200,000–1/100,000 to retard absorption by causing local vasoconstriction.

(2) Tablets of hexamethonium bitartrate have been administered as a supplement to subcutaneous injections to lessen the rise of blood-pressure between injections and on occasion to diminish the total number of daily injections.

(3) 16% H.M.B. for subcutaneous injection has been dissolved in 25% polyvinylpyrrolidone (P.V.P.) to retard absorption.

(4) 8% 'M. & B. 1863' (hexamethylene bis-ethyldimethylammonium bromide) has been dissolved in 25% P.V.P. for the same purpose.

(5) The absorption of each of the two solutions mentioned above has been further retarded by the addition of 1/200,000 adrenaline mucate.

(6) Doses of H.M.B. by mouth have been used as a supplement to the slow-absorption injections to prolong their actions further.

(7) 16% H.M.B. for subcutaneous injection has been dissolved in 20% aqueous solution of dextran (molecular weight 75,000) to delay absorption.

(8) 10% M. & B. 1863 or 20% H.M.B. for subcutaneous injection has been dissolved in a 20% aqueous solution of dextran (M.W. 20,000).

(9) These solutions have been used also with 1/2000 ephedrine hydrochloride added to delay the absorption further, and hexamethonium bitartrate has been administered by mouth as a supplementary dose to prolong the effect of the injection.

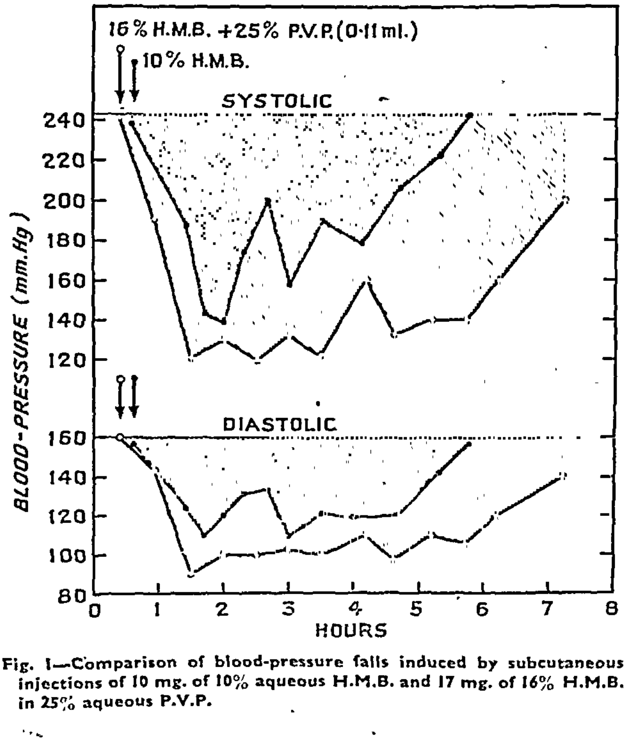

Fig. 1—Comparison of blood-pressure falls induced by subcutaneous injections of 10 mg. of 10% aqueous H.M.B. and 17 mg. of 16% H.M.B. in 25% aqueous P.V.P.

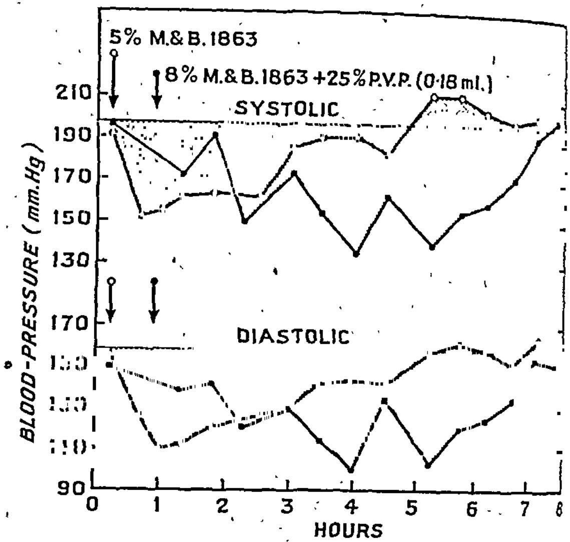

Fig. 2—Comparison of blood-pressure falls induced by subcutaneous injections of 7·5 mg. of 5% aqueous M. & B. 1863 and 15 mg. of 8% M. & B. 1863 in 25% aqueous P.V.P.

Many of the observations on which the present report is based represented, in the first place, attempts to deal with problems arising in the control of blood-pressure in individual patients. No attempt is made to describe the effects of all of the above combinations.

POLYVINYLPYRROLIDONE

P.V.P. is related to the plastics, and in the second world war solutions of it were used as a substitute for human plasma (Hecht and Weese 1943) and are said to have been given to more than 500,000 German casualties. Infusion of as much as 500–1500 ml. of a 3% solution is recommended, and up to 6000 ml. within a few days has been given in emergency. Ill effect appears to be infrequent, but the possibility of storage phenomena (Hueper 1942a and b) cannot be overlooked when large amounts are used for transfusion. There seems to be comparatively little risk, however, in using these substances to slow the absorption of injected material. The total quantity so administered in a year might be no greater than the quantity given in a single infusion of plasma substitute. P.V.P. has already been used as an agent to slow the absorption of insulin (Murat 1949). Much of the P.V.P. first produced had a molecular weight up to 200,000. The material supplied to us is described as having no molecules greater than 100,000, and less than 5% greater than 60,000. Storage phenomena are much less likely with material of lower molecular weight.

DEXTRAN

Dextran is a generic term applied to a carbohydrate polymer of high molecular weight produced by bacterial action and to lower polymers produced from it by controlled depolymerisation. The dextran available to us commercially has an average molecular weight of about 75,000. We have used 20% solutions of this dextran, and of a dextran with a molecular weight of 20,000, as vehicles for injections of H.M.B. and of M. & B. 1863 to retard the absorption of these substances. Solutions of dextran (M.W. 75,000) have been used extensively in transfusions as a substitute for human plasma (Grönwall and Ingelman 1945, Bull et al. 1949, Ricketts et al. 1950). An advantage of dextran is that any unexcreted colloid is likely to be broken down in the body. From the literature available it seems very unlikely that important toxicity will arise from the comparatively small amounts injected subcutaneously. The substance appears to be free from pyrogenicity and antigenicity (Bull et al. 1949) and storage phenomena such as those reported by Hueper (1942a and b) when pectin, polyvinyl alcohol, or methyl cellulose is used for intravenous infusion.

RESULTS

Retardation of Absorption of Hexamethonium Bromide from Subcutaneous Tissues by Adrenaline

It has been mentioned already (Smirk and Alstad 1951) that the addition of 1/200,000–1/100,000 adrenaline hydrochloride or adrenaline mucate may be used to diminish the rate of absorption of H.M.B. from subcutaneous tissue. These amounts of adrenaline are sufficient to cause local constriction of blood-vessels but insufficient to affect the heart or blood-vessels after absorption. A dose of 100 mg. of H.M.B. in 10% solution has a volume of 1 ml., and this contains 0·005–0·010 mg. of the adrenaline salt. The main effect of the admixture with adrenaline is to reduce the depth of the trough of the fall in blood-pressure which ordinarily takes place shortly after the injection. The hypotensive effect of the H.M.B. is diminished if the same dose is used, but this may be offset by an appropriate increase of dose. A typical graph has been published elsewhere (Smirk and Alstad 1951).

In some instances the addition of adrenaline leads to useful prolongation of the action and reduces the depth of the initial trough—in other words, it leads to a more uniform fall of blood-pressure. Reference is made later to the use of adrenaline and of ephedrine hydrochlorides to prolong further the action of M. & B. 1863 when the latter is dissolved in 25% P.V.P. or in 20% dextran (M.W. 20,000).

Retardation of Absorption of H.M.B. or of M. & B. 1863 from Subcutaneous Tissues by P.V.P.

When H.M.B. is dissolved in a viscid 25% solution of P.V.P., absorption is delayed; and, when the dose is increased to offset the slower absorption-rate, a more gradual and prolonged fall in the blood-pressure results. The effects of H.M.B. in simple aqueous solution and in solution with P.V.P. are compared in fig. 1. M. & B. 1863 can also be dissolved in 25% P.V.P., and its action also can be prolonged in this way (fig. 2). At first we used a 16%, but later a 20%, solution of H.M.B. in P.V.P. to limit the volume of injected material. With M. & B. 1863 initially an 8%, but later a 10%, solution was used, these solutions being about equivalent in effect to 16% and 20% H.M.B. respectively, since the M. & B. 1863 is about twice as active as the H.M.B. In a few instances we have used 20% M. & B. 1863 for patients who have required very high doses. This needs a tuberculin syringe if the volume injected is small. In general the duration of effective hypotension is increased from an average of three hours for simple aqueous solution to six to eight hours in the presence of 25% P.V.P.

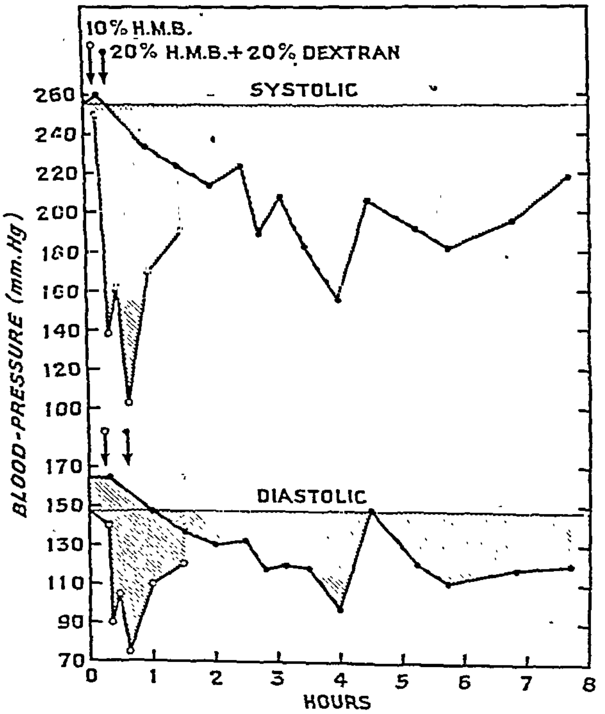

Fig. 3—Comparison of the blood-pressure falls induced by subcutaneous injections of 25 mg. of 10% aqueous H.M.B. and 20 mg. of 20% H.M.B. with 20% aqueous dextran M.W. 20,000.

In this instance the trial with H.M.B. and dextran took place earlier than the trial with aqueous H.M.B.; hence, owing to development of drug toleration, the effect per mg. is greater with the earlier than with the later dose.

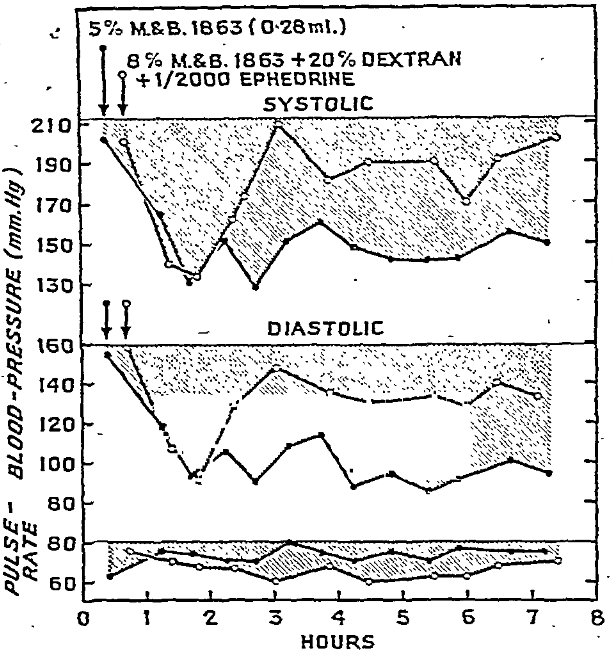

Fig. 4—Comparison of blood-pressure falls induced by subcutaneous injections of 14 mg. of 5% aqueous M. & B. 1863 and 20 mg. of 8% M. & B. 1863 with 20% aqueous dextran M.W. 20,000 and 1/2000 ephedrine hydrochloride.

Retardation of Absorption of H.M.B. from Subcutaneous Tissues by Dextran M.W. 75,000

This was studied in 32 observations on 19 patients. The initial results were confusing because sometimes the H.M.B. solutions without dextran caused a more prolonged fall of blood-pressure than did H.M.B. with 20% dextran. The explanation seems to be that, where absorption is sufficiently slowed, the concentration of H.M.B. in the blood and tissues only rises above the threshold for activity for a short time. Hence it can happen that retardation of absorption may lead to a shorter instead of a longer period of blood-pressure fall. The prolonged action in such cases is only observed when the dose injected is increased until the magnitude of the greatest fall of blood-pressure is the same as with the simple aqueous solution; then the fall of blood-pressure induced by the slowly absorbed preparation is demonstrably prolonged in almost all instances. Unfortunately, in most patients the preparation with dextran M.W. 75,000 caused tender subcutaneous lumps, and it was decided to try dextrans of lower molecular weights.

Retardation of Absorption of H.M.B. and M. & B. 1863 from Subcutaneous Tissues by Dextran M.W. 20,000

Solutions of 16% H.M.B. or of 8% M. & B. 1863 were made in a 20% aqueous solution of dextran M.W. 20,000. Subsequently we changed to 20% H.M.B. and 10% M. & B.

1863. Retardation of the absorption of these methonium salts resulted, of a degree comparable with that already observed with 25% P.V.P. or with 20% dextran M.W. 75,000 as a delaying agent. Most patients find these solutions in 20% dextran M.W. 20,000 only mildly irritant, and the addition of 0·5% chlorbutol lessens pain and serves as an antiseptic. No instances of any toxicity have been encountered, and so far no subcutaneous lumps have been discovered after injections of dextran M.W. 20,000. A comparison of the duration of hypotension after injections of simple aqueous H.M.B. solutions and after solutions in 20% dextran M.W. 20,000 are set out in figs. 3 and 4.

In general the duration of effective hypotension is extended from an average of three hours with simple aqueous solutions to five to eight hours in the presence of 20% dextran M.W. 20,000, and sometimes slightly longer if 1/2000 ephedrine hydrochloride is added (fig. 4).

Combinations of Methods for Improving Control over Blood-pressure Levels in Arterial Hypertension

A more prolonged and uniform decrease of the blood-pressure in arterial hypertension can be obtained in many cases by combinations of methods already described. Thus either H.M.B. or M. & B. 1863 with either P.V.P. or dextran M.W. 20,000 has been combined with supplementary doses of either H.M.B. or M. & B. 1863 by mouth. These supplementary doses, given as the blood-pressure starts to rise again, sometimes extend the period of activity of the methonium salts even when oral therapy alone has been unsuccessful. This is because residual amounts of the drug are present in the body after a subcutaneous injection; hence it is possible to manage with a smaller oral dose, thereby avoiding side-effects.

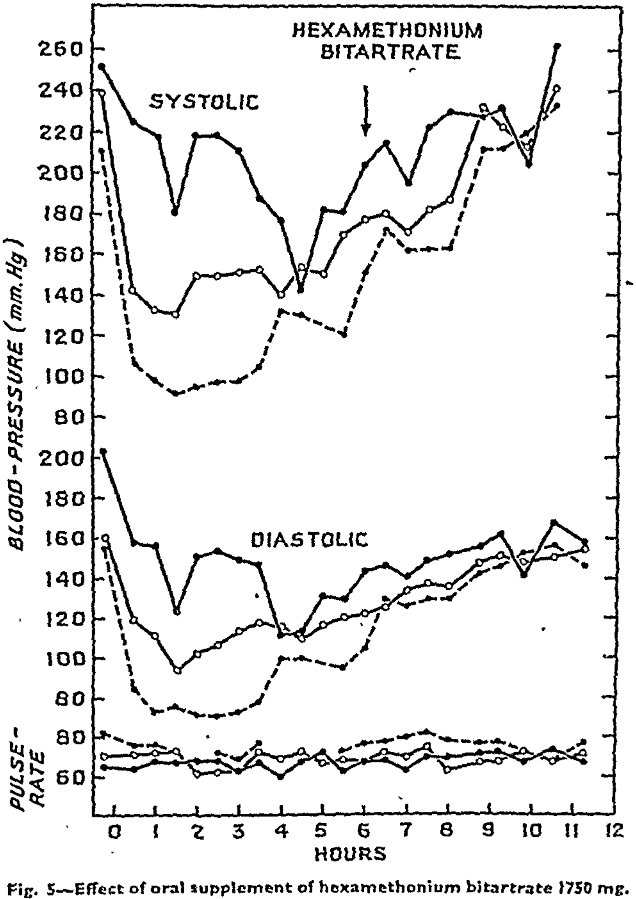

Fig. 5—Effect of oral supplement of hexamethonium bitartrate 1750 mg. to prolong further the action of an injection of 20% H.M.B. 360 mg., 20% dextran M.W. 20,000, and 1/2000 ephedrine hydrochloride. Blood-pressures were read in the following postures: --●--, standing; —○— sitting; and —●—, lying.

The duration of action of H.M.B. or of M. & B. 18 may be extended further by adding 1/2000 ephedrine hydrochloride. The H.M.B. (250–1250 mg.) or hexamethonium bitartrate (350–1750 mg.) was given orally as the blood-pressure began to rise again after the subcutaneous injection. With this combination it is usually possible to extend the fall in blood-pressure from a single subcutaneous injection over a period exceeding eight hours (fig. 5).

Such combinations usually provide a better control than can be obtained by the injection of three doses of simple aqueous H.M.B. Sometimes, however, it is preferable for the patient to accept three well-separated injections to control the blood-pressure during the day and night. The slow-absorption preparations have the advantage of greater ease of control, in so far as the blood-pressure does not vary so greatly in the course of the day, and measurement of the blood-pressure in the standing and sitting postures some two and a half hours after the subcutaneous injection will give some idea of the amount of fall of the blood-pressure provided the patient is not emotionally excited by the visit to the clinic.

DISCUSSION

It has been shown that either polyvinylpyrrolidone or dextrans of average M.W. 75,000 and 20,000 may be incorporated in a solution for subcutaneous injection to prolong the period of absorption of methonium drugs. Further prolongation may be effected by the addition also of 1/200,000–1/100,000 adrenaline hydrochloride or mucate, or of 1/2000 ephedrine hydrochloride. The duration of activity of these slow-acting compounds varies to some extent with the dose administered. With fully effective doses in which the trough of the blood-pressure fall may be only a little above 120/85 mm. in the standing posture, and sometimes 100 mm. or more below the starting blood-pressure, the duration of significant action is about five to eight hours and occasionally longer. When the absorption of an otherwise effective dose of H.M.B. is slowed by injecting it in a suitable vehicle it is necessary to increase the dose to obtain effective prolongation of action. The [illegible] dose can be [illegible] ed determined only by direct trial [illegible] Usually the dose of H.M.B. or of M. & B. 1863 must be raised by at least 30% when transfer is made from a simple aqueous to a slowly absorbed preparation.

The use of oral supplements of H.M.B. when the blood-pressure is beginning to rise again has been shown to make it possible, in some instances, to obtain as good a control over blood-pressure levels by one slow-absorption injection plus oral supplements as has been obtained previously with three subcutaneous injections of the simple aqueous solution. Though this constitutes a gain it is preferable to have two or three injections and a good measure of control than one injection and a more moderate degree of control. Convenient injection times are 8 A.M. and 6 P.M. for two injections, and at six-hour intervals for three injections. Where, however, as in some elderly patients, the treatment is largely symptomatic, the one injection may be preferred.

Polyvinylpyrrolidone is probably safe in the amount used, but a much longer trial will be needed, and initially we have been confining its use to elderly patients with very high blood-pressure and to patients where the great height of the blood-pressure between injections made us feel that any risk of toxicity is smaller than the risk from the blood-pressure rises. With P.V.P. of comparatively low molecular weight, objections may not apply. Theoretical objections to P.V.P. do not seem to apply to the use of dextrans as agents for prolonging absorption from the subcutaneous tissues. Although a dextran with a molecular weight of 75,000 causes local irritation with the formation of lumps, the dextran with a molecular weight of 20,000 seems practicable for the purpose.

SUMMARY

The duration of the hypotensive action of subcutaneous jections of hexamethonium bromide and of M. & B. 1863 ay be prolonged to five to seven hours by dissolving iese substances in 25% polyvinylpyrrolidone or in 20% extran of molecular weight 20,000.

Further prolongation may be effected by addition of local vasoconstrictor (1/2000 ephedrine hydrochloride) o the injection solution.

Even in patients whose blood-pressures cannot be well ontrolled by oral administration of hexamethonium alts, oral administration of hexamethonium bromide hen the blood-pressure is due to rise again may someimes further prolong the action of the injected salt.

When a slowly absorbed preparation is used, the dose nust be increased to provide an adequate tissue oncentration over the extended period.

My thanks are due to Miss M. Poppelwell for secretarial vork, and to Miss J. Rivers, Miss N. Hoggan, and Miss B. Stanton for technical assistance. Messrs. May & Baker Ltd. upplied the hexamethonium bromide, M. & B. 1863, and olyvinylpyrrolidone, and Messrs. Bengers Ltd. and Crookes aboratories Ltd. the dextrans. The expenses of the work vere defrayed in part by the Medical Research Council of New Zealand.

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VENOUS VELOCITY IN BEDRIDDEN MEDICAL PATIENTS

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It has been shown by Wright et al. (1951) that the velocity of venous blood-flow in the limbs of patients after surgical operations varied considerably according to their convalescent régime. In those who were allowed out of bed, with active movements, soon after the operation the venous flow-rate remained normal, or was even increased, in the following days. In those who were confined to bed, on the other hand, there was a gradual slowing of the blood flow-rate, which was apparent by the third day and persisted until the patient was once more up and walking about. These changes were observed in both upper and lower limbs but were far more pronounced in the lower.

An immediate explanation of these findings presented itself—i.e., the enforced rest was responsible for the slowing of the flow-rate in the bedridden patients—and it was with the object of investigating this hypothesis that the present study was undertaken.

METHOD AND MATERIALS

The method, using $NaCl^{24}$ as tracer, for the measurement of venous velocity in the leg was identical with that previously reported by Osborn and Wright (1949). The only deviation from the original procedure was that the patients, being examined in bed, did not have their feet immersed in water before the measurements but were all ascertained to be comfortably warm. Bed-temperatures were found all to lie between 33° and 35°C (Wright et al. 1948).

The cases for this study were carefully selected so that they fell into two distinct groups:

Group I comprised 42 men and women, aged 22–77, in whom cardiac, active respiratory, or renal disease was absent, and whose blood-pressures were normal. Their hæmodynamics could be considered normal and any recorded alterations of venous flow-rate might be directly attributed to their confinement to bed. The diagnoses of the cases in this group were as follows:

Diagnosis	*No. of cases*	*Diagnosis*	*No. of cases*
Duodenal ulcer ..	9	Carcinoma, larynx ..	1
Gastric ulcer ..	8	Carcinoma, stomach	1
Rheumatoid arthritis	6	Hodgkin's disease ..	1
Phthisis (closed) ..	5	Cerebral tumour ..	1
Diabetes	4	Rheumatic fever ..	1
Obstructive jaundice	2	Pernicious anæmia ..	1
Slipped lumbar disc	2		
		Total	42

Each patient was seen within six days of admission to hospital and weekly for three weeks or until he became ambulatory. Only those were selected who were expected to remain in bed for this period or longer.

Group II included 22 patients, aged 39–80, with hemiplegia. They obviously all presented various circulatory abnormalities and impaired hæmodynamics. They offer, however, a second method of assessing the influence of immobilisation on blood flow-rate. Each patient was seen on one occasion only, flow-rate measurements being made on both the non-paralysed and the paralysed legs. Every case therefore acted as its own control, and the comparative velocities in the two legs may be analysed irrespective of any generalised circulatory changes. The paralysed limb represents complete immobilisation, while the unaffected one was moved about voluntarily.

RESULTS

The velocity measurements obtained in the two groups show a significant difference. In group I the average flow-rates were remarkably steady throughout the period of investigation, and correspond closely to those found in normal persons under standard conditions. The day-to-day variations were also similar to those reported in normal volunteers (Wright and Osborn 1952). The results for each three-day period during the first three weeks of rest in bed are set out, with the standard errors of their means, in the accompanying table. It is apparent that the enforced rest caused no appreciable retardation of the leg venous flow-rate in these cases.

Group II, however, shows a different picture. The flow-rate in both legs has been analysed, first to determine whether the unparalysed leg shows any divergence from the normal, and secondly to detect whether the complete immobilisation due to paralysis has had any effect on the venous velocity on the affected, as compared with the unaffected, limb.

It was found that the unparalysed leg showed a slight but constant slowing of the venous flow-rate compared with the normal (4·35 cm. per sec.), a mean of 3·88 ± 0·58 cm. per sec. being obtained for the group. This figure falls near but within the lower limit of normality. In the affected leg, however, a greater retardation of venous velocity was apparent, the mean being only 1·47 ± 0·36 cm. per sec. The probability that the observed differences in the paired limbs was due to chance was found by Fisher's method to be less than 1 : 100 ($p < 0{\cdot}01$). This significant difference in venous flow-rate in the legs of hemiplegic people may be referable mainly to the state

AVERAGE RATES OF VENOUS FLOW IN BEDRIDDEN PATIENTS

No. of days of complete rest in bed	Venous flow-rate (cm. per sec.)	No. of observations
1–3	4·8 ± 0·56	18
4–6	4·3 ± 0·48	16
7–9	4·5 ± 0·52	16
10–12	4·8 ± 0·49	14
13–15	4·3 ± 0·54	9
16–18	4·7 ± 0·54	13
18 +	4·3 ± 0·48	13

of immobility, lack of muscular tone, and atrophy on the affected side.

DISCUSSION

It has generally been believed that complete rest in bed decreases the rate of venous blood-flow in the legs, and that the consequent stagnation is a potent factor in the onset of thrombosis. That venous thrombosis is of common occurrence in medical cases is beyond dispute (Burke 1938, Neumann 1938, Pilcher 1937, Westerborn 1946, Zimmerman et al. 1949), but comparatively few experiments have been made to elucidate the sequence of events which precedes their formation.

Frimann-Dahl (1935), using a phlebographic method, showed that venous flow was retarded in both the femoral and saphenous veins in normal people confined to bed. His observations were not, however, confirmed by Deitrick et al. (1948), who followed the effects of complete immobilisation in four healthy young volunteers. At the end of six or seven weeks in whole-body plaster spicas, the arm-tongue, arm-perineum, and arm-foot times, measured with 'Decholin' and 'Macasol' (Spier et al. 1936), showed no appreciable change over the pre-immobilisation figures.

The direct measurements of venous flow-rate in the legs presented in group I are in agreement with those of Deitrick et al. (1948) since no significant diminution of velocity was apparent during the first three weeks' confinement to bed.

The highest incidence of venous thrombosis and consequent fatal pulmonary embolism occurs among medical cases with circulatory defects (Barker et al. 1941, Lillie et al. 1949). It must be emphasised, however, that in the present study all such patients were carefully excluded, and that the group was composed of people who might be considered as "normal" so far as their hæmodynamics were concerned.

In the previous report (Wright et al. 1951) on patients convalescent after surgical operations we noted a gradual retardation of the flow-rate during the first fifteen days' confinement to bed. Evidently no such change takes place in the medical cases under similar conditions of rest. This may be explicable in two ways: (1) after surgical interference, pain and fear of postoperative complications cause the patient to lie exceptionally still, with respiration shallow and diaphragmatic movement minimal, with the result that the respiratory pump is less effective (such factors are absent in our medical cases); and (2) it can be seen from the list given above that the types of case included here are mainly such as benefit by rest in bed; by the end of the first week they are usually feeling better and consequently are more actively moving about (sitting-up, reaching into lockers, &c.), though still technically bedridden. A similar return to activity occurred rather later in convalescence in the surgical group.

The results in group II show that complete immobilisation apparently does have a material effect on the venous velocity in the legs. In this group the unaffected limb is usually kept comparatively still. This, together with their cardiac condition, which in itself decreases circulation-time (Blumgart and Weiss 1927, Fishberg et al. 1933, Kvale and Allen 1939, Kvale et al. 1939), explains the decreased flow-rate observed in the unparalysed leg. The still greater reduction in velocity in the paralysed leg is probably due to the failure of the massaging action of the muscles on the blood-vessels and to the lack of muscular tone (Wakim et al. 1948), and presents the most extreme degree of slowing due to immobilisation. The mean flow-rate of 1·47 cm. per sec. is considerably lower than that found at any time in non-ambulant surgical patients, whose lowest rate was 2·7 cm. per sec.

In the light of these findings it seems probable that a slowing of the venous velocity is common to cases of cardiac failure and arteriosclerosis, and to postoperative surgical patients, and that the continued high incidence of thrombosis in all these groups depends to some degree on this factor.

SUMMARY

Venous velocity was measured in the legs of 42 medical patients without cardiac complications during three weeks' confinement to bed. No significant changes were observed during the period of rest.

Venous velocity was also measured in paralysed and non-paralysed legs of 22 patients with hemiplegia. That in the non-paralysed limbs was within the limits of normality. In the paralysed limbs it was greatly reduced.

We wish to thank the physicians of University College Hospital and Lord Amulree, director of the geriatric unit, St. Pancras Hospital, for permission to examine their cases. This work was supported by a grant from the Medical Research Council.

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THE CONSERVATIVE TREATMENT OF FRACTURES OF THE SHAFT OF THE RADIUS AND ULNA IN ADULTS

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THE treatment of fractures of the radius and ulna i adults is mainly concerned with the restoration of th rotatory function of the forearm. Sound union i adequate alignment and recovery of a full range of movement at the wrist and elbow joints can, in most cases be obtained by either conservative or operative treatment. We attempt to assess the results of conservative treatment in nearly one hundred forearm fractures treated in the University department of orthopædics at the Manchester Royal Infirmary.

HISTORICAL

Before the advent of radiography the treatment of forearm fractures was based on the correction of clinical deformity, followed by the application of two short wooden splints with a firm pad to preserve the interosseous space and with the arm in the mid-prone position (Erichsen 1884). Limited rotation was often ascribed to cross-union.

Treatment with wooden splints continued to be the standard practice for many years. Plaster-of-paris, although introduced as long ago as 1852 by Mathijsen in the treatment of fractures, was not applied in forearm juries, no doubt from fear that rigid encasement of a mb might lead to ischæmic paralysis. From 1929 nwards, following the example of Böhler (1929), the laster cast, applied with due precaution, became the outine method of controlling forearm fractures.

In the early years of the 20th century, operative eduction with internal fixation was practised only by uch pioneers as Lane and Lambotte. In the hands of ess experienced surgeons the wound not uncommonly ecame infected, and the effectiveness of the fixation was sometimes impaired by electrolytic changes round he metallic plates and screws. The latter complication was eliminated by the introduction of vanadium-steel lates in 1913 (Sherman), but it was not until the nvention of the relatively inert molybdenum steel and, ter, 'Vitallium' (a cobalt-chromium alloy), that nternal fixation came to be widely used.

The routine position of the forearm during immobilisaion, which at one time had been mid-prone, was varied in ccordance with special circumstances. Thus certain urgeons argued that all fractures should be held in upination, because this movement was always difficult o restore at the conclusion of immobilisation. Magnuson 1922), on anatomical grounds, recommended that fracures above the insertion of the pronator radii teres muscle hould be held in full supination, and those at or below this evel in the mid-prone position. He also advocated the use of continuous traction with the patient recumbent nd the forearm held vertically. Patrick (1946) pointed out that, if fractures of both bones of the forearm are perfectly aligned in both anteroposterior and lateral adiological views, the degree of rotation must ipso facto be correct. In practice this corresponds to the positions dvocated by Magnuson. Patrick also considered that imitation of rotation in these fractures was due to the spread of callus, hæmorrhage, and fibrous tissue into the nterosseous space, especially from the ulnar side, leading to shortening and fixation of the interosseous membrane. Evans (1945) has introduced a radiographic technique which enables the degree of rotation of the upper fragment to be deduced and thus makes possible a more ccurate correction of rotatory deformity. He points out that merely placing the lower fragments in the correct degree of rotation in relation to the upper fragments is often enough to secure a good reduction.

Most of the modern monographs recommend closed methods of treatment; but open reduction, with or without internal fixation, is regarded as necessary where t is impossible to achieve or to maintain reduction by conservative methods (Watson-Jones 1949, Campbell 1949, Charnley 1950). Carrell (1938) estimated this to be necessary in about 15% of cases. If either of the bones does not unite, a bone-graft can be substituted for the plate. Böhler, on the other hand, claims that, by strong traction—skeletal where necessary—and direct manipulation under fluoroscopic control, closed reduction is possible in all cases, and admits of no failures. All the series of fractures of the radius and ulna treated by closed methods which have been reported, notably by Bagley (1926) and Whipple and St. John (1917), are mainly composed of fractures in children, who present an easier problem. Buxton (1939) reported on 44 cases in adults but gave no detailed results. Evans (1951) also reports on 50 cases, more than half of which are children, without separating the results in the adults from those n the children. This analysis gives 90% "good" results for conservative treatment.

MATERIAL

In many cases in the present series the immediate post-reduction position of the fractures was not fully maintained. Where secondary displacement occurred, an attempt was made to restore the original position by re-manipulation. This was unsuccessful in most cases. Many of them would now be considered suitable for operative reduction and fixation. Advocates of the operative method claim a quicker, easier, and more perfect restoration of function than is obtainable by conservative means. Our investigation of the results obtained in 92 patients treated in 1939–50 by the closed method has convinced us that, as a routine, conservative treatment has many advantages. All the patients were aged more than 21 at the time of their injury, and at least nine months—in most cases much longer—had elapsed between injury and final assessment. Particular attention was paid to the recovery of rotation and to the occurrence of complications.

Age-incidence.—The age-incidence was as follows:

	Age (yr.)						
	20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*
No. of patients ..	10	13	25	16	19	7	2

Sex-incidence.—38 were males and 54 females.

Sites of fractures.—The fractures were in the upper third of the shaft in 10 cases, in the middle third in 38 cases, in the lower third in 41 cases, and at different levels in 3 cases.

Presence of wound.—In 72 cases the injury was a closed one; in 20 cases a wound or wounds were present, sometimes with associated damage to muscle or tendon. In 1 case the tendon of the extensor pollicis muscle had been divided; the tendon was repaired, and a full recovery resulted. In another case multiple severe lacerations in the arm, with division of major vessels and nerves, led to amputation. In a third case there was laceration of the hand with loss of the thumb.

Nerve lesions.—The following nerve lesions were discovered on first examination, and before the fractures were manipulated: (1) ulnar nerve palsy in 1 case, in which the nerve recovered while the patient was under treatment; (2) paralysis of the posterior interosseous nerve in 2 cases, in both of which the nerve recovered in the course of treatment; and (3) in 1 case an associated severe lesion of the brachial plexus with complete paralysis of the arm, and in this case there was no recovery, subsequent amputation becoming necessary.

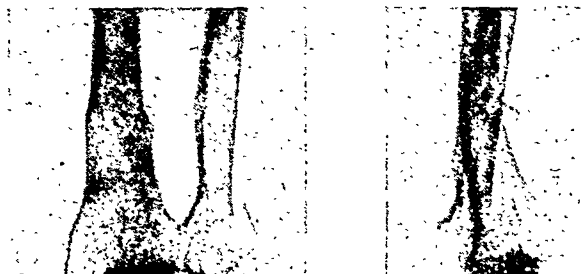


Fig. 1—Fractures of lower quarters of radius and ulna.

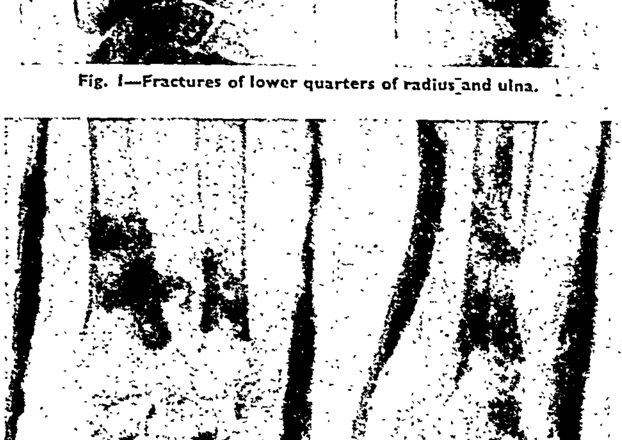


Fig. 2—Same fractures as in fig. 1 after manipulative reduction and plaster fixation.

Delayed complications.—In 1 case a very painful stiff wrist developed after immobilisation, with spotty osteoporosis of the radius, ulna, and carpus. This was regarded as an example of Sudeck's atrophy, and a good recovery ensued under conservative treatment.

TREATMENT

Reduction of the Fracture

These patients were treated by successive senior assistants in the fracture clinic, and at least ten different people have been responsible for the results. This fact seems to eliminate the personal element of technical skill as a factor in achieving the results. In compound injuries, excision and closure of the wound or wounds where necessary, followed by manipulative reduction and plaster fixation, was the routine. Assisted by a [illegible] tractor, or by gauze stuck to the fingers, strong traction was applied to overcome shortening; the ulnar fracture was usually reduced first, followed by the radial fracture. The best position was found by trial and error in different degrees of rotation until a stable position was obtained. This was done with the forearm horizontal and a webbing sling over the upper arm as a means of counter-traction, or more recently by suspending the forearm vertically. In practice the forearm was usually found to lie in full supination for the upper-third fractures, and in the mid-position for those at a lower level.

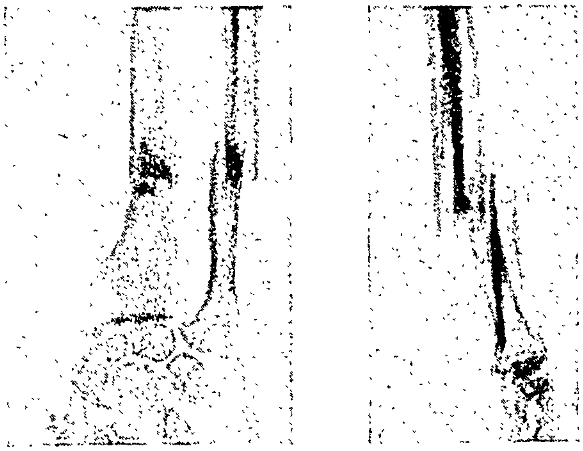


Fig. 3—Fractures of lower thirds of radius and ulna.

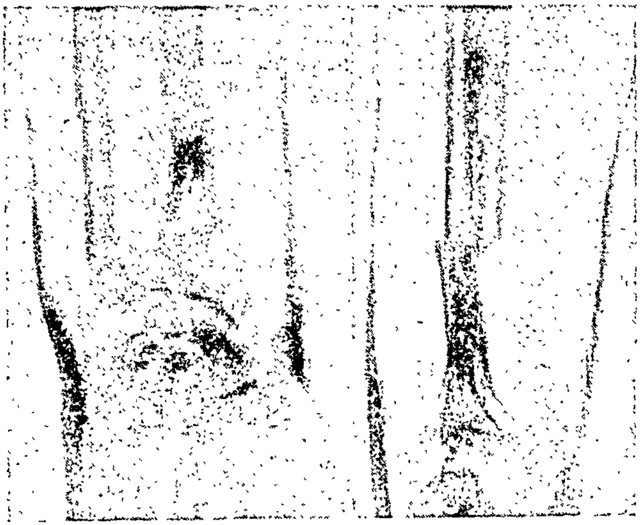


Fig. 4—Same fractures as in fig. 3 after manipulative reduction and plaster fixation.

A lightly padded, moulded plaster cast from the axilla to the knuckles was applied, and the forearm section was moulded into an oval to preserve the interosseous space, and to prevent the radius and ulna from collapsing towards each other during the subsequent immobilisation. The position of the bones was next checked by radiography. We regarded a reduction as acceptable when full length was restored, alignment in each bone was within 5° of normal, and both bones were in contact. In some of the older patients a less perfect reduction was sometimes accepted, especially where a further anaesthetic was undesirable. Plaster fixation was usually maintained with frequent X-ray checks, for 10–12 weeks, or until clinical and radiological tests confirmed that the bones had united. The arm was next supported with a sling for a further few weeks, and function was restored by physiotherapy.

In common with other workers, we found that the difficulty in many cases was not the reduction of the fractures, which was usually easily done, but the maintenance of reduction while the plaster was being applied, and the prevention of redisplacement of the fractures in the early days or weeks which follow (figs. 1 and 2).

In the present series the mean duration of fixation was 13 weeks, the longest 56 weeks, and the shortest 6 weeks. The average is raised by a few cases of delayed union or non-union immobilised for long periods. It was not found necessary to immobilise the fractures of the lower quarters of both bones for longer than 6–8 weeks.

Number of Manipulations

In 74 cases one manipulation sufficed to bring the fractures into an acceptable position; in 16 cases two manipulations were necessary; in 1 case three manipulations were necessary; and in 1 case four. It was often found that re-manipulation did little or nothing to

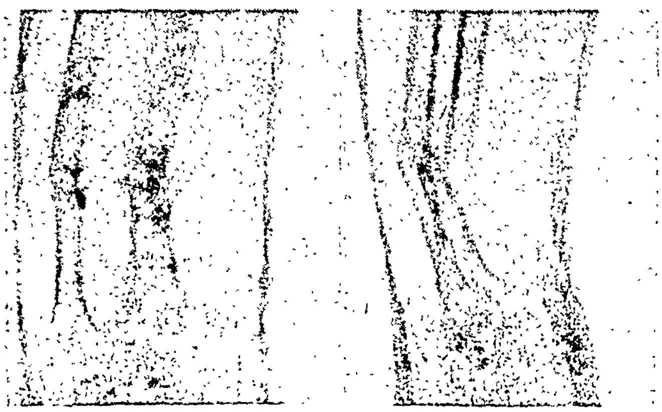


Fig. 5—Same fractures as in fig. 3. Secondary displacement occurred in plaster. This was the best position that could be achieved by re-manipulation. Radiograph taken 9 weeks after injury.

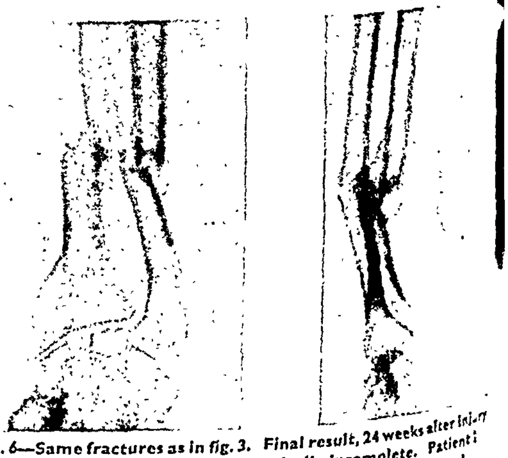
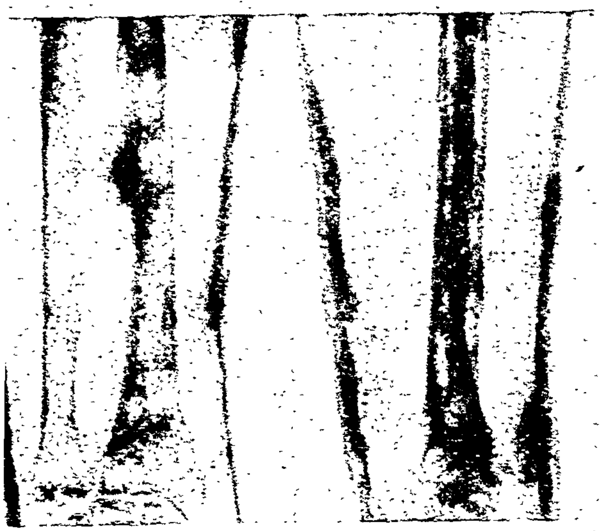
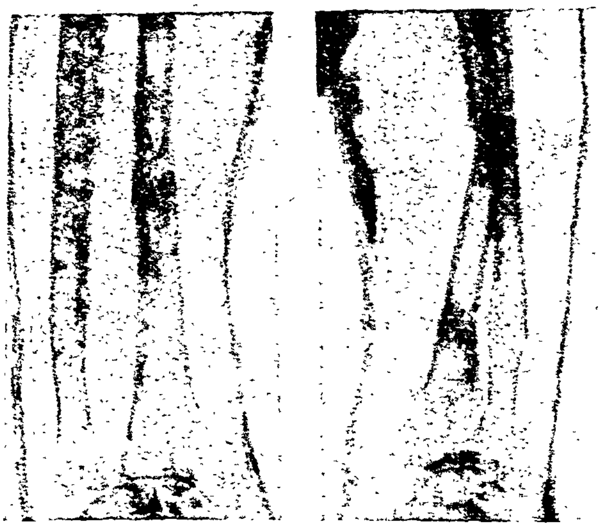


Fig. 6—Same fractures as in fig. 3. Final result, 24 weeks after injury. Union clinically firm but radiologically incomplete. Patient [illegible] full pronation, but no supination. Operation was refused.



g. 7—Fractures of mid-shaft of radius and ulna after reduction and plaster fixation.



ig. 8—Same fractures as in fig. 7, showing secondary displacement in plaster after two weeks. This was not corrected by re-manipulation. Patient regained a full range of rotation.

improve a position which had originally been acceptable but had subsequently slipped during plaster immobilisation (figs. 3–6). In 14 cases there was radiographic evidence that displacement occurred in the plaster after reduction and was not corrected by further manipulation (figs. 7 and 8). Of these 14 patients 10 regained either full rotation or minimal limitation of a third or less of supination or pronation. Displacement may have taken place in more cases, but it was impossible to verify this point. These observations do not apply to cases where the first manipulation did not produce an acceptable position and re-manipulation to correct this was undertaken immediately.

RESULTS

All the cases have been included except the 2 requiring amputation. Those which developed delayed union, non-union requiring operation, and mal-union necessitating resection of the lower end of the ulna to restore rotation, have also been included, and have been classified as poor results of conservative treatment, in spite of the fact that after appropriate reconstructive treatment the final result in these cases was good. This leaves 90 cases for analysis.

Union

Sound bony union took place in 80 cases. There were 4 cases of non-union treated by bone-graft operations usually within a year of the original injury (figs. 9–12). There was delayed union in 4 cases, in all of which prolonged fixation led to sound bony union with satisfactory results. Mal-union was observed in 2 cases in which there was subluxation of the inferior radio-ulnar joint with severe loss of rotation.

Anatomical Results

These have been subdivided into good, moderate, and poor. Cases with little or no bowing at the fracture site are classified as good. A noticeable but not a gross bow has been classified as a moderate result, and a severe bow as poor. 56 cases were good, 22 were moderate, and 12 poor. It must be admitted that this is a clinical rather than a radiological classification. It was noticed that in all the cases where a moderate or severe bow was present the bow was convex to the ulnar side. This deformity seems to be most difficult to prevent, and may be caused by the use of a collar-and-cuff sling rather than a triangular bandage, as pointed out by Patrick (1946).

Functional Results

Cases classified as a good result were those which had full movement, including full rotation and good muscle power in the arm. Also included in this group are cases where there was a slight degree—i.e., a third or less—of limitation of either supination or pronation or of terminal limitation of movement at the wrist or elbow which did not inconvenience the patient. Where there was a more severe limitation of rotation or limitation of movement in more than one joint, together with any complaint of weakness, the results were classified as either moderate or poor according to the severity. According to these criteria 53 cases were good, 26 moderate, and 11 poor.

Rotatory function of the forearm is considered in more detail. Cases in which operation was necessary are excluded from this section. Cases which developed delayed union are, however, included. This gives 84 cases for analysis. Full rotation was obtained in 37 cases. Rotation was limited in 47 cases. Supination only was limited in 27 cases, but was limited by a third or less in 17 of these. Pronation only was limited in 13 cases but was limited a third or less in 7 of these. Thus full rotation or minimal limitation of either pronation or supination, with no inconvenience to the patient, was seen in 61 of 84 patients considered in this section. More serious limitation of either supination or pronation resulted in 16 cases, and in a further 7 cases both pronation and supination were limited. These results in relation to the sites of fracture were as follows:

Site	*No. of fractures*	
Upper third:		10
Full rotation observed in	3	6
Supination limited by a third or less in	3	
Pronation limited by a third or less in..	0	
Supination more seriously limited in	2	4
Pronation more seriously limited in	2	
Both pronation and supination limited in	0	
Middle third:		33
Full rotation observed in	8	19
Supination limited by a third or less in	8	
Pronation limited by a third or less in..	3	
Supination more seriously limited in	7	14
Pronation more seriously limited in	2	
Both pronation and supination limited in	5	
Lower third:		39
Full rotation observed in	25	35
Supination limited by a third or less in	6	
Pronation limited by a third or less in	4	
Supination more seriously limited in	1	4
Pronation more seriously limited in	2	
Both pronation and supination limited in	1	
Fractures at different levels:		2
Fracture of radius in upper third and ulna in lower third		
Followed by full rotation	1	
Followed by limitation by a half of both pronation and supination	1	

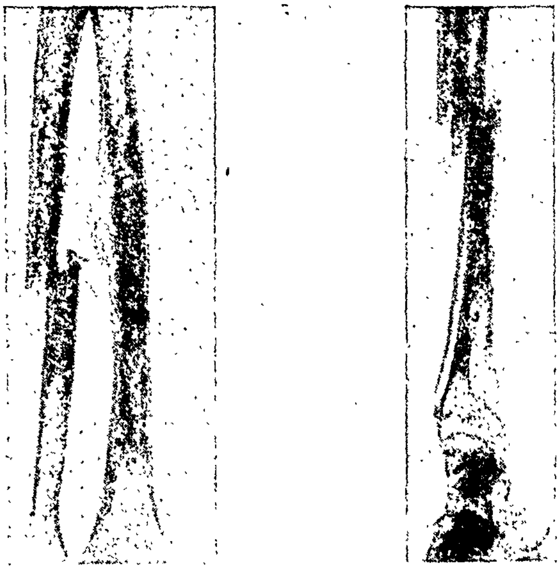


Fig. 9—Fractures of both bones of the forearm.

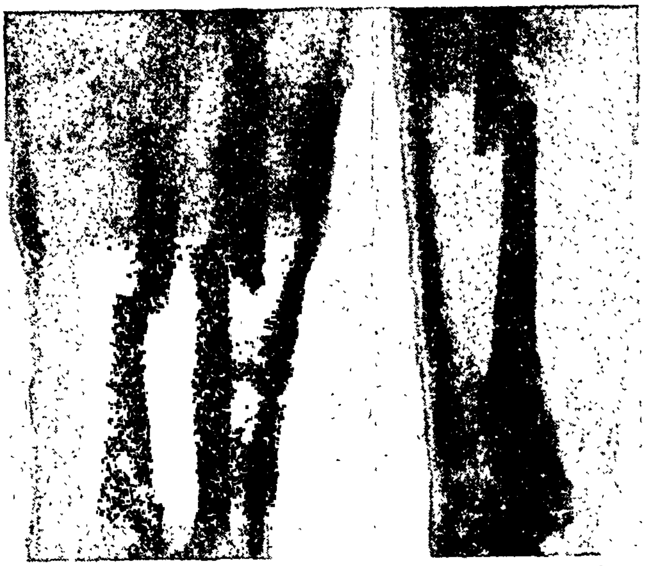


Fig. 10—Same fractures as in fig. 9, showing best position that could be secured by manipulative reduction. Alignment is good. Contact is imperfect.

Thus in 6 out of 10 cases in fractures of the upper third the result as regards rotation was good. In the middle third the good results were 19 out of 33 cases, and in the lower third 35 out of 39. From a superficial examination of these figures it seems that the lower the site of fracture in the forearm bones the better is the prognosis as regards recovery of rotation. Unfortunately no more precise statement can be made than this in view of the relatively small number of patients in each group. What can be said is that in 61 patients out of 84, considered specially from the point of view of recovery of rotation, regained either a full range of movement or nearly so.

Permanent limitation of other movements was a serious feature in but few cases in this series. In 2 patients there remained a terminal limitation of elbow movements, and in 6 others dorsiflexion and palmar flexion of the wrist-joint were limited to a half [illegible] pointed out, this has led to the [illegible] result as moderate or poor according to the severity of the limitation.

Subjective Results

Sixty patients said they were satisfied with their arms and had no complaints; 21 were not satisfied, the common complaints being weakness, aching when the arm became tired, occasionally lack of movement, and rarely deformity. In 9 cases the subjective results were unknown.

Economic Results

A good result is one where the patient returned to the work he was previously doing, and was earning the same wage. A moderate result was one where the patient could not do his previous work but did find some suitable lighter work and his income had not been much affected. A poor result was one where the disability entailed a substantial financial loss. 53 were good, 10 moderate, and 11 poor. In 16 cases the results were unknown.

SUMMARY

92 patients with fractures of both bones of the forearm were treated conservatively and the late results studied.

All were aged more than 21 at the time of the accident.

The anatomical result was excellent in 62% and good in 24%.

The functional result was good in 59% and moderate in 29%.

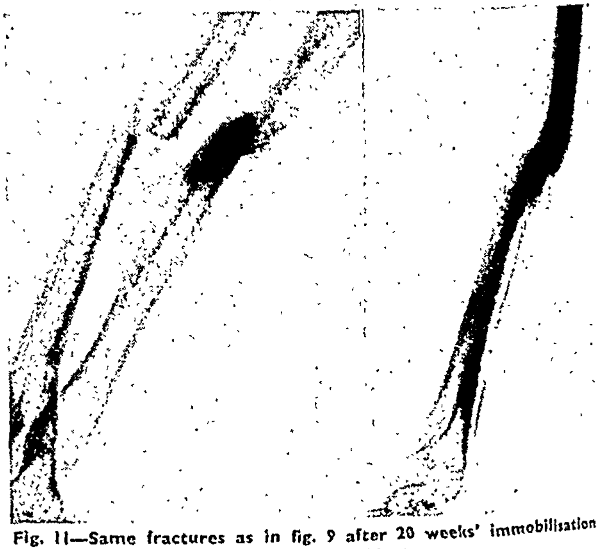


Fig. 11—Same fractures as in fig. 9 after 20 weeks' immobilisation. Non-union is evident.

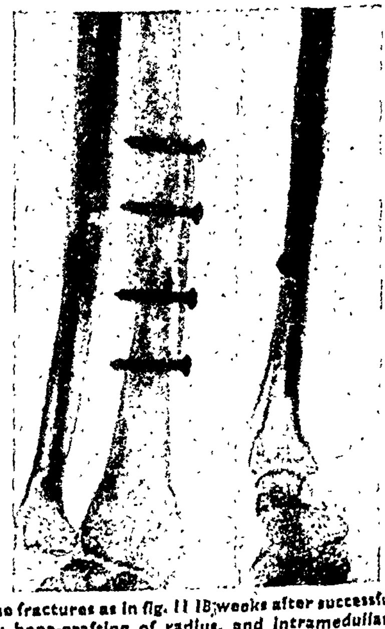


Fig. 12—Same fractures as in fig. 11 18 weeks after successful open reduction, onlay bone-grafting of radius, and intramedullary fixation of ulna. Patient regained two-thirds range of rotation.

The economic result was satisfactory in 70%.

61 patients out of 84 recovered full or almost full rotation.

Non-union occurred in 4 cases, delayed union in 4 cases, and serious mal-union necessitating operation in 2 cases.

We suggest that this method should be retained as a routine treatment for cases where none of the accepted indications for open reduction are present.

We wish to thank Prof. Sir Harry Platt, in whose department this work was undertaken, for much helpful criticism and advice, and Mr. John Charnley for his constant interest.

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CYCLOPROPANE ANÆSTHESIA FOR DENTAL EXTRACTION AND OTHER SURGERY IN OUTPATIENTS

REVIEW OF 1000 CASES

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Nitrous oxide, alone or with oxygen, has long been the accepted anæsthetic for outpatients. In this paper I criticise this use of nitrous oxide and argue that its low potency, hitherto regarded as an advantage, is in fact both a defect and a danger. Contrary to current belief, a narcotic of high potency might be not only more effective but also safer, and my experience with cyclopropane leads me to think that more nearly than any other it meets the requirements for outpatient work. Of these requirements, safety and simplicity come first, the others being effectiveness, rapid induction and recovery, pleasantness, and low cost.

CYCLOPROPANE

Pinson (1944) described the use of cyclopropane as an anæsthetic for dental extractions in 500 children under the age of twelve: a quarter of the administrations were by students. Disadvantages he found were salivation, and, during recovery, vomiting, which occurred in 21% of cases (Pinson 1945). He concluded that his method was simple and safe, but his technique was somewhat cumbrous and it does not seem to have been widely tried. No reports on the subject seem to have been made since the meeting at the Royal Society of Medicine in 1944 when Marston (1945) advocated cyclopropane for dental extraction in anæmic patients and in those who were difficult or resistant. At the same meeting Gillies (1945) spoke of the administration of cyclopropane to over 800 ambulatory dental patients, and emphasised the value of full oxygenation and "very adequate anæsthesia and muscular relaxation with consequent avoidance of 'smash and grab' surgery." None of them suggested, however, the general adoption of cyclopropane in place of nitrous oxide in outpatient anæsthesia.

The present report is based on 1000 unselected administrations to outpatients, 606 for extraction of teeth and 394 for other minor surgery: 48 were by students under supervision; 134 were by resident anæsthetists; and 91 were by registrar or senior-registrar anæsthetists who were not supervised. 230 patients were under seven and 13 were over seventy years old; the youngest was fourteen months and the oldest eighty-four years. In 20 patients nitrous oxide had failed on a previous occasion and the operation had had to be abandoned.

METHOD

Cyclopropane was given with oxygen from a bag of rather more than 6 litres' capacity. The flow of oxygen and cyclopropane was measured by rotameters, that for cyclopropane being calibrated up to 1600 c.cm. per minute. The gases were conducted to a special angle-piece * (Waters's fitting) containing a sleeve valve. This angle-piece connected the bag to a mask, and the valve enabled the gases to be retained in the bag until the mask had been applied to the patient's face and fitted accurately over the mouth and nose. The valve was then rotated and the patient breathed in and out of the bag. Carbon dioxide could be absorbed by inserting a Waters canister; but, apart from those dental patients who were intubated, in only 1 patient was this made necessary by the length of the operation.

Induction was the same for all patients. The flow of cyclopropane was always 1500 c.cm. per minute and accompanied by an equal flow of oxygen. For induction about 2 litres of each gas was admitted to the bag, and this single dose provided sufficient narcosis for most children and some adults. In the remainder, as soon as inhalation from the bag began, oxygen and cyclopropane were turned on and left flowing at the rate of 1500 c.cm. per minute until the correct depth of anæsthesia was reached. The dose of cyclopropane was thus regulated by duration and not by rate of flow, in the same way that a dose of thiopentone is regulated by quantity not concentration of solution.

In all patients consciousness was lost in from 3 to 6 breaths. At this moment, or a little later, there was often a pause in respiration. Guedel (1940), who employed an identical method of induction, attributed this pause to depression of the respiratory centre, but for the following reasons I regard this interpretation as incorrect:

(1) The pause often occurred at inspiration.

(2) When breathing was resumed it was immediately deeper than before the pause.

(3) In experiments on adult patients not included in this series, carbon dioxide absorption by Waters's to-and-fro method was employed from the start, cyclopropane and oxygen were left running at 1500 c.cm. each per minute, and excess gases were allowed to escape from an expiratory valve. In these patients, as in the others, strong respiration returned immediately after the pause; only after 4–7 min. did respiration show the effects of narcotic depression, which was gradual in onset and slowly progressive. It was further noted that if, when respiration had become considerably depressed, the inhalation was stopped and the patient was allowed to breathe air, not only did full respiration return within two or three minutes but anæsthesia became much lighter as shown by a brisk corneal reflex and other evidence.

During induction and after loss of consciousness motor excitement was evident. Tonic (sometimes followed by clonic) contractions were seen and were occasionally vigorous. In 1 patient, who was an epileptic, they resembled an epileptic attack. This led to the examination by electro-encephalography of 13 patients undergoing this form of anæsthesia, and I am indebted to

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* From Messrs. A. Charles King Ltd., Devonshire Street, London, W.1.

Dr. T. J. Hutchinson for these examinations and for the following report:

> "At the stage of surgical anæsthesia the record was dominated by high-voltage slow activity at 2 c/sec. These were the appearances one associates normally with that degree of unconsciousness. Normal rhythms became dominant within eighty seconds of terminating the anæsthetic. No E.E.G. evidence of epileptic activity was seen at any time."

After this phase of motor excitement, which usually lasted less than a minute, patients entered surgical anæsthesia and were relaxed. Respiration was normal. This subsidence of excitement was the best sign that the inhalation of cyclopropane could be stopped and the operation started. Another sign was the disappearance of the eyelash reflex. A sign of yet deeper anæsthesia was cessation of oscillating movements of the eyeballs. These last two signs were described by Romberger (1935).

In dental extractions the mouth-prop was inserted after the inhalation of anæsthetic had been stopped, and a pack was then placed in the mouth behind the site of extraction. When difficulty was encountered by the surgeon, as when a tooth was broken, administration of cyclopropane and oxygen was renewed for a few breaths from time to time. When it was obvious that the operation was going to be considerably prolonged, the patient was intubated, the throat was packed off, and anæsthesia was continued with carbon dioxide absorption.

Intubation.—31 adult patients were intubated in the dental chair. After anæsthesia had been induced, as described above, they were given succinylcholine chloride (von Dardel and Thesleff 1951, Bourne et al. 1952), the dose being 0·25 mg. per pound (0·55 mg. per kg.), previously made ready with needle in vein. Inhalation of cyclopropane/oxygen mixture was continued until the succinylcholine had taken effect. Intubation was then performed, the mouth was propped open, the throat was packed with a proprietary vaginal tampon sterilised by autoclaving, and anæsthesia was continued by Waters's to-and-fro method with carbon dioxide absorption. Very little more cyclopropane was needed, even when the operation lasted forty minutes.

RESULTS

Of the whole series of 1000 patients, 21% vomited; but vomiting was never seen during induction or maintenance of anæsthesia, and it occurred only when reflexes had recovered sufficiently to prevent danger. Nausea without vomiting or retching occurred in a further 12% of patients. To prevent nausea and vomiting a small dose of hyoscine by mouth was given to many patients. This experiment, however, was not sufficiently well controlled, and further trials with motion-sickness remedies are being undertaken.

Of patients who had previously been anæsthetised with nitrous oxide and were able to compare their experience of the two methods, 146 expressed preference (usually strong) for cyclopropane while 25 preferred nitrous oxide mainly because after cyclopropane they suffered nausea. Of the 146 patients who preferred cyclopropane several had vomited with cyclopropane but nevertheless preferred it to nitrous oxide. They made remarks like: "I had gas last week and wasn't sick. I was sick today but would still far rather have this." Or "If it was always like this I wouldn't mind coming up any day." Or "Beautiful sensation. Much nicer than gas; lovely." On the other hand, there were a few who said that, though they preferred "going off" clopropane because it was so quick, they would ave nitrous oxide because it did not make it.

the kindness of Prof. F. C. Wilkinson, Sir sev Fry, and Dr. Victor Goldman, over 400 s were anæsthetised for dental tman Dental Hospital, London. At this hospital during the previous twelve months some 8300 patients had been anæsthetised with nitrous oxide/oxygen for dental extraction, and it was therefore possible to compare the two methods. The following conclusions were reached:

(1) As quick induction made up for slight delay in recovery, the length of stay in the dental chair was scarcely any longer with cyclopropane than with nitrous oxide. In one session when cyclopropane was used 15 children were operated upon in forty-five minutes.

(2) With cyclopropane at its worst, operating conditions equalled those with nitrous oxide at its best.

(3) With cyclopropane, bleeding was less than with nitrous oxide.

(4) Even when cyclopropane was administered to more than 40 patients in one day, clearance of the recovery room was almost as quick as when nitrous oxide was used.

(5) The administration of cyclopropane was much easier than that of nitrous oxide.

(6) Vomiting was more frequent after cyclopropane.

(7) The average cost per patient of nitrous oxide was 1*s.* 3*d.* and of cyclopropane 2*s.*

DISCUSSION

Nitrous oxide used with 25% oxygen, as described by Brennan (1952) and supplemented by thiopentone and other narcotics, is regarded by an increasing number of anæsthetists as the anæsthetic of choice for inpatients. In outpatients, however, where effective doses of these supplementary narcotics are precluded by their long action, an attempt is generally made to establish surgical anæsthesia with nitrous oxide and oxygen alone. In all but a few patients nitrous oxide, when used with oxygen at atmospheric concentration, is too weak for this purpose; so, to overcome this difficulty, it is used with concentrations of oxygen that are less—often grossly less—than atmospheric. Thus Clement, who succeeded McKesson at Toledo and in twenty-five years' experience estimated (1951a) his administrations of nitrous oxide/oxygen at 50,000, wrote: "The production of true or surgical anesthesia with N_2O necessitates a restriction of the oxygen intake in the majority of instances" (Clement 1951b); and referring to the "resistant group," he said: "The essentials for success during the induction a[illegible]sure [of gas], the minimum of oxygen in the mixtu[illegible] time element and a disregard of cyanosis" (Clement [illegible]). Kaye (1951), in a study of nitrous oxide anæsth[illegible] in 339 patients, found that "*in . . . 189 cases it was obvious that the third stage of anæsthesia could be reached only by gross restriction of the supply of oxygen.*"

This restriction of oxygen, which permits the highest possible concentration of nitrous oxide, helps in two ways:

(1) The brain is saturated with nitrous oxide as quickly as possible.

(2) Oxygen deprivation itself is employed as a supplementary agent of anæsthesia.

Since, when oxygen is restricted, these two aids are simultaneously present, it is not surprising that opinions differ concerning their relative values. Clement (1951d) said: "The induction of anesthesia with 100 per cent nitrous oxide constitutes a primary saturation. It produces unconsciousness rapidly by a primary saturation of the blood with the anesthetic gas." Macintosh (1952a), on the other hand, has referred to nitrous oxide anæsthesia, when it is brief, as "controlled anoxia." Macintosh and Bannister (1943a) repeated in 50 patients the old experiment of producing anæsthesia sufficient for dental extraction by nasal administration of nitrogen. They found that "anæsthesia" was on the whole satisfactory, and the fact that nitrous oxide was not being used was unknown to dentists and patient. Macintosh (1952b), speaking of dentists' demand for quick recovery following anæsthesia for dental extraction and the means by which it may be achieved, writes :

> "It is virtually impossible to fulfil these requirements with any anæsthetic. . . . There is one condition, however, which gives rise to sudden unconsciousness, leads rapidly to a state approaching death and yet can be reversed almost equally rapidly so that the patient recovers quickly and there are negligible after effects. I refer to acute asphyxia (anoxia)."

But Clement (1951e), also in further statements, admitted that " control of anesthesia is synonymous with control of the oxygen" and " often as little as 1% perceptibly alters the depth of narcosis " (Clement 1951f).

In an interesting annotation in THE LANCET (1868) entitled " The New Anæsthetic (?)," the views of Dr. Richardson, president of the Medical Society of London, were expressed : " Respecting the mode of action of the nitrous oxide Dr. Richardson explained that it was not in the true sense the agent that caused insensibility. . . . In fact, *nitrous oxide is an asphyxiating agent*."

Many anæsthetists have said, and most are aware, that satisfactory anæsthesia is more nearly obtained with nitrous oxide if time is spent over induction. Mushin (1952) has said : " it is a common but erroneous belief that nitrous oxide anæsthesia is a quick method. . . . An average time for induction is 7 to 10 minutes." Kaye (1951) suggested that ten or fifteen minutes were needed, and Clement (1951g) pointed out that time was an important factor with nitrous oxide as with other inhalation agents.

From these and other considerations it would seem that with nitrous oxide there are two different kinds of anæsthesia. The first is seen in the quick " whiff of gas," which probably comprises the majority of outpatient anæsthetics, including those given for the easy extraction of one or two teeth. The anæsthetic and operation are completed in three or four minutes and full consciousness is regained as soon as the patient has taken a few breaths of air. This kind is almost entirely anoxic in character and it could probably be accomplished nearly as well with nitrogen, or any other inert gas, as with nitrous oxide.

The second is the long " gas " lasting ten to twenty minutes or more. Here necessary time is taken for saturation with nitrous oxide, and assistance rendered by deprivation of oxygen can be gradually reduced to a minimum. This kind more nearly approaches true nitrous oxide anæsthesia. Nevertheless, the number of patients in whom oxygen deprivation can be dispensed with altogether is small and consists only of those with low resistance. These are frail people or those rendered frail by severe anoxia during induction by so-called " primary saturation." Between these two kinds of anæsthesia are found every gradation of mixture of both.

Skill in giving a " gas " lies mainly in limiting at all stages the element of oxygen deprivation to the minimum needed for surgical anæsthesia. The field of surgical anæsthesia offered by this method is narrow. On one side is delirium, on the other anoxia in dangerous excess. This may be illustrated by further statements by Clement :

> ". . . nitrous oxide-oxygen anesthesia . . . may be very dangerous in the hands of the novice. The margin of anesthesia . . . is very narrow . . ." (1951h).
>
> ". . . the transition from the light to the deep or even profound plane may occur with bewildering rapidity " (1951i).
>
> " During the induction children respond rapidly to an overdose of nitrous oxide (or lack of oxygen) with manifestations of fourth stage anesthesia and they react equally rapidly to a slight excess of oxygen " (1951j).
>
> " *Alcoholics* usually resist the anesthetic strenuously for a time and then, not infrequently, a sudden *drop into the* dangerous fourth plane may occur with little or no warning " (1951k).

It is small wonder, when the field of surgical anæsthesia is so narrow, that a great deal of training and experience are needed for its safe accomplishment and that anæsthesia is even then not always satisfactory. It is fortunate that the signs of " overdose " are so alarming that practitioners generally err on the side of giving too little. This perhaps explains why the method has been proclaimed safe and why it is possible to produce statistics of very large numbers of administrations with but few deaths. Hewer (1944) stated that a questionary in the United States of America revealed only 2 deaths in 1,161,820 administrations for dental surgery. Marston (1945) referred to 1,271,431 administrations at Guy's Hospital and Dental School without a single fatality. Macintosh and Bannister (1943b), on the other hand, stated :

> " Statistics can be entirely misleading as a guide to the relative safety of the various anæsthetics. Figures may be produced to show that one death has occurred in, say, 50,000 administrations of nitrous oxide, 20,000 of ether, and 10,000 of ethyl chloride. Such figures are valueless because they do not take into consideration such important factors as the skill and experience of the anæsthetist, the state of health of the patient, the nature of the operation, its duration and severity, and they do not show how many times an operation had to be abandoned on account of difficulties in connection with the maintenance of anæsthesia. This last factor is significant, particularly in dental work where every dentist is familiar with the case in which it has been impossible to complete extractions because the length of anæsthesia, or the facilities afforded by *nitrous oxide*, were *inadequate*. Such a case would be classified for statistical purposes as a successful anæsthetic (i.e., not fatal), although it failed completely to enable the operation for which it was given to be performed."

Macintosh (1949), speaking of the danger to a patient with poor heart muscle from the anoxic insult of a " whiff of gas " in the dental chair, stated that he had reports of 5 deaths in as many consecutive months—the coroner in each case being quite satisfied that the anæsthetic had been properly administered. Other evidence suggesting that death or mental disturbance following nitrous oxide anæsthesia are not always so rare is furnished by Courville, who, after describing fatal cases, wrote :

> " While the literature is almost entirely silent on psychosis after nitrous-oxide-oxygen anesthesia, no doubt if the effects were known a goodly number of these unfortunate individuals would be found in the insane asylums of this and other countries " (Courville 1939a).

And, speaking of transitory mental and emotional manifestations, he added :

> " These patients go through an anoxemic episode, present dramatic and alarming symptoms shortly thereafter, but recover more or less promptly, apparently little the worse for the experience. It is very likely that if the facts were known such cases would prove to be more common than is now realized. Doubtless, the anesthetist is glad enough to see the patient safely through the episode, and the story goes unrecorded " (Courville 1939b).

Betten and Courville (1940) stated their belief " that mental disturbances may occur more frequently after nitrous oxide anesthesia than has been generally supposed." " It is likely," they said, " that cerebral and lenticular damage are due to the accompanying asphyxia (anoxic anoxemia) and not to the toxic effects of nitrous oxide itself."

In this paper, however, I am criticising nitrous oxide/oxygen anæsthesia less for its risks than for the unsatisfactory operating conditions it so often produces. It is common knowledge that the standard of anæsthesia for outpatients is far below that now attained for inpatients. A consequence of this unsatisfactory anæsthesia may sometimes be unsuccessful surgery.

Seeking a better solution, some workers have added supplements of one kind or another to the nitrous oxide/oxygen mixture, and have reported degrees of success. To me, however, it seemed that to retain nitrous oxide at all was merely to adhere to tradition; that nitrous oxide, considering how little help it gave in outpatient anæsthesia, occupied too much space in the anæsthetic mixture; and that this space would be occupied to better advantage by oxygen if to oxygen could be added a narcotic that was always effective.

A review of the alternative agents led me to think that cyclopropane might prove to be the most suitable. It could be easily respired at a concentration of 50%, and at this or lower concentration it was capable of producing in all patients anæsthesia of any depth. Its administration, therefore, could be accompanied from the start by oxygen at a concentration greatly in excess of atmospheric. With this method, provided that other respiratory depressants were not given, the field of surgical anæsthesia that lay between too light anæsthesia on the one hand, and respiratory depression on the other, was wide and traversed relatively slowly. In this cyclopropane differed from thiopentone, with which drug respiratory arrest sometimes occurred before surgical anæsthesia was reached. With cyclopropane it is easy to know when the field of surgical anæsthesia has been entered, and in no patient in this series has respiratory depression been encountered.

Hazards with Cyclopropane

1. *Explosion.*—The mixture used was explosive. No flame, therefore, or other source of ignition was allowed near the patient. If there was present even a remote risk of ignition—e.g., when it was intended to use a dental drill—some other method was employed. Risk of explosion was thought to be, for practical purposes, no greater with cyclopropane than with ether, ethyl chloride, or 'Vinesthene,' given with nitrous oxide or oxygen.

2. *Arrhythmias.*—Guedel (1940), in a study of more than 8000 administrations of cyclopropane in inpatients, used a method of induction which was identical with the one employed here and followed induction by yet heavier doses of cyclopropane. He concluded that "cardiac arrhythmias . . . although they must be respected, need not be feared."

Griffith (1951) reported a series of 20,000 unselected hospital inpatients to whom he had given cyclopropane with only 1 death under anæsthesia, the cause of which was not stated. He thought that, in spite of pulse irregularities which it sometimes initiated, cyclopropane was the anæsthetic of choice for patients with serious heart-disease.

Waters and Gillespie (1944), in a study of 47 deaths occurring during anæsthesia in 44,894 patients, ascribed 24 in whole or in part to anæsthesia. 5 of these patients died, they said, in a manner suggestive of abrupt cardiac failure during anæsthesia with cyclopropane. Later in their report they suggested other possible causes of death in 3 of these 5. In the remaining 2 they stated that death was undoubtedly due to primary cardiac failure. It is, however, noteworthy that in 1 of these 2 patients there was mild obstruction to respiration, and that in the other death occurred in deep anæsthesia and at necropsy coronary sclerosis was found. These authors concluded: "In our hands cyclopropane has proved no more dangerous than other agents."

It is impossible as yet to say how great may be the hazard of primary cardiac failure in outpatients who are unpremedicated and usually fearful. Questions equally unanswerable are: What is the true mortality with nitrous oxide? How often is mental impairment produced by the anoxia which accompanies it? Is the risk with cyclopropane greater or is it less than with nitrous oxide?

SUMMARY AND CONCLUSIONS

Though nitrous oxide has been widely used for many years, it may have been responsible for a higher mortality and morbidity than is generally supposed.

Apart from this, it does not fully meet the requirements of outpatient anæsthesia. Its administration is neither simple nor highly effective. Induction and, to a less extent, recovery are rapid only with the short "whiff of gas" when the main agent of anæsthesia is not nitrous oxide but anoxia. Induction is not always pleasant; unconsciousness during operation is sometimes incomplete; and nausea and baneful symptoms from anoxia not infrequently attend recovery when anæsthesia is prolonged. Its low cost is offset by the expense of unsuccessful surgery, which sometimes results from bad operating conditions.

Provided cyclopropane is given by someone who is sufficiently instructed and experienced to give an anæsthetic safely, it is both more effective and also safer than nitrous oxide. But the anæsthetist has always to bear in mind the following facts:

(1) Cyclopropane is explosive.

(2) An equal or greater flow of oxygen must always accompany its flow.

(3) With cyclopropane, as with any other anæsthetic, a clear airway must always be maintained.

(4) If any difficulty arises 100% oxygen must at once be administered, if necessary under pressure by compressing the breathing-bag.

Unlike the use of nitrous oxide, the use of cyclopropane is simple and easily learnt. Induction is very rapid and recovery sufficiently so for all practical purposes. While induction is usually considered pleasant and unconsciousness is always complete, recovery is frequently marred by nausea or vomiting. The cost is not high.

Whereas it is now an accepted principle of inpatient anæsthesia that anoxia is harmful and to be avoided, in outpatient practice anoxia is still deliberately employed as an agent of anæsthesia. Outpatient anæsthesia will not be improved so long as nitrous oxide continues to be used.

I am grateful to Mr. J. D. Robson and Mr. P. Shemilt, of Salisbury, on whose patients much of this work was done; to Dr. Victor Goldman for inviting me to work at the Eastman Dental Hospital; and to Dr. J. Hendrie, anæsthetic registrar, for his kind assistance.

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PHLEBOTHROMBOSIS AND NERVOUS STRESS

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IN recent years considerable attention has been directed to phlebothrombosis and pulmonary embolism, and much evidence about their causal factors has accumulated; but the application of treatment developed from these studies has not consistently altered the incidence of fatal embolism.

MASSIVE THROMBOSIS

"Massive thrombosis" here denotes the bland non-infective propagated clot whose liberation causes pulmonary embolism. The incidence of this condition, cited by Jorpes (1946), has varied in different clinics. Before the advent of early postoperative exercises and ambulation, fatal postoperative pulmonary embolism occurred in 0·1–0·5% of cases. Early postoperative exercise has reduced the incidence by more than half in many series of cases; but not in all. The mortality of thrombo-embolism, when it occurs, is over 20%.

Massive thrombosis was originally thought to be a complication of surgery. Later it was shown that it can occur in an even higher proportion of medical inpatients, but in comparing medical and surgical cases it must be recognised that the pathological material concerned is likely to be very different and the ætiological factors not exactly the same. The medical wards will often have a higher proportion of cases with circulatory defects, whereas the surgical patients are likely to be subjected to pecial nervous stresses. Pathological studies of necropsy material have shown that in a large proportion of bodies blood-clots are found in the veins of the legs and feet. Hunter et al. (1945) found, in 169 necropsies, such clots in 17·9% of patients who had been exercised up to forty-eight hours before death, and in 53·1% of patients who had not been so exercised. Hunter et al. (1941) noted that the age of the clot corresponded to the length of time the patient had been in bed.

Raeburn (1951), as a result of histological studies on veins obtained at necropsy, believes that venous thrombosis in the leg is a chronic additive process. The theory now generally held is that the small primary venous thrombus, which is so often present, merely needs the stagnation of the blood-stream by confinement to bed to allow rapid propagation of the clot. The stagnation of venous blood due to confinement to bed has become the all-important factor of massive thrombosis:

"The common denominator in phlebothrombosis and pulmonary embolism is *confinement to bed*. The reason for going to bed is unimportant" (Hunter et al. 1945).

If the immobilisation of a patient in bed is the main requirement for producing massive thrombosis, the incidence of this condition should be the same outside as inside hospital; but this does not appear to be so. In 1944–49 in the town of Ossett, with 11,000 inhabitants over school age, there were notified only three cases of fatal pulmonary embolism. No non-fatal case was recognised during this period. A fourth patient with pulmonary embolism was admitted to hospital, where she died. Only one of these patients had been confined to bed with illness immediately before death.

The confinements to bed in Ossett in 1944–49 may be divided into (1) those of the normal nightly retirement and (2) those of a few days or more due to illness. Three of these thrombosis cases were in the first category, and only one in the second. The incidence in the first category is about 1 in 8,000,000 adult retirements, and in the d much less than 1 in 18,000 adult illnesses. The figures for the second category are obtained from the practices of four out of the five general practitioners and by a conservative estimate of the cases attended by the remaining doctor, whose records are no longer available. Almost all of these cases will have been confined to bed for at least two days. Chronic sick cases, although adding their quota of 1 (the only case in the second category) to the thrombosis death returns, have not been included in the figures, owing to the difficulty of obtaining the necessary data and because this will compensate for some of the cases being outside the district under discussion. In both categories it is obvious that there is a great difference between home and hospital conditions, and that mere confinement to bed is no more than an added factor to something also of importance which probably initiates the formation of the clot.

Even though we do not dispute the importance of venous stagnation in the legs, we are bound to look for some difference between treatment at home and treatment in hospital. Some light may be thrown on this subject by the observation that sometimes a clot is found suddenly during emotional stress.

ILLUSTRATIVE CASE-RECORD

A woman, aged 24, who had lost a considerable amount of weight in the last few months, consulted her doctor about it and about lack of energy, but continued in active employment as a rag-sorter. She had no cough or other symptom.

On examination she was small and slim, and had obviously lost weight, but apart from anæmia no other physical abnormality was found. She was agitated and worried because her sister had died of phthisis a year previously and she had a brother in a sanatorium with the same disease.

A specimen of her urine was delivered a few days later by her mother, to whom was explained the necessity for hospital investigation. The patient was informed of the arrangements the same evening. This produced great agitation, and she expressed the fear of what the X rays might reveal. Next day she complained to her family of pain in both legs: this persisted for two days. She was fully ambulant during each day. On the third day after the arrangements had been made for her admission to hospital, her doctor was called and found her suffering from severe chest symptoms which suggested pulmonary embolism. She died soon after admission to hospital.

Necropsy showed that death was due to a pulmonary embolus, there was ante-mortem clot in the left external iliac vein, and the lungs were filled with miliary tubercles. The leg veins were not examined.

In this case factors other than emotion might have added their effects to the result; but there was a definite nervous stress associated with the initiating of the clotting process. It seems likely that many cases of acute coronary occlusion occurring after emotional stress are due to a similar process. Thrombosis of piles and varicose veins may also sometimes be associated with nervous stress. An elderly patient attended by me developed thrombosis of a varicose vein immediately after finding that her house had been burgled.

AUTONOMIC NERVOUS SYSTEM AND BLOOD-CLOTTING TIME

Ample evidence has been published to demonstrate the effect of autonomic-nerve stimulation on blood-clotting time (B.C.T.). Cannon et al. (1914) obtained consistent reduction in B.C.T. in cats by injecting adrenaline and by producing nervous excitement in them. With larger doses of adrenaline the B.C.T. was first retarded and then considerably reduced. Similar results have been obtained by other workers. Mills et al. (1928) demonstrated that the rate of clumping of platelets was related to the speed of clotting of shed blood, and that adrenaline injections accelerated both processes.

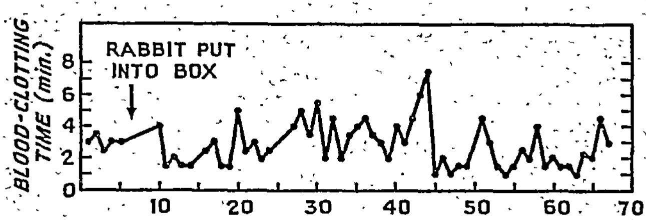

Fig. 1—Changes produced by nervous excitement in the clotting-time of venous blood in a rabbit placed in a box with its head protruding.

In experiments on rabbits, dogs, and man, in which the B.C.T. was followed minute by minute with a multiple coagulometer (Stoker 1945) I repeatedly recorded distinct changes apparently due to nervous excitement. In one such experiment (fig. 1) the excitation consisted of putting a struggling rabbit into a box from which its head protruded. Fig. 2 shows the result of an intravenous injection of adrenaline on the B.C.T. of a rabbit. Consistent results were obtained in six such experiments in which adrenaline 0·025–0·05 mg. per kg. of body-weight was used. In other experiments, unconnected with this group, the few minutes of very short B.C.T. were sufficient so to occlude the vein that it was useless for further withdrawal of blood.

In the course of examining the B.C.T. by means of capillary punctures in a young medical student a venepuncture was made. The student fainted, and the resulting changes in B.C.T. are shown in fig. 3. This graph is very similar in appearance to those obtained by Cannon et al. (1914) when small doses of adrenaline were injected. A similar result in another student coincided with an acute headache which began in the middle of the experiment. As the headache disappeared the B.C.T. returned to normal.

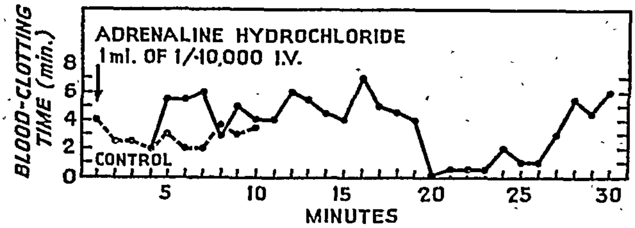

Fig. 2—Changes produced by intravenous adrenaline in the clotting-time of venous blood in a rabbit.

DISCUSSION

In recent years little reliability has been placed on blood-coagulation tests in relation to thrombosis; yet this is essentially a blood-clotting process. It may, of course, be argued that the B.C.T., within limits, will not determine the formation of a clot, and this view seems reasonable provided that there does not exist the nidus upon which a clot can be rapidly formed. The nidus, a preformed clot, such as pathological investigations suggest, is often present in adult veins. If the blood-stream is slowed and if, at the same time, the coagulability of the blood is greatly increased, there is likelihood of a propagated clot. This increase in blood coagulability may be much greater than published B.C.T. results indicate. On three occasions I have seen this reduced to a fraction of a second—twice in experiments on animals and once on the hospital operating-table. In each case, when the veins were cut, the blood mushroomed out to consolidate in a raised mass before it could flatten out on to the surrounding tissue. Reference to the accompanying figures will show that this state of hypercoagulability may last only a few minutes. In other words, it may be an acute process which may be entirely missed by occasional blood-tests.

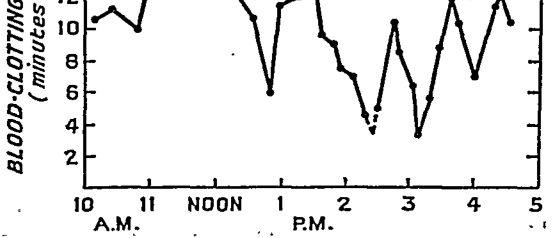

Fig. 3—Changes produced by a faint in the clotting-time of capillary blood in a medical student.

That confinement to bed can be no more than a contributing factor in massive thrombosis is seen by the statistics of patients treated at home and in hospital. The blood stagnation due to recumbency is common to both and, in fact, will be even greater in home cases than in those receiving prophylactic treatment in hospital. The great variation in the hospital statistics is significant and suggests that confinement to bed is only a part of the story.

Clinical experience shows that intravascular clotting can be initiated by nervous excitement or stress. Experimental evidence shows that rapid blood coagulability may be produced by nervous stress as well as by operatively handling the body. We must accept the numerous pathological reports that thrombi, as potential starting-points of massive thrombosis, are present in a large proportion of adults at least after a brief period recumbent in bed, and the view that slowing of the venous stream in the legs is an important factor in this disease. The patient in hospital will have all these factors at work. Which is lacking in the patient at home in his own bed? Nervous stress is surely one such factor.

Most hospital workers do not appreciate the many causes of nervous stress in patients. Mere admission to an unknown hospital ward may cause nervous tension, and the work of Hunter et al. (1941) suggests that this may be a dangerous time. The age of their clots corresponded to the duration of recumbency. Small matters, in the view of the hospital staff, such as shyness in asking for a bedpan, the fear that it will not be available when needed, and the self-consciousness in using it in close proximity to others, may be a severe nervous strain. Many doctors will have heard these views voiced. In larger matters, such as waiting in dread for the operation, the solution should be easy. Apart from the question of thrombosis such points might well receive more attention from a purely humanitarian point of view.

Hadfield (1950) states:

> “The rate of venous flow in the lower limbs of a healthy young adult can be diminished to a surprising but never to a dangerous degree by simple confinement to bed. It falls to an appreciably lower level in those with an ageing *myocardium*, to a lower level still if the vigour of respiration is diminished, and, if to these handicaps were added general muscular immobility, *the stage is set for peripheral venous thrombosis*.”

The stage is at present receiving considerable attention. The prevention of the actor, nervous stress, from playing his part must be a matter of clinical *trial*. Sedation begun before admission to hospital and continued in doses sufficient to meet emergencies might produce good results.

SUMMARY

The incidence of phlebothrombosis and pulmonary embolism in a small provincial town is discussed.

Experimental evidence is reviewed to show that nervous stress may be a deciding factor in producing massive intravenous thrombosis.

It is suggested that the apparent increased risk of massive thrombosis in hospital is due to nervous stress, and that such nervous stress is less in patients treated at home.

I wish to thank Drs. F. Cane, J. S. Coad, W. D. Mitton, and A. M. Ramsay for making available their sick-attendance records; Dr. W. G. Evans, M.O.H. of the district, for supplying the figures of the death returns; and Prof. D. Burns in whose department of physiology in Newcastle upon Tyne the illustrating experiments were made.

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HUMAN ECTOPIC FASCIOLIASIS

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THE liver fluke, *Fasciola hepatica*, is a common parasite of sheep and to a lesser extent of cattle and hogs, causing the disease known as " liver rot." Although of world-wide distribution, it is most common in Cuba and has there become of importance owing to the infection of man.

It might be expected that human infestation would correspond to that of animals, but in fact fascioliasis rarely affects man. Burgi (1936) collected 186 cases of human fascioliasis, and well over 200 cases have now been published. In this country 14 cases have been recorded, the first in 1852. There seems to be little doubt, however, that many more examples of infestation are encountered during operations on the biliary tract without being recorded.

Normally the adult fluke inhabits the bile-ducts, its eggs being excreted with the fæces. Rarely, however, the parasite may be found in various ectopic situations—e.g., blood-vessels, subcutaneous tissues, and brain. Burgi (1936) reviewed 16 cases of ectopic fascioliasis published up to 1933. Since then 8 more cases have been published, making a total of 24, of which only 1 has apparently occurred in this country—in a sailor who had been abroad for many years and had therefore probably been infected outside this country.

CASE-RECORD

A hotel housekeeper, aged 30, first attended the outpatient department at the Manchester Royal Infirmary on June 28, 1950, with a tender swelling in her abdominal wall. A week previously she had had some tenderness in her right iliac fossa, followed next day by a swelling there. Two days later the swelling had moved to the right lumbar region and become bigger, and thence to the right rib margin. The patient's general health remained good.

On examination a non-tender subcutaneous mass $1\frac{1}{2}$ in. in diameter was found overlying the ninth costal cartilage. It was thought to be due to low-grade inflammation, and short-wave diathermy was prescribed. A week later there was no apparent change in the swelling, and it was decided to admit the patient for its removal as a possible fibrosarcoma.

On admission on July 16 the patient said that the overlying skin had recently become discoloured. The swelling had become attached to the skin, there being a hard nodular superficial part with a softer and less defined deeper portion tethered to the external oblique aponeurosis.

Biopsy.—The mass was excised and found to consist of yellowish fatty tissue containing pus-filled necrotic areas, from one of which a small parasite measuring 4×2 mm. was expressed. This was kindly identified by Dr. F. O'Rourke, of the Liverpool School of Tropical Medicine, as an immature specimen of *Fasciola hepatica*.

Investigations.—Numerous unsuccessful attempts were made to recover ova from the duodenum and fæces. Eosinophilia was, however, found, varying between 744 and 978 per c.mm.

Treatment and progress.—Emetine hydrochloride gr. $\frac{1}{2}$ daily was given for eighteen days, while the patient was under the care of Prof. Robert Platt. Immediately afterwards the eosinophil-count was 792 per c.mm. Two weeks later it was 336 per c.mm., and in six months it was back to normal at 82 per c.mm. (for this latter count we are indebted to Dr. G. Anderson, of Bedford General Hospital, the patient having by that time left Manchester). It seems reasonable to assume that the patient no longer harboured any parasites.

Despite inquiry, particularly by Dr. Metcalfe Brown, medical officer of health for Manchester, no source of the infection was traced.

DISCUSSION

Location of Parasite

It was formerly believed that after ingestion of the cercariæ by the definitive host, the immature flukes passed up the common bile-duct to reach their final habitat; but it has now been shown (Krull and Jackson 1943) that the young flukes migrate through the gut wall into the peritoneal cavity, penetrating the liver capsule and substance to reach the bile-ducts. This observation helps to explain the location of the parasite in certain ectopic cases.

The finding of parasites in ectopic sites has led some observers (Braun and Seifert 1925, Bugge 1928) to postulate a venous route for migration to the liver and thence to various sites throughout the body. Faust (1939) supports this view, and it appears to be the most reasonable explanation in some cases.

In the 24 ectopic cases published, excluding the present case, the sites were as follows: portal vein 1, peripheral veins 2, stomach 1, appendix abscess 2, peritoneal granuloma 1, cerebrum 1, urine 1, subcutaneous tissue 14, and unknown 1. Of the infections involving the subcutaneous tissues 9 were in the right hypochondrium.

Thus it seems likely, as Burgi (1936) has suggested, that the parasite may reach the subcutaneous tissue directly by a relatively small deviation from its usual route to the liver. The finding of parasites in the stomach, peritoneum, and appendix can be explained in a similar way.

Blood spread seems likely to be the mode of distribution of more distantly located ectopic parasites, though Giesker and Frey (cited by Burgi 1936) claim that their patient with a parasite in the sole of the foot was directly infected by cercariæ penetrating the skin.

Migration of Parasite

This was a notable feature of the present case, the swelling first appearing near the right inguinal ligament and migrating to the right costal margin in some seven days. This phenomenon has been previously seen. Malherbe (cited by Burgi 1936) describes a case in which a painful swelling near the left scapula moved downwards about 10–15 cm. in fourteen days, when a young fluke was removed. In the case reported by Chatron and Rondeau du Noyer (cited by Burgi 1936) a swelling as big as a hazel nut to the right of the umbilicus decreased in size, and later a new swelling appeared higher up, which contained a 4 mm. fluke.

Immaturity of Fluke

The immaturity of the fluke in the present case accords with the findings in other cases of ectopic fascioliasis, and seems to be due to the lack of essential environmental factors necessary for full maturation which are found only in the liver and bile-ducts.

Source of Infection

This is of interest because of the great rarity of human cases in this country. Contaminated watercress or other vegetation is the usual source of ova. Our patient could not remember having eaten any possibly contaminated food. She had never been further abroad than Jersey, which she visited in the previous year, and for the four months preceding her attendance at hospital she had not left the Manchester area.

Within fairly wide limits it may be possible to fix the time at which infestation occurred, because it takes only 4–6 days after ingestion for the fluke to traverse the peritoneal cavity. Thus infestation may be reasonably presumed to have taken place not less than a week, and probably not more than a month, before the appearance of the swelling.

We must therefore conclude that infestation was contracted in this area, but the source and mode are unknown. The medical officer of health for Manchester kindly informed us that no other cases had been reported in the area.

We are grateful to Prof. A. M. Boyd for permission to report this case; to Dr. F. O'Rourke, of the Liverpool School of Tropical Medicine; and to Dr. Metcalfe Brown, medical officer of health for Manchester.

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HÆMOPHILIA-LIKE SYNDROME FROM ANTICOAGULANTS AFFECTING THE PRODUCTION OF THROMBOPLASTIN

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Some syndromes resembling hæmophilia are due to circulating heparin-like antithrombins, and others to an anticoagulant apparently inhibiting the production of plasma-thromboplastin. Eighteen of the latter type of case have been published, of which the earliest was that of Lozner et al. (1940). We report here a further such case.

CASE-RECORD

A man, aged 73, with advanced widespread rheumatoid arthritis for ten years, had enlarged axillary glands, and cutaneous nodules over the right elbow and hip. His liver and spleen were not enlarged. He had never had any gold therapy. The bleeding disorder, which started in January, 1951, was manifested by extensive subcutaneous and intramuscular hæmorrhages (including two into the root of the tongue, embarrassing respiration), hæmatemeses, melæna, and hæmaturia. He died of massive hæmorrhages in November, 1951.

Treatment with hæmatinics, transfusions, antihæmophilic globulin, and adrenocorticotropic hormone (A.C.T.H.) 100 mg. the first day and 40 mg. daily for six more days had no effect on the underlying disorder.

Investigations.—The erythrocyte-sedimentation rate was moderately raised. White-cell counts were within normal limits. The plasma-protein level and liver-function and Congo-red tests were normal. The Wassermann reaction was negative. Serum-mucoproteins were somewhat increased. Splenin B was found in considerable amount, and splenin A was virtually absent (Greene et al. 1952). Clotting-times ranged between 10 and 60 minutes (Lee-White). Bleeding-times, platelet-counts, capillary fragility, serum-calcium, and plasma-fibrinogen were all normal. The blood-group was A Rh-negative. The presence of an anticoagulant was repeatedly demonstrated by the prolongation of clotting-time of normal blood on addition of the patient's blood—e.g., 25 minutes, compared with 13 minutes in the control.

The anticoagulant was investigated by one of us (I. S. C.). Prothrombin and thrombin times were normal, as were the results of titration with protamine sulphate (Allen et al. 1949). The serum-prothrombin time was short: 29 sec. compared with 100 sec. following clotting of normal blood (a rather weak thromboplastin was used in this experiment). Dr. R. G. Macfarlane and Dr. R. Biggs, using special techniques, showed that our anticoagulant inhibited the formation of plasma-thromboplastin but had no effect on this substance once it had been formed. Excess of a potent platelet-factor suspension supplied by Professor van Creveld (van Creveld and Paulssen 1951, 1952), restored to normal the clotting-time and serum-prothrombin time of mixtures of normal blood with our anticoagulant (table I). The suspension contained no thromboplastin, as was confirmed by its failure to make any significant alteration in the clotting-time of recalcified normal plasma: 2 min. 23 sec. compared with 2 min. 35 sec. in the control. Comparable experiments with antihæmophilic globulin failed, the preparation seeming to have anticoagulant properties of its own in excess. Activity of the anticoagulant was apparent in a dilution of 1 part of patient's plasma to 3 of normal plasma but not in a dilution of 1 : 10. The anticoagulant retained its activity after four months at −20°C, and was active after three days at room-temperature, but deteriorated somewhat after seven days.

TABLE I—NEUTRALISATION OF ANTICOAGULANT BY PLATELET FACTOR

Normal blood	+	+	+
Anticoagulant	−	+	+
Platelet factor	−	−	+
Clotting-time (min.)	17	23	11
Serum-prothrombin time (sec.) ..	62	15	120

It was not destroyed by heating to 65°C for 5 minutes. The residue after dialysis retained anticoagulant activity. Chemical and electrophoretic fractionations were made by Dr. R. A. Kekwick. Studies of these fractions appeared to show activity in both the beta and gamma globulins but not in the albumin and alpha-globulins.

Necropsy findings.—There were large recent ecchymoses of the chest wall and neck, old and recent bilateral hæmothoraces with adhesions, and altered blood in the gut. The liver showed siderosis. The sternal, costal, vertebral, and femoral bone-marrow was uniformly erythroblastic. The spleen was enlarged to almost twice the normal size, very soft and autolytic, and siderosis was increased.

Histological examination confirmed these findings and showed amyloid change in the axillary lymph-glands but none in the liver. No discovery of note was made in the pituitary, suprarenal, or thyroid glands. There were general cardiovascular changes commensurate with the patient's age, and the urinary tract showed appearances associated with prostatectomy for adenomatous prostate.

DISCUSSION

The outstanding features in the present case and in eighteen similar cases previously published are compared in table II.

Ætiology

The patients fall into three main groups:

(1) The first consists of eight apparently typical hæmophiliacs. In these the anticoagulant has usually been found

TABLE II—ÆTIOLOGY AND PHYSICAL PROPERTIES OF THE ANTICOAGULANTS

References	Sex	Age	Antecedent illness	Duration	Dialysis	Stability		Active fractions
						Storage	Heat	
6, 14	M	44	Hæmophilia	Recurrent	Not dialysable	Stable		Gamma-globulin
16–18	M	36	,,	1.5 yr.	,,	,,	Stable	,,
13, 23	M	21	,,	Recent	,,	,,	,,	
6	M	21	,,	,,				
4	M	38	,,	,,	,,		,,	,,
25	M	21	,,	,,				
22	M	4	,,	,,	,,		,,	
26	M	28	,,	,,			,,	Globulin
3, 5	F	33	Recent pregnancy	4 yr.		,,	,,	,,
9	F	39	,,	9 yr.				
12	F	?	,,	6 yr.		,,	Unstable	
8	F	30	,,	Recent	,,	,,	Stable	,,
15	M	61	Tuberculous lymphadenopathy	Died	,,	,,	,,	
4	M	67	Non-specific lymphadenopathy	Recent	,,		,,	
7, 20	M	68	Pemphigus	,,		Unstable	,,	
25	M	68	Dermatitis herpetiformis	1 yr.				Gamma-globulin
22	M	67	Idiopathic	Transient	Dialysable		,,	
19	F	43	,,	20 mos.		Stable	,,	
Present case	M	73	Rheumatoid arthritis	Died	Not dialysable	,,	,,	Beta and gamma globulins

after multiple transfusions or the giving of antihæmophilic globulin. The anticoagulant disappeared after treatment was stopped in one of the cases reported by Frommeyer et al. (1950). Precipitins to antihæmophilic globulin have been reported in two cases by Craddock and Lawrence (1947) and in five cases by Frommeyer et al. (1950). It has been suggested that antihæmophilic globulin acts as a foreign protein in hæmophiliacs, leading to the appearance of antibodies.

(2) The second group is made up of four women whose anticoagulants appeared shortly after a pregnancy. Dreskin and Rosenthal (1950) collected seven previously published cases of pseudohæmophilia in women, in four of whom the disorder appeared shortly after pregnancy. It has been suggested that the development of the anticoagulant is an auto-immunisation phenomenon.

(3) Six of the seven remaining patients were elderly males, in five of whom the hæmorrhagic disorder appeared during some other illness. The natures of these illnesses were consistent with the suggestion that the anticoagulants appeared in response to some disturbance of immunity mechanisms.

The anticoagulants have always been found in the globulins, particularly the gamma-globulins obtained on chemical and electrophoretic fractionation of the plasma (table II). This is consistent with the suggestion that these anticoagulants are antibodies.

Action of Anticoagulants

Prothrombin-times were normal in all these cases, excluding any abnormality or inhibition of prothrombin, thrombin, fibrinogen, or the various accelerators of the conversion of prothrombin to thrombin, but not of thromboplastin, because the excess of tissue thromboplastin added in doing this test would probably obscure such an effect. Serum-calcium and plasma-fibrinogen levels were normal where estimated. Heparin-like antithrombins have been excluded by further tests in all but one of these cases (Singer et al. 1950).

It follows that the anticoagulants interfere with either the action of thromboplastin or its formation from platelet factor and antihæmophilic globulin. This has been confirmed by the finding of impaired prothrombin consumption, as shown by short serum-prothrombin times in all the cases where these have been estimated. Attempts to determine which of these three substances are primarily affected by the anticoagulants have not been entirely successful. The results of certain types of experiment devised for this purpose have been capable of more than one interpretation. Certain investigations and tentative conclusions, however, can be recorded. Investigations have failed to reveal any satisfactory evidence that the anticoagulants antagonise plasma-thromboplastin, and most observers consider such an action unlikely. The most hopeful approach to distinguishing between effects on platelet factor and those on antihæmophilic globulin has been to show neutralisation of the anticoagulant by an excess of one or other factor. This has been successful with platelet factor (Lamy et al. 1946, Conley et al. 1950, Singer et al. 1950, and ourselves). It should be noted that the patient reported by Lamy et al. belonged to the hæmophilic group. These results cannot be regarded as conclusive, because they may be due to a mass-action effect. Shinowara (1951) has shown that platelet factor is an extremely potent lipoprotein—like tissue thromboplastin (Chargaff et al. 1944) and probably plasma-thromboplastin—a few microgrammes possessing physiological activity. Platelet-counts have been estimated in most cases and found normal, and the platelets from one patient restored to normal the clotting-time of platelet-freed normal plasma (Dieter et al. 1949). Neutralisation experiments with antihæmophilic globulin have been unsuccessful, but this may be due to a technical cause. It should be remembered that precipitins to antihæmophilic globulins have been demonstrated in several cases from the hæmophilic group (see above).

To summarise: these anticoagulants probably interfere with the formation of plasma-thromboplastin, though how they do so is unknown.

Identity of Anticoagulants

These anticoagulants have largely similar physical and chemical properties (table II). Such differences as are reported may have technical explanations. The anticoagulants are mostly non-dialysable and are comparatively resistant to storage and heating. They have been found in the globulin and, where investigated, the gamma-globulin fractions. Their similarities and the possibly common ætiological mechanism suggest a related if not identical group of substances. Tocantins (1943) found an anticoagulant in normal plasmas. It is conceivable that the underlying disorders provoke the appearance of some such anticoagulant in abnormal titre. Investigations into the action of the anticoagulant throw no conclusive light upon the matter but suggest a possible difference between those arising in hæmophiliacs and those arising in non-hæmophilic persons.

Clinical Features

The disorder closely resembles hæmophilia, but the hæmorrhages favour somewhat different sites. Massive subcutaneous and intramuscular hæmorrhages are common. Hæmorrhages into the root of the tongue, causing embarrassment of respiration, are notable features. Hæmorrhages into joints are less common. Gastro-intestinal hæmorrhages and hæmaturia are common. An important difference lies in the response to transfusions. These correct the lack of antihæmophilic globulin in hæmophilia; clotting-times are improved; and bleeding ceases. They do not affect the anticoagulant; clotting-times are largely unaffected; and hæmorrhage may continue.

Many of the cases have been reported a few months after the appearance of the anticoagulant; hence information about the possible duration of the illnesses is limited. The available information is collected in table II.

Treatment

Treatment is unsatisfactory. Nothing is known which affects the underlying disorder. Cortisone was tried without avail by Singer et al. (1950) and A.C.T.H. by ourselves. All that can be done is to correct the anæmia with transfusion. The development of a thromboplastin which could be used safely by the intravenous route would be helpful. The use of placental blood (Pons and de Torregrosa 1952) may be a step in this direction, because its efficacy is quite possibly due to a high content of thromboplastin.

Frommeyer et al. (1950) found an anticoagulant had appeared in no less than 5 out of 27 cases of hæmophilia. He advised against the use of antihæmophilic globulin, and recommended that transfusions should be used only sparingly, in hæmophilia, to avoid this complication.

SUMMARY

In a man, aged 73, with rheumatoid arthritis, a condition resembling hæmophilia developed, due to a circulating anticoagulant.

Eighteen previously published similar cases are reviewed.

The anticoagulants are thought to interfere with the formation of plasma-thromboplastin.

Their appearance may be in response to some disturbance of the mechanism of immunisation.

Physical and chemical similarities between the anticoagulants are noted. It is possible, though perhaps improbable, that they are a related group of substances.

We wish to thank our house-physician, Dr. M. H. Aitken, for her help; Dr. J. F. Heggie and Dr. A. B. Anderson for much laboratory investigation and facilities; Dr. R. G. Macfarlane and Dr. R. Biggs for a specialised investigation; Professor van Creveld for the supply of platelet factor; Miss J. Vaughan-Morgan, B.SC., for the splenin investigation; Dr. J. F. Bach for the supply of A.C.T.H.; and Dr. C. J. C. Britton, Dr. Raymond Greene, and Dr. Macfarlane for encouragement and advice. We are particularly indebted to Dr. R. A. Kekwick, of the Lister Institute, for the lengthy fractionations he kindly undertook for us.

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CAROTENÆMIA

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GENERAL PRACTITIONER

An excess of carotene in the blood-plasma is produced by the ingestion of large quantities of foods rich in carotene, such as carrots, pumpkins, and papaw. Consumption of these foods for six months or more causes yellow discoloration of the mucosæ and skin, especially the horny layers of the palms and soles. The sclera are never affected, and the urine is not darker than normal.

The condition was first observed by von Noorden (1907), who regarded it as a diabetic manifestation. Moro (1908) noted that normal infants developed a similar yellow pigmentation when carrots were added to their diet. van den Bergh and Snapper (1914) showed that lipochrome pigments were circulating in the blood of those diabetic patients who exhibited an orange pigmentation.

Single cases have been reported from various parts of the world (Head and Johnson 1921, McGill 1922, Niehaus 1924, Stoner 1928, Stannus 1929, Potts 1929, Levin and Silvers 1931, Curtis and Kleinschmidt 1932, Rutledge 1933, Gandy 1935, Sequeira 1936, Wood and Agnor 1941, Schafer and Slentz 1949). Anderson and Soley (1938) collected and reported on thirteen cases from California; Josephs (1944) searched the records of Johns Hopkins Hospital and found six cases and reported a further case himself. In this country Almond and Logan (1942) reported four cases, in one of which the pigmentation was passed to a child through the mother's milk. These cases occurred during the war 1939-45 and seemed to be a direct consequence of Lord Woolton's appeal to the civilian population to eat carrots, which were then plentiful. The present two cases were encountered during the autumn of 1951.

Carotenæmia is said to be more likely to develop in diabetes mellitus, where it is probably a result of the diet rather than the disease, and in myxœdema, where there is some evidence that the carotene antagonises thyroxine (Anderson and Soley 1938).

CAROTENE

Carotene is the yellow colouring matter in the lipochrome of carrots, spinach, palm oil, and nettles. It is a highly concentrated hydrocarbon, $C_{40}H_{56}$, which exists in three forms—alpha, beta, and gamma. All three forms are precursors of vitamin A, but the alpha form produces twice as much as the other two, and is the one present in the largest quantities in natural products. Lycopene is the isomer of carotene and the colouring matter of tomatoes, rose hips, and bitter-sweet berries but does not form vitamin A. Carotene is the principal lipochrome in human serum. It is always associated with its hydroxyl derivative or xanthophyll.

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Lutein is the xanthophyll of alpha carotene and is the lipochrome in egg yolk and green leaves. The normal daily requirement of carotene is 3 mg. or 5000 units. There is 2000 units in $^1/_4$ lb. of carrots.

DIFFERENTIAL DIAGNOSIS

The importance of carotenæmia lies in its recognition. When the offending articles of diet are withheld, the yellow pigmentation slowly clears. The four cases reported by Almond and Logan (1942) had been previously diagnosed as gall-stones, jaundice, pernicious anæmia, and hæmolytic anæmia. White sclerotics are the key to the diagnosis.

A simple test for lipochrome in serum consists in shaking up equal parts of the serum, alcohol, and petroleum ether, and allowing them to settle. The alcohol precipitates the protein and absorbs the bilirubin, and the lipochromes are absorbed by the petroleum ether.

CASE-RECORDS

Case 1.—A married woman, aged 42, with one child aged 8 years, had been depressed, bad tempered, and tired for three weeks. For some years she had been catering, first in a youth hostel and later in a guest-house. She described herself as a "liverish" person who could not eat fats. She was plump and had voluntarily tried to cut down on starches. About eight years ago she read that carrots were good for catarrh, and gradually began to consume them in increasing quantities. During this summer she had been living almost exclusively on them. Her daily consumption had been $1^1/_2$–2 lb. of raw carrots daily. Several weeks before she sought medical advice she had noticed that her hands and feet were yellow, and was afraid to mention it to anyone. Five days ago her husband noticed it and assumed that she had jaundice.

On examination the whole of her skin was tinted yellow, and there was yellowish staining on her buccal cavity. Her palms and soles were particularly yellow, the discoloration being greatest on the callosities. Her sclerotics were white, and her urine pale straw-coloured without albumin or sugar. Her blood-pressure was 150/90 mm. Hg and heart sounds were normal. She had slight tenderness in her epigastrium and complained of flatulence. Her fæces were of normal colour. She could see well in the dark.

Investigations.—The serum-carotene level was 500 mg. per 100 ml. (normal 240 mg. per 100 ml.). The serum-vitamin-A level was 51 mg. per 100 ml. (normal 70–160 mg. per 100 ml.). A blood-count showed Hb 78%, red cells 4,900,000 per c.mm., and white cells 7500 per c.mm.

Treatment and Progress.—When the carrots were discontinued, her yellow discoloration gradually faded in six weeks.

Case 2.—A married woman, aged 40, with children aged 13 and 3 years, complained of lassitude and nervousness. During the last five months of her first pregnancy she had eaten large quantities of carrots. Three years ago, during her second pregnancy, she had a persistent craving for carrots, and now, for the past six months or more, she had a return of the craving and had eaten them to the extent of 1 lb. a day. She noticed yellowness of her hands but had thought that it was sunburn wearing off.

On examination she was plump and over-weight (11 st.) and had generalised yellow pigmentation of the skin, which was quite bright on her palms and soles. Her sclerotics were white. Her blood-pressure was 130/80 mm. Hg. No other signs of disease were observed.

Investigations.—The serum-carotene level was 330 mg. per 100 ml.; serum-vitamin-A level 27·5 mg. per 100 ml.; blood-cholesterol level 200 mg. per 100 ml.; Hb 70%, red cells 4,400,000 per c.mm., and white cells 12,000 per c.mm.

Outcome.—On being assured that the condition was not serious, the patient declared she would rather be yellow with carrots than pale and carrotless, and refused to discontinue her diet.

DISCUSSION

These two cases have several points in common. Both patients were rather plump women approaching their menopause; both complained of lethargy and nervousness; both had slight hypochromic anæmia; and both had an insatiable desire for carrots, the second patient so much that she refused to give them up.

I have met carotenæmia once before, when it was again in a middle-aged woman, whose dietetic indiscretion was papaw. This was in India during the war, and I was unable to investigate it.

I wish to thank Dr. G. Stewart Smith, pathologist to the Royal Devon and Exeter Hospital, for help and advice in investigating these cases.

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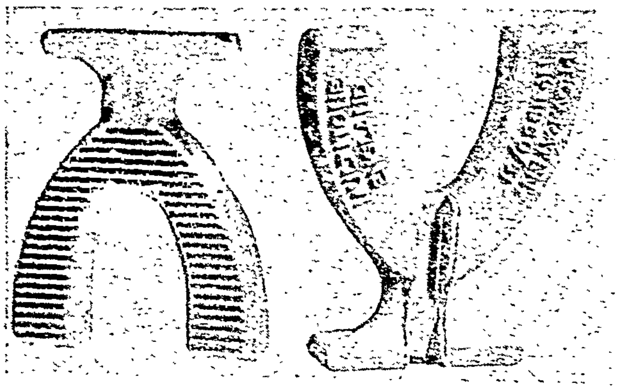
New Inventions

MOUTH GAG FOR ELECTROCONVULSION THERAPY

It has been customary to use transverse indiarubber gags for electroconvulsion therapy and similar procedures. These, however, distort the mouth, impede respirations, and place the strain of the clenched jaws on the front and premolar teeth, with the result that these are often loosened or broken. Fractures of the mandible have also been reported. Relaxants are seldom advisable to the extent that convulsion is entirely eliminated, and even with relaxants the spasm of the jaws remains strong.

The gag illustrated was designed to engage all the patient's teeth. It is made of toughened indiarubber and is easily sterilisable. It does not distort the mouth, and the tongue is left free though protected against protrusion between the teeth; respiration is not impeded by the gag; and the channel in the upper surface will accommodate an endotracheal tube if required. With this gag the strain of the muscle spasm is placed mainly on the molars, which are better adapted to stand this strain, and whose position relieves the weakest part of the mandible of strain. A stem and crosspiece facilitate insertion and removal.



The gag has been in regular use for some months and is greatly preferred to other forms. The spreading of the area of bite leads to less damage to the gag as well as to the patient. The gag is manufactured by Messrs. Multitone, 223–227, St. John St., Clerkenwell, London, E.C.1, from whom it may be obtained.

London, N.W.1

HENRY BACK
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Reviews of Books

Brain Tumors of Childhood

H. M. CUNEO, M.D., assistant clinical professor of neurological surgery, University of Southern California; C. W. RAND, M.D., clinical professor of neurological surgery, University of Southern California. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 224. 42*s.*

THIS useful and concise account of brain tumours of childhood is a further addition to the American Lecture Series and is based on 83 verified cases treated in the Children's Hospital in Los Angeles within ten years. As the authors indicate, the diagnosis is often made late because the possibility of brain tumour being responsible for the symptoms is not sufficiently borne in mind. The warning that young children do not complain of failing vision until they are almost blind is timely, and it is clear that the routine use of the ophthalmoscope in clinical examination would bring some cases under observation much earlier.

The book is arranged according to tumour type, and each chapter begins with a summary of current opinion, with adequate references. Not every neurosurgeon will agree with the conclusion that all children suspected of a cerebellar tumour should have preliminary ventriculography; there are many cases in which the diagnosis is not in doubt and in these circumstances air studies may only upset an already ill child.

The production and illustrations are first-class. Two clinical photographs express most poignantly the problem and the challenge in this subject.

History of Neurological Surgery

Editor: A. EARL WALKER, M.D., professor of neurological surgery, Johns Hopkins University. London: Baillière, Tindall, & Cox. 1951. Pp. 583. 91*s.* 6*d.*

THESE lectures, delivered by members of the Johns Hopkins University, have been welded into a historical survey of the progress of neurological surgery. Much of it is a bald citation of facts which in themselves make an enthralling story of conquest, and reconquest, in an unusually difficult field. We all know how ancient is the operation of trepanning, but it is strange to realise how widely it was practised over the world, and that in some forgotten way infection was avoided. Air ventriculography was accidentally demonstrated in 1913, but its possibilities were not perceived, and it was left for Dandy to rediscover and develop it in 1918. Neurological surgery began in England, but its great progress in America was very largely due to the influence of one man—Harvey Cushing—who insisted that the surgeon undertaking to operate on the nervous system must also be a neurologist. The neurosurgeon no longer operates at the behest, and according to the directions, of the physician, but on his own initiative; and since a frightening power of altering personality lies in his hands, it is right that he should be a man of high intellectual attainments and culture. But neurological surgery, like all surgery, is a mechanical art; its scope, now still expanding, will be restricted when the more subtle secrets of physiology ultimately become clear to us.

Il Cuore Artificiale

E. TOSATTI. Milan: Istituto Sieroterapico Milanese S. Belfanti. 1951. Pp. 151. 700 Lire.

THE great progress in cardiac surgery has brought into prominence international attempts to perfect a pump-oxygenator capable of taking over temporarily the work of the heart and lungs. This little book, in Italian, is the first general review of the subject. The author, an active worker in this field, discusses the problem from both theoretical and practical standpoints, and presents the principal solutions offered up till the end of 1951. The various machines described are well illustrated by actual photographs, and numerous diagrams make clear the techniques employed in using them. At this early stage in the development of these machines no one is completely satisfactory; but the problem is a real one, and this book is most helpful in providing a basis for judging the merits of these and future attempts.

The Temporomandibular Joint

BERNARD G. SARNAT, M.D., M.S., D.D.S., F.A.C.S., professor and head of department of oral and maxillofacial surgery, College of Medicine and Dentistry, University of Illinois. Springfield, Ill. Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 148. 35*s.*

THIS monograph is founded on various lectures on anatomical, pathological, and clinical aspects of the joint given by various members of the faculty of the University of Illinois.

The internal pterygoid muscle is not regarded as playing any part in side-to-side movements of the mandible as has been widely taught in the past. A discussion of the relation of the mandibular condyle and the growth of the neck of the condyle to the growth of the jaw as a whole is followed by a section on pathological conditions of the jaw: the conclusion that Costen's concept of a syndrome connected with mandibular overclosure should be abandoned will find general agreement in this country where it has never had much currency. The section on those abnormal conditions of the joint which result in pain and clicking is unfortunately rather short, and by no means everyone who deals with this type of case will agree that restoration of correct occlusion of the teeth, where this is faulty, will cure all but a few cases. Most of the clicking jaws seen in this country are in young women in whom there is usually a history of anxiety at the time when the habit started. In many cases clicking occurs not at the beginning of the opening movement but later in opening the mouth, and it is hard to see how malocclusion can account for clicking at this juncture. Lack of muscular balance, which eventually becomes a habit, may often account for the condition. It is a pity that there is not fuller discussion of this subject rather than an analysis of three cases treated by a particular method.

The book is illustrated by good photographs and diagrams.

The Foot (4th ed. London: Baillière, Tindall, & Cox, 1952. Pp. 466. 25*s.*).—Mr. Norman C. Lake still finds that the foot presents him with puzzles; but in every edition of this useful little work he is able to announce that a few more of them have been solved. The revised and informative text is supplemented with good illustrations, 30 of them new.

Progress in Clinical Medicine (2nd ed. London: J. & A. Churchill. 1952. Pp. 426. 27*s.* 6*d.*).—The editors, Dr. Raymond Daley and Dr. Henry Miller, have carefully continued their policy of including only those advances which promise to be of permanent value; and they have firmly excluded, as of no great interest to the general physician, the latest news from the highly specialised fronts of medicine. New chapters have been added on industrial medicine and physical methods of treatment in psychiatry; and sections are now included on cerebral angiography, electrolyte and water balance, cortisone and A.C.T.H., hypersplenism, toxoplasmosis, electrocardiography, parkinsonism, and the newer antibiotics. The editors and their fellow contributors have done wonders in very little room, and they have produced an excellent book.

Emergencies in Medical Practice (3rd ed. London: E. & S. Livingstone, 1952. Pp. 587. 32*s.* 6*d.*).—Dr. C. Allan Birch and his team of twenty-one contributors have had to decide, as usual, which emergencies shall rank as medical; and in this new edition they have decided to include *ileus*, acute dilatation of the stomach, and tetanus as being surgical emergencies with medical aspects. Otherwise, the book has been improved by revision and pruning, and embellished with some new illustrations in colour. Colour is an uncertain ally, however. The plate illustrating the colouring of mushrooms is discredited by the fever-pink hand supporting them; and the coloured photographs of blood-transfusion technique are woolly and too small. The coloured photographs of ocular conditions are good, however, and most of the other illustrations are clear and helpful. The book remains the friend on whom the doctor with a patient in a tight place can call for help; but perhaps it is even better read beforehand.

THE LANCET

LONDON: SATURDAY, OCT. 11, 1952

Future of the Occupational Health Services

SINCE the Dale Committee on the Industrial Health Services produced its disappointingly modest proposals nearly two years ago, there has been a lull on this front. Even the interdepartmental advisory committee which the Dale report recommended has not yet been formed. Recently, however, some guns got into action at Margate, where the Trades Union Congress and the Royal Sanitary Institute held their annual meetings. In the T.U.C. the general council accepted a resolution by Dr. BRUCE CARDEW calling on the Government to set up "a comprehensive occupational health service to be welded into the National Health Service"—though it "wanted to be careful that such welding does not produce integration for the sake of administrative ease."[1] This reservation was an echo of BERTRAND RUSSELL's warning (quoted by Dr. R. S. F. SCHILLING[2] at the other Margate meeting) of the "administrative fallacy in which the tidiness of the plan is regarded as a model of order—an end in itself—and of men in control . . . who forget what human beings are like and try to fit men to systems, rather than systems to men." Dr. CARDEW seriously overstated his case when he said that, while the National Health Service was the best in the world, when "once a man left his home for his office, shipyard, factory, or mine the provisions for his health became perhaps the worst in the world." And Mr. ALFRED ROBERTS went a little too far when he spoke of the "appalling lack of knowledge of occupational hazards and diseases among general practitioners." But at the Royal Sanitary Institute's meeting the statements were more measured.

Prof. I. G. DAVIES, medical officer of health for Leeds, in a thoughtful and well-balanced paper[3] on the future organisation of the occupational health services, drew attention to the danger of an artificial separation between treatment at work and at home. Any proposed industrial health arrangements must not, he said, have the effect of creating fresh divisions among the medical profession: rather should they aim at drawing the existing sections closer together, and, where possible, making a common service. There is urgent need, in his opinion, for development of a preventive health service for all places of work, including those beyond the scope of the Factories Act, and this could be done by fusing the duties of the three kinds of medical officers who are already operating statutory services of the kind required—namely, the medical inspectors of factories and mines, the appointed factory doctors, and the medical officers of health. One difficulty here, he thought, would be the administrative gulf (almost an abyss) which lies between officers appointed by central and by local government departments. But "it is worthy of serious consideration that, as a first step, legislative and administrative means be found to fuse the statutory health officers already engaged in preventive health services into one preventive health unit enforcing and maintaining health standards." Dr. DAVIES claimed that this step would solve the essential and immediate problem for the small factories. For the large industrial organisations, and for single industrial units employing large numbers, special arrangements may be necessary; but even there, he held, the main bias of the service must essentially be preventive in character, leaving treatment to the N.H.S. He recognises that this may make too sharp a distinction between preventive and curative medicine; but preventive medicine, he said, requires the enforcement and maintenance of standards arrived at after research and investigation and then embodied in law and administrative procedure. He thinks that a new medical inspectorate at three levels—central, regional, and local—should be created to work under the authority of statute and in close association with the general inspectorate, both centrally and locally. The present medical inspectors of the Ministry of Labour would provide the regional level, and it would be one of their functions to establish medical liaison with the administrative medical officer of the regional hospital board and through him with the hospital and specialist services. At the local level it is suggested that the medical officer of health and his staff, assisted by the appointed factory doctor, should be responsible, in association with the local factory inspectorate, for detailed enforcement and maintenance of health standards and for medical examinations. Dr. DAVIES believes that such an arrangement could be made now at very little additional cost and without disturbance of medical man-power.

This approach by a medical officer of health to the problem of occupational health is refreshing and original, and seems to us more promising than that of the Glasgow city council, which is endeavouring to solve its local problem directly by setting up an industrial medical service staffed by full-time medical officers of its own. It is natural, and in a way logical, that medical officers of health should wish to take over industrial health, but in urging their case they have sometimes tended to play down the importance of occupational medicine and to ignore the experience and pioneering work of the Factory Department and others in the field. The Ministry of Health, too, has not been altogether guiltless in this respect, and its attitude has probably contributed to the resistance of the Ministry of Labour to the proposal that the health departments should control all health affairs. This conflict came into the open at the Caxton Hall conference in 1943, when Mr. ERNEST BEVIN and Mr. ERNEST BROWN each put forward the claims of his own Ministry, and it may be partly responsible for inactivity and lack of progress in occupational health matters.

Addressing the Association of Industrial Medical Officers six months ago, Dr. H. WYERS[4] said that industrial medicine must come to terms with the medical officer of health sooner or later, and the sooner the better: "his passion for administration should be exploited, but his pre-occupation with community health tempered." In Dr. WYERS's view, preventive and curative medicine should be united. Certainly

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[1] *Manchester Guardian*, Sept. 3, 1952.

[2] *J. R. sanit. Inst.* 1952, 72, 534.

[3] *Ibid.* p. 528.

1. *Trans. Ass. industr. med. Offrs*, 1952, 2, 64.

Dr. Davies's idea of the rôle of the medical officer of health should be more acceptable to the other interested parties than that put forward by some previous spokesmen of the public-health service, who have not recognised that occupational health is a field in which they have little or no experience. Dr. Davies appreciates the objection to his scheme that it would entail delegation of central functions to local authorities, but he thinks that a medical officer of health could be seconded for medical inspectorial functions to the factory inspectorate without the actual responsibility being placed in the hands of the local authorities. It would be essential to such an arrangement that the medical officer of health should work in close association within the administrative framework of the local factory inspectorate, as indeed he does now to some extent. In this way, Dr. Davies believes, liaison with the N.H.S. could be secured—at regional level with the specialist and hospital services, and at local level with general practitioners through the medical officer of health.

In a paper which we published a few weeks ago [5] Dr. Peter Nash urged that occupational-hygiene laboratories should be set up in various parts of the country. This attractive idea cannot be said to be new, for it has been put forward from time to time by various individuals and organisations over the past fifteen years or so. Nor is the concept of the "health engineer" really a novelty in Britain, for the engineering and chemical branch of the Factory Department has long been carrying out the procedures he describes. It is true that there is no special laboratory for the use of the Factory Department; but work is done by the Government Chemist and the National Physical Laboratory, and the Mines Department is fortunate in that routine and emergency tests of environmental conditions are made in the Safety in Mines Research Laboratories in Sheffield. At the same time we cordially agree that there is need for extension of the facilities and staff in the Factory Department and we welcome Dr. Nash's paper as a basis for discussion. He usefully drew attention to the precedent set by the laboratories of the Public Health Laboratory Service, administered by the Medical Research Council: there are 18 special or reference laboratories and a further 49 constituent laboratories. For work on occupational hygiene, fewer centres would be needed, and possibly some of the public-health laboratories could be used or adapted. As Dr. Nash says, there is a strong case for the centres to become part of the Factory Department of the Ministry of Labour, and another possibility is that industry itself should be encouraged to set up such centres. The need for them is shown by the fact that his own laboratory at the London School of Hygiene and Tropical Medicine is getting more requests for help than it can deal with.

Surely the time has come for the interested Ministries to get together and hammer out an acceptable scheme for the better organisation of the occupational health services to cover all occupations? New legislation will be needed and it is inevitable that one or more Ministries or departments should surrender some of its sovereignty, though we must always bear in mind that a tidy administrative plan is not necessarily the best. Until this is done, little or no progress can be expected.

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[5] *Lancet*, Sept. 6, 1952, p. 478.

Cervical Osteo-arthritis and the Spinal Cord

The association of cervical osteo-arthritis or cervical spondylosis with disorder of the spinal cord has only lately been recognised as a fairly common occurrence. Spillane and Lloyd [1] [2] have described 21 cases, and Russell Brain, Northfield, and Wilkinson [3] 38; and as a result of their work the condition should be diagnosed more readily. Men are affected more often than women, the commonest age of onset being the early fifties. Disability usually starts with stiffness and weakness of the legs, which gradually increase, and may be associated with paræsthesiæ and clumsiness in the hands and, less commonly, with pain in the arms. Only rarely does the patient complain of pain in the neck. The symptoms slowly become worse over the course of two to three years, and then not uncommonly become stationary, without further deterioration, for a considerable time. There is a variable degree of spastic paraparesis, and some patients have atrophy of the shoulder-girdle muscles, often with fasciculation, while others have only a slight generalised weakness. The arm reflexes vary; it is perhaps commonest to find that all the arm-jerks are pathologically brisk, but in some cases the biceps jerks are diminished, and there is inversion of the radial reflexes. Sensory impairment is less constant than motor disability, but there may be diminution of position sense in the hands, giving a clumsiness to the finger movements, and, less frequently, a loss of position and vibration sense in the feet. Cutaneous sensory impairment was found in three-quarters of the patients in the London Hospital series [3]; it was commoner in the arms than in the legs, but it was seldom more than a slight loss. There may be surprisingly little to find on clinical examination of the neck; passive movements are usually free and painless, but occasionally there may be some limitation of movement. In the majority of patients lumbar puncture gives a normal response in the Queckenstedt test, and the cerebrospinal fluid shows no abnormality; but in a few cases there may be a slow rise on jugular compression, The protein content of the C.S.F. was raised to between 70 and 80 mg. per 100 ml. in 5 of Spillane's patients, and it was over 50 mg. in 10 patients in the second series, the highest value being 160 mg. per 100 ml.

X-ray examination of the cervical spine is the most helpful investigation; but at times the results may be difficult to interpret, for osteo-arthritic changes, unassociated with clinical symptoms or signs, are not uncommon in middle age. In cases where there is uncertainty about the diagnosis, myelography is necessary. The most important abnormalities to be found on straight X-ray examination are narrowing of one or more of the intervertebral disc spaces; osteophytes on the anterior and posterior aspects of the vertebral bodies (the latter being particularly significant); changes in the articular surfaces of the neurocentral joints; and projection of osteophytes into the intervertebral foramina (best shown in oblique projections). If myelography is needed, it should be carried out with the patient prone, 3–5 ml. of opaque oil being injected. The significant findings are one or more transverse breaks in the oil column opposite disc spaces; the delay in the passage of oil across these breaks often lasts several minutes when the patient is tilted head downwards at an angle of 70°. The lateral view may show indentation of the oil column opposite one or more disc spaces in the cervical spine. In the control myelograms that SPILLANE performed on patients in similar age-groups who were suffering from other forms of paraplegia, these characteristic features were absent. Obviously the clinical syndrome of cervical osteo-arthritis with cord changes resembles certain intrinsic diseases of the spinal cord—particularly motor-neurone disease, subacute combined degeneration, and disseminated sclerosis. So, when these conditions have atypical features, X-ray examination of the cervical spine, and if necessary myelography, should be carried out.

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[1] Spillane, J. D., Lloyd, G. H. T. *Lancet*, 1951, ii, 653.
[2] Spillane, J. D., Lloyd, G. H. T. *Brain*, 1952, 75, 177.
[3] Brain, W. R., Northfield, D., Wilkinson, M. *Ibid*, p. 187.

BEDFORD, BOSANQUET, and RITCHIE RUSSELL[4] have described the post-mortem findings in one such case. There were well-marked ridges in the disc spaces between C5 and 6 and C6 and 7, "which expanded laterally into two discrete osteophytic protrusions." An atrophic 7th cervical root was stretched over one of these spurs. The ridges in the disc spaces were formed by disc protrusions covered by bony outgrowths from the edges of the adjacent vertebræ. The spinal theca was adherent to the posterior longitudinal ligament, and it had been held firmly enough against the bone for the ridges to have caused indentations in it. The cervical enlargement of the cord was shrunken, but there was no kinking of the cord, and the theca on the posterior surface lay quite loosely over the shrunken cord. Sections of the cord showed degeneration of both grey and white matter in the C5 and 6 segments; many nerve cells ere destroyed, and there was gliosis and ascending nd descending degeneration in the long tracts. Similar changes in the spine were recorded in 6 of the London Hospital cases, and the nerve-roots of the affected segments were bound up in adhesions between their dural sheaths and the edges of the intervertebral foramina.

Injuries of the cervical spine may give rise to sudden protrusion of a disc with damage to the cord; or, more rarely, progressive protrusion of a cervical disc may gradually compress the cord, giving the clinical picture of an extradural tumour; but the condition associated with cervical osteo-arthritis is of a different kind. It is probable that the intervertebral discs undergo a degeneration which excites an osteophytic reaction in the bodies of adjacent vertebræ. The damage to the cord is due, in part at least, to pressure of the transverse ridges against the front of the spinal theca and to narrowing of the anteroposterior diameter of the spinal cord. Moreover, the tethering of the nerve-roots in the intervertebral foramina reduces the normal mobility of the cord and makes it more liable to injury during movements of the cervical spine. The adhesions may also interfere with the blood-supply to the cord.

If this is the way in which the cord is damaged, conservative treatment should consist in immobilisation of the cervical spine, preferably with halter extension of the neck followed by a plastic collar or other device to prevent constant cervical movements. In a number of patients, particularly in the early stages of disability, this treatment will stop the progress of the disease and definite improvement may take place. Surgical treatment has also been tried, with variable results. Removal of the hard bony ridges is technically very difficult and there is a danger of injury to the spinal cord. The usual operation has been a full laminectomy at the affected level, followed by "unroofing" of the intervertebral foramina, opening of the dura, and division of the denticulate ligament. This procedure is designed to give greater mobility to the spinal cord and to relieve pressure on the nerve-roots. In the London Hospital series 21 patients had this operation: there was definite improvement in 4 cases, a lesser degree in 10 others, and no change in the condition of another 4; and there were 2 postoperative deaths. The younger patients and those whose symptoms had been present for only a short time did best; these are the people who also responded well to immobilisation, which seems to be the method of treatment favoured by the evidence so far.

Withdrawal of Teaching

MEMORY is the most essential of the servants of reason, and the least reliable. Knowing this, every good teacher uses devices to make his teaching memorable. He points his argument with wit, illustrates it with examples, develops imitable mannerisms, sets his class chanting mnemonics and rhymes, excels in coaxing the timid or galvanising the slack, cultivates understatement or overstatement, or shies things about. But whatever method his temperament drives him to adopt, his aim is to ballast the free-floating fact with affect and image. The simpler the student and the more complex the subject, the greater the need of such ballast.

The Ministry of Health have the ultimate responsibility for teaching many complex subjects, both to the population at large and to informed or semi-informed groups within it. For this vast educational undertaking they have for years been developing the use of documentary films. The value of those made for the general public is now well established: the decline in diphtheria mortality, a steady rise in standards of handling food, and the growing public interest in child care owe much to such films. In the territory of medicine and nursing the Ministry have been equally enterprising in passing round essential information quickly, economically, and memorably. Three recent examples may be described to illustrate the exceptional value of this method of teaching.

All physicians and surgeons are aware of the importance, in the prevention of cross-infection, of capable and conscientious nursing technique. Yet it is a formidable task to teach a girl fresh from school, often with no background of science classes, to think imaginatively about the transfer of infective organisms from one patient to another, and to govern her conduct accordingly. To instruct her in unfamiliar principles in classroom and ward is one thing; to get her to build them into her professional conscience—so that she suffers unbearable guilt if she fails to apply them—is quite another. The remark of one nurse, "Asepsis is something you don't bother about when sister isn't there," suggests that ordinary teaching methods do not always succeed in creating an equally powerful but interior autocrat.

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[4] Bedford, P. D., Bosanquet, F. D., Russell, W. R. *Lancet*, July 12, 1952, p. 55.

The documentary film, *Prevention of Cross-infection: Gastro-enteritis in Infancy*, made for the Ministry of Health by the Central Office of Information (C.O.I.), and written and directed by Margaret S. Thompson, shows the results of failure in technique in terms of a healthy baby brought close to death; the emotional significance of the film is thus strong. The nurse responsible is guilty of only one small breakdown in an otherwise faultless barrier technique. The path taken by the infected material is made visible in the form of black markings, transferred, from the napkin of a child with gastro-enteritis, first to the hands of the nurse, thence to the lid of the napkin bucket, thence back to her newly washed hands, thence to her apron, thence to a borrowed pencil, and so to the hands of the lender of the pencil, and finally to the teat of a bottle from which a healthy child is to take a feed. The last shot of the critically ill baby could not easily be forgotten.

This film serves the double purpose of showing every step in correct barrier nursing as well as the outcome of the one false step. A single showing might well do as much as a dozen lectures to establish the preventive outlook; and moreover it can be shown to a large group of nurses at a time.

One exacting duty of the Ministry is to get our hospitals to profit from each other's experience. Many improvements never get beyond the walls of the hospital which makes them, simply because they are never heard of elsewhere.

The film *There's a Way*, directed by Gerry Bryant, is the engrossing story of a hospital in need of a reablement unit. The doctor in charge of the small overworked physical-medicine department, the Scottish surgeon who supports him, the various members of the hospital management committee, the almoner, and all the other hospital characters, come plausibly to life. The patients are alive already, and most of the time kicking, walking, running, twisting, catching, or otherwise exercising disabled limbs. A plan to build a full-scale reablement department has been turned down by the regional hospital board on grounds of expense, and the film shows how an effective department was improvised at very little cost in an old Army hut. First the hospital management committee has to be won over; and then six months pass before the R.H.B. sanctions the scheme. At last, with old materials from the hospital storeroom, the enthusiasts convert half the hut into a gymnasium, and fit part of the rest up with physiotherapy cubicles and an office for the almoner. The gym class is in full swing within a month; but the hospital still lacks an occupational-therapy department. An industrialist on the management committee contributes a lathe, and other equipment is given by the townspeople. The work of this department is illustrated cleverly from the case-histories of genuine patients, and the whole film is a trustworthy picture of the way a reablement unit can be contrived with very little outlay and an addition of only four members to the staff. The story is told with the skill and veracity which distinguished the work of the Crown Film Unit.

This film is addressed to hospital medical and administrative staff, physiotherapists, almoners, and other social workers. A third group of films addressed purely to a medical audience is concerned with curable cancer.

These substantial documentaries, six in all, each run for 30–40 minutes; and each shows such a range of cases of cancer in a given site as could scarcely be assembled in any single hospital, and would certainly not be seen by a family doctor in a lifetime of practice. The film dealing with cancer of the skin, for instance, shows rodent ulcers at every stage, from the first unbroken nodule to the ulcer which has destroyed an entire face. Moreover, it shows what treatment can nowadays achieve: how the malignant process can be stopped by radiotherapy, even when structural damage is extreme; how extensive are the areas of malignant infiltration which can be successfully excised; and what the plastic surgeon and the maker of prostheses between them can achieve in the way of repairs. Other types of skin cancer, including the dangerous melanoma, are also shown, appropriate warnings being given in sound-track and captions. A film on breast cancer follows the same plan, the emphasis here being on the survival-rate of 80% for cases treated early. A third film, on cancer of the larynx, shows how radiotherapy, or, failing that, surgery, can completely deliver the patient of his disease and restore him to normal life with very little disability. An interesting sequence here shows the training—sometimes very successful—of laryngectomised patients in the use of the œsophageal voice. There are also films on cancer of the lip and tongue, the rectum, and the cervix and uterus.

These films have an extraordinary impact, not only because they state memorably the results of neglect but also because they give such a vivid idea of what can be done. Receiving both impressions together, the watching doctor is bound to experience a strengthening of his sense of responsibility.

All these films would formerly have been seen by very large audiences. Until early this year the C.O.I.'s mobile film units, serving not only the Ministry of Health but all the Ministries, were able to show educational films wherever they were wanted: hospitals, medical and nursing schools, local authorities, and other responsible bodies only had to write and ask for a booking. In April, however, when the mobile units and—more unfortunately still—the Crown Film Unit were disbanded, as a minor Government economy, this first-class piece of educational work was abruptly cut down. The film projectors of the mobile units are to be distributed, but even if some of them find their way into hospitals among 2800 hospitals they will not, of course, go very far. When a hospital now wishes to show its medical or nursing staff an educational film it usually has to begin by borrowing a projector for the purpose; and moreover, it now has to pay for the hire of films which formerly were shown free of charge. The charges compare favourably with commercial rates, but the misfortune is that there should be charges at all. As a result, less use is being made of the Central Film Library of outstanding educational films, and the skilled and experienced staff who made many of these films have been scattered.

It seems essential that the mobile units should somehow be replaced: and surely one of the voluntary bodies interested in medical education will think this a worthy object? But even if existing films can again be put into circulation, it is unlikely that the beautifully economical system by which the mobile units served all the Ministries could be repeated. This miserable little economy has meant a saving of about £50,000 a year on the mobile units—not a very noticeable figure in the national budget—and of about £180,000 on the service as a whole, including the cost of running the Crown Film Unit. The loss cannot be measured in money at all.

Annotations

USES OF PUNISHMENT

THE effects of a generous and regular allowance of punishments—expensive ones, too—are conveniently apparent in the case of the old lag. It is a waste of time and money to go on punishing someone in the same old way for something he is going to go on doing. As Dr. Minski points out in our correspondence columns this week, the recidivist looks on society as his enemy, and every fresh term of imprisonment confirms this impression. Why should he put himself out for an institution which dislikes him so much?

A similar frame of mind, as parents know to their cost, can sometimes develop in children. Prof. Richard Ellis, in his Blackader oration[1] to the Canadian Medical Association this year, pointed out that the response of a child to punishment depends, in the first place, on his relation with his parents. Where the child is secure in the knowledge that the predominant feeling his parents have for him is love, where the parents are at one with each other, and where the child is able to express his own affection for them, punishment is likely to be most often effective and least often necessary. But the child feels for his parents hostility as well as love, and rightly opines that they feel much the same for him. If at some moment he fears that their hostility outweighs their love, he may go on provoking them to punish him, in order to prove to himself that they are not as dangerous as he fears, and—more important still—to make certain there will be a satisfactory reconciliation afterwards. He is seeking reassurance and love, though his behaviour often gives the opposite impression. But if his fears are well grounded—if he believes with some justice that one or other of his parents is rejecting him—punishment assumes a much more frightening and damaging rôle. It is no longer an incident imposed on a background of affection: it is an expression of enmity; and every time he is punished without satisfactory reconciliation he becomes further estranged from his parents and more convinced that at bottom they hate him. Punishment then loses its effect on his behaviour; and of course this may lead to excessive punishment. From being defiant the child assumes a "don't care" attitude, which is the despair of parents because it makes him inaccessible. Really it is the child's defence against his "intensely painful and damaging" sense of being unloved. Punishment is now an incident against a background of hostility, which the child feels powerless to change. Professor Ellis might have added that the parents, too, may feel powerless to change it. Love is not to be commanded, and some emotionally disturbed children, like some normal children, are harder to love than others. The very utmost their parents may feel able to offer them is kindly treatment; but very few disturbed children are taken in by the counterfeit. In such circumstances they may well be less harassed, and less harassing, with others, anyhow for a time, than they are with their own family: better tepidity from a stranger than dislike from one's own flesh and blood.

The emotionally disturbed child is, of course, likely to get into conflict with more than his parents, and to make himself a nuisance to society at large: and the part which punishment should play in helping him to adjust himself needs consideration. Professor Ellis recognises five types of punishment—vengeance, deterrent punishment, punishment by restitution or atonement, vicarious punishment, and self punishment. While vengeance notoriously relieves the feelings of the bystanders, public opinion has gradually reacted against it. We no longer favour public executions, or the pillory; and we are, he thinks, slowly turning against the use of corporal punishment in schools. Whether or not a given punishment will act as a deterrent, either of the offender, or of others minded to commit his fault, will depend on the attitudes and relationships of the people concerned. If a boy at the gang age feels more loyalty to the gang than to the society he has offended, the deterrent effects of punishment may well be small. Punishment by atonement is a function of self-punishment: a lively conscience demands that the wrongs done to others are made good. Vicarious punishment went out with whipping boys. In the last analysis, punishment by a parent with whom the child is on good terms is reassuring, enabling him in time to take over the ethical standards of the community he lives in, and also the responsibility for seeing that he maintains them. Those who have to deal with maladjusted or delinquent children have therefore to remedy the underlying defect rather than to concentrate on the superficial manifestations of emotional disorder. Their first task is to get the child to realise that adults are not fundamentally hostile, and to provide the background of affection and security which the child lacked in his own home; for, unlike the old lag, he has seldom acquired an irreversible belief in society's hostile intentions. But it is both useless and harmful to persist with methods which have already convinced him that he is among enemies.

This constructive view of punishment, so plainly stated by Professor Ellis, is also implicit in a London County Council pamphlet, *Punishment in Schools*,[2] intended by the council's education inspectorate, who are responsible for the suggestions in it, to stimulate discussion. They note that punishment in schools is declining, that harsh methods by teachers foster harsh standards in pupils, and that corporal punishment should be reserved for special cases which threaten the well-being of the school or class and then used only after other methods have failed. Even then, the pamphlet says, is corporal punishment likely to succeed? The staff, in some schools are so doubtful of its results that they have given it up altogether. Criticism should be good-humoured, sarcasm discarded, detention ordered sparingly. The children should share in the task of maintaining discipline, and be encouraged to take responsibility for their acts and to control their desires. "To be lasting, conformity must come from within, not be imposed from without."

THE STORY OF PERNICIOUS ANÆMIA

A CLOSER acquaintance with the history of medicine adds colour to the plain facts of the textbook, and gives a new significance to the great names of the past. Dr. S. C. Dyke did just this in the first Foundation Lecture of the Association of Clinical Pathologists, which he gave before the meeting of the association in London on Oct. 2. He went back over the past 130 years to trace the Development of the Concept of Pernicious Anæmia.

His story began with James Scarfe Combe, who wrote his examination papers to the sound of the guns of Edinburgh Castle proclaiming the Victory of Waterloo; but the cannonade was not wholly welcome to young Combe, for it meant the frustration of his ambition to become a military surgeon. However he did well enough in civil practice, and in 1824 he wrote the earliest known account of a case of pernicious anæmia. But his work aroused no great interest, and Thomas Addison is generally, though in Dr. Dyke's view mistakenly, considered to have been the first in the field. Addison's supporters point to the description of "a very remarkable form of general anæmia, occurring without any discoverable cause whatever" which prefaces his famous paper of 1849 on the Constitutional and Local Effects of

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[1] Canad. med. Ass. J. 1952, 67, 202.

[2] London County Council: 1952. To be had from any bookseller, or from Staples Press Ltd., Mandeville Place, W.1. Pp. 8. 11d.; postage extra.

Disease of the Suprarenal Capsules; but Dr. Dyke thought there was little justification for preserving the name addisonian anæmia.

The next great figures on the scene were Anton Biermer, a Zürich physician who described 15 cases of "progressive pernicious anæmia" in 1872; Julius Cohnheim, the German pathologist, who first noted the fœtal type of bone-marrow; and Samuel Fenwick, physician to the London Hospital, who found the clue to the fundamental lesion in his study of the gastric mucosa. Then, in 1877, Sir Stephen Mackenzie, also of the London, published an account of the natural history of the disease to which little of importance was added for some years. But the pathologists were also at work; the prolific Ehrlich took a hand by introducing revolutionary staining methods and identifying the megaloblast.

A diversion came in 1903 when William Hunter argued convincingly that the disease was a specific infectious fever connected with "an exposure to drain poison," and his views gained wide acceptance. However, the subject soon advanced on to firmer ground; the work of Price-Jones and Boycott on red-cell diameters established that the anæmia was the result of faulty production of red cells and not of excessive destruction; and Peabody, of Boston, fixed the blame on the immature megaloblast.

As Dr. Dyke pointed out, the next and perhaps the most important discovery came in an unexpected way—from work on nutrition. The discovery of the effect of liver in pernicious anæmia earned for Minot, Murphy, and Whipple the Nobel prize in medicine and physiology for 1934. The disease was now being rapidly conquered, and Cohn, of Harvard, made things even better when he prepared liver extracts that were active parenterally. To round off his story, Dr. Dyke outlined the remarkable progress that followed Castle's discovery of the significant defect in gastric digestion—progress with which his audience were more closely familiar. The large pharmaceutical firms had, he said, fostered much of the research on pernicious anæmia in the past ten years or so—research that had culminated in the simultaneous and independent isolation of vitamin B_{12} by Lester Smith in the Glaxo laboratories and by Rickes and his colleagues in the United States.

The Foundation Lectureship of the association has been created in honour of Dr. Dyke, who has been a distinguished member of the association since its earliest days twenty-five years ago, and after the lecture Sir Lionel Whitby presented him with the first Dyke medal.[1]

OTITIS EXTERNA

MUCH bacteriological and mycological work has been done on otitis externa since the outbreak of the late war, for the disease was very common among troops serving overseas and became a serious cause of absence from duty. The latest information comes from Singer and his colleagues[2] in Florida and Texas, who have recently examined cultures from 1377 normal external ears and 646 diseased ones. They isolated over 3000 strains of various organisms and determined their sensitivity to each of seven drugs. Their findings confirm the growing opinion that fungi play only a small part in otitis externa, and that this irritating disorder is usually caused by bacterial infection with *Pseudomonas pyocyanea*; this organism was isolated from as many as 65·5% of the infected ears, but it was found in only 1% of the cultures from normal ears. Most of the organisms were sensitive in vitro to terramycin and many to sulphadiazine, and Singer et al. recommend that these drugs should be given first place in treatment, though they leave the actual method of application to clinical trial.

Alonso[3] studied a smaller series of 82 patients in Puerto Rico, and he was able to isolate fungi from only 7 of them. A distinction was drawn between the acute cases, in which staphylococci were predominant, and the chronic cases, all of which grew *Ps. pyocyanea* on culture. These were also the commonest pathogens in another 100 cases of otitis externa reported from Helsinki by Vaheri and Savolainen[4]; they report good results from local application of the drugs that were indicated by sensitivity tests. They regard otitis externa as primarily a disease of the skin in which infection plays an important but not the only part, either as cause or effect.

In short, laboratory investigations in the last decade or so have shown that otitis externa is commonly a bacterial (and not as was formerly believed a fungous) infection, that the organisms responsible in most cases are *Ps. pyocyanea* and staphylococci, and that good results follow treatment with an antibiotic selected by sensitivity tests. Further clinical trials must be made with terramycin, but it seems probable that complete control of the infective element in otitis externa may still leave an active underlying dermatosis.

DIAGNOSIS OF UNDULANT FEVER

UNDULANT fever is a sporadic disease which simulates many others, and consequently a definite diagnosis can be reached only with the help of the laboratory. The one way of making a certain diagnosis is by recovering the organism from the patient. This is possible in almost all cases during the acute febrile stage or during exacerbations. Blood-culture requires suitable media, which are not available at all centres. In their second report[5] on brucellosis a committee of the National Research Council of America recommends "trypticase-soy" broth or Albimi brucella medium in preference to the older liver-infusion media. Cultures must be incubated in 10% carbon dioxide. Subcultures should be made every 4 days for a month if necessary; Castaneda's technique, which makes use of a rectangular blood-culture bottle layered on one side with agar, avoids the danger of contamination. The bottle is tipped every 48 hours, and the blood-broth mixture flows over the agar surface, thus seeding the foreshore. Since brucella localise in the reticulo-endothelial cells, bone-marrow culture may be positive even after repeated negative blood-cultures; and the organism may also be isolated from lymph-nodes. Occasionally brucella is found in the urine, and in some cases of chronic cholecystitis it has been recovered from the bile. The isolation and identification of brucella from any of these sources takes many days, and repeated examinations may be needed.

A more rapid pointer towards diagnosis is the routine Widal test, although cases may be missed if the serum is not put up in a sufficiently wide range of dilutions. According to the American committee optimal results with the agglutination test are obtained only if incubation at 37°C is continued for 48 hours—a much longer time than is sometimes allowed in this country. There is no easy way of interpreting such tests, but in bacteriologically proved cases of the disease the serum almost always agglutinates at 1 : 100 or over. The agglutination test has the advantage that it is not usually affected by antibiotic therapy, which often sterilises the blood and as often leaves the organisms entrenched in the tissue cells. With clinical recovery from an attack of undulant fever, the serum agglutinins are not usually detectable after a year; but they may persist and cause confusion during some other illness. Immunisation against cholera is yet another pitfall, for the H antigen of the vibrio stimulates agglutinins for the brucella group of organisms. Nevertheless agglutination methods are much easier to carry out than the complement-fixation test, which yields similar results, and the opsonocytophagic test, which is no longer recommended. As with all serological procedures it is wise to demonstrate [illegible]; and this is absolutely essential if the patient has had contact with farm animals.

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[1] See *Lancet*, 1948, i, 530.

[2] Singer, D. E., Freeman, E., Hoffert W. R., Keys, R. J., Mitchell, R. B., Hardy, A. *Ann. Otol., &c., St Louis*, 1952. 61, 317.

[3] Alonso, M. *Laryngoscope, St Louis*, 1951, 61, 1114.

[4] Vaheri, E., Savolainen, T. *J. Laryng.* 1952, 66, 253.

[5] Spink, W. W., McCullough, N. B., Hutchings, L. M., Mingle, C. K. Report no. 2 of the National Research Council, Committee on Public Health Aspects of Brucellosis. *J. Amer. med. Ass.* 1952, 149, 805.

In the United States dermal sensitivity tests have been widely used, and brucellosis is sometimes diagnosed from a positive test found in a patient with symptoms suggestive of the disease. In deprecating this practice the committee points out that 10–25% of healthy people give positive skin tests, and that the number of positives is directly proportional to the number of infected animals in the area. Few of these people give a history of the disease, and there is not even much correlation between the severity of proved infections and the degree of sensitivity. Skin tests thus do not help the clinician in diagnosis, although they may have a place in epidemiological studies since there is little doubt that the dermal reaction is specific for brucella. In this country skin-test antigens have fortunately never been much used, although intravenous brucellin is still thought by some clinicians to be of value in treating the disease.

VENOUS VELOCITY

THE therapeutic possibilities of anticoagulants have made the study of venous blood-flow and its influence on venous thrombosis of unusual interest. Dr. Payling Wright and her colleagues have been studying the conditions under which the flow of blood in the veins may be accelerated or retarded, and they describe some of their results in an article which we publish this week. They have estimated the mean rate of venous blood-flow in the legs by injecting a minute quantity of radioactive sodium into a vein on the dorsum of the foot and then timing its arrival at the femoral triangle by means of a Geiger counter. They had previously found[1] that, compared with a standard rate of flow in the horizontal position, the linear velocity in the leg veins was reduced to half by standing and to two-thirds by sitting, but, strangely enough, it was uninfluenced by sitting with legs crossed. In this position the upper knee is higher than the groin, and this may make up for any speed lost in the dependent part of the leg below the knee. They also showed that in a sloping head-down position the rate of flow in the leg veins might be doubled, and that active movements of the foot could produce the same result.

Their latest work shows that merely putting a patient to bed does not lead to slowing of the venous blood-flow in the legs. In the paralysed legs of hemiplegics, however, venous flow is grossly retarded to about one-third the normal rate; and after surgical operations the rate of flow gradually decreases during the first two weeks in bed.[2] The reason may be that pain and discomfort cause the surgical patient to lie exceptionally still. Similarly, respiratory discomfort may make the patient with heart-disease immobilise his limbs completely. This retardation of flow must obviously favour the onset of thrombosis, but Dr. Wright and her associates have demonstrated that a little pedalling movement of the feet may make all the difference in accelerating flow through the veins.

Veins seem to have been neglected by physiologists, who perhaps regard them as passive conduits of little interest compared with the arterial system with its fascinating hæmodynamic problems. Moreover, in clinical medicine, occlusion of the arteries of the limbs is relatively easy to recognise, and its effects are readily measured or predicted. By contrast, thrombosis of veins in the legs may proceed insidiously, and its extent is almost impossible to assess; but its treacherous embolic consequences inflict appalling damage or sudden death. To minimise the risk of these disasters, the simple precaution of encouraging foot movements in bed, the value of which is underlined by these experiments, should be accepted and applied. Much suffering and disability may thereby be averted.

FINDING TUBERCLE BACILLI

IT is well to recall from time to time that the bacteriologist is not infallible, and that failure to find tubercle bacilli in the sputum may not mean that there are none to be found. The results of sputum culture depend both on the technician's skill and the methods he uses. There are, for instance, many different ways of homogenising sputum. To clarify the conflicting reports on their merits, the Public Health Laboratory Service has carried out an extensive investigation, the results of which have now been published.[1]

Four methods of homogenisation were compared by 12 laboratories, using over 3000 samples of sputum, and the thoughtfully designed and carefully executed experiment has given a clear-cut answer. The sodium hydroxide method proved a convincing winner; 28% of the microscopically negative sputa that were homogenised by this method gave positive cultures, against only 16% by trisodium phosphate, the least efficient method.

In the difficult matter of estimating progress in pulmonary tuberculosis, repeated examinations of sputum cultures, laryngeal swabs, and gastric washings give the clearest picture of the true state of the bronchial secretions. But they remain merely estimates, subject to chance errors of sampling and to inaccuracies inherent in the laboratory methods. Thus, differences between the reported rates of sputum conversion at two centres may be caused by different laboratory methods and not by variations in treatment. A patient may be classed as "non-infective" simply because trisodium phosphate was used, and not sodium hydroxide; or a "minimal lesion"—a clinical concept with no pathological basis—may seem to progress from quiescence to activity because of a change in laboratory technique, or indeed merely by chance. In clinical practice diagnosis is based on reasonable probabilities, and certainty can rarely be achieved. More efficient laboratory methods will help the physician in the difficult task of assessing these probabilities; but, on the other hand, his ideas on the management of tuberculosis may require considerable modification should the bacteriologist become able unfailingly to detect the presence of the tubercle bacillus.

OVERSEAS APPOINTMENTS

AT present hospital consultants and S.H.M.O.S who accept short-term appointments overseas must resign their posts in the National Health Service. Though their superannuation rights can be protected, they cannot claim reinstatement in their posts on their return to this country. They are away too long for their appointments to be filled by locum tenentes; nor can regional hospital boards fill these vacancies by short-term appointments, for no period of tenure can be inserted in contracts for officers of these grades. This insecurity has, not unnaturally, discouraged recruitment to overseas posts; but the Minister of Health—like the rest of us—thinks that it is in the "national interest and that of medicine generally that candidates for overseas posts should be forthcoming in this country." He has accordingly modified the present arrangements (R.H.B.[52]106) so that regional boards may grant leave of absence without pay for a period not exceeding three years to consultants or S.H.M.O.S who wish to take up posts overseas, and to fill these vacancies boards will be allowed to make appointments for a limited time.

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1. Wright, H. P., Osborn, S. B. *Brit. Heart J.* 1952, 14, 325.
2. Wright, H. P., Edmonds, D. G. *Lancet*, 1951, i, 22.

1. *Mon. Bull. Minist. Hlth Lab. Serv.* 1952, 11, 187.

Public Health

THE NOTIFICATION OF DISEASE

With Special Reference to Infectious Disease

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IN presenting the following survey, I hope to demonstrate the interdependence of the two great divisions of medicine, therapeutic and preventive; to show that the doctors' powers of observation and notification are vital in the campaign for public and private health; and to suggest an increased potential in the power of notifying disease, together with further collaboration between the various sections of the profession.

The Present Position

Before 1889, a few administrative authorities in this country recognised the value of the notification of certain infectious diseases, as cases occurred, to public-health departments, whence preventive measures could be instituted against the spread of disease. Notification, however, was neither compulsory nor nation-wide, and when it first became statutory in 1889 by the Infectious Disease Notification Act, it did not apply to London and was adoptive elsewhere. Ten years later, notification of the diseases listed became generally compulsory. It had been made compulsory in London in 1891. Other diseases have been added to the list mainly by regulations made by the Minister of Health under the Public Health Act, 1936, and the corresponding London Act (which repealed these earlier laws) and under preceding Acts, and by the Food and Drugs Act, 1938. Some which have been notifiable are no longer so. Apart from industrial diseases made notifiable by the Factories Acts (dating back to 1895) and by regulations made by the Minister of Labour, only infectious diseases or conditions which are believed to be frequently infectious are subject to statutory notification.

The list applicable throughout the country at present includes under the Public Health Act, 1936, smallpox, cholera, diphtheria, membranous croup, erysipelas, scarlatina or scarlet fever, typhus, typhoid, enteric or relapsing fever; under the Food and Drugs Act, 1938, food-poisoning; and under current regulations, the dates of which are included in parentheses, plague (1900), acute primary pneumonia, acute influenzal pneumonia, malaria (whether naturally acquired abroad or in this country, or if artificially induced in an institution, when the disease is likely to be a source of risk to others on discharge), dysentery (all 1927), ophthalmia neonatorum (1928), measles and whooping-cough (1940), meningococcal infection, acute poliomyelitis (paralytic and non-paralytic), acute encephalitis (infective or post-infectious) (all 1949), puerperal pyrexia (1951), leprosy (1951), and tuberculosis (1952).

Notification of some diseases may, however, be limited to persons in certain areas, or to persons of certain ages, and applied only for a defined period. Thus, although the Public Health Act, 1936, omitted puerperal fever and continued fever from the existing list of notifiable diseases, the corresponding Act for London continued the requirement to notify them. Acute rheumatism in children under 16 years of age is required to be notified in Bristol, Sheffield, Lindsey with Grimsby, and Lincoln, since 1947, and now Salford, Hull, and Cornwall; and infectious jaundice (at all ages) in East Anglia was made notifiable in 1947 for three years, but renewed. Criteria of diagnosis are applied both to rheumatism and tuberculosis: thus, tuberculosis diagnosed solely by means of a tuberculin test is not notifiable.

Local authorities, including the London County Council, but excluding other county councils, have the power with the consent of the Minister, in accordance with the provisions of the Public Health Acts, 1936, to declare infectious diseases to be permanently or temporarily notifiable in their own areas, the most usual instance being chickenpox, temporarily, during the occurrence of smallpox.

What are called the quarantinable diseases are notifiable to the Ministry by port medical officers and medical officers responsible for aerodromes; they include cholera, smallpox, louse-borne typhus and relapsing fever, yellow fever, and plague. International control of these grave infections is effected by cross-information through the World Health Organisation.

Although the duty of notification in respect of any of the infectious diseases listed in the Public Health Act falls in the first instance on the head of the family, then (in default) on the nearest relatives present or in attendance, then on persons in charge of or in attendance on the patient, and then on the occupier of the building, it is also placed concurrently on the medical practitioner in attendance or called in to visit the patient; and in fact the notification is invariably made only by the practitioner. In regard to all the other diseases the onus is placed only on the doctor. Notifications must be sent to the medical officer of health of the local sanitary authority of the area in which the case is diagnosed; but there is one exception, leprosy—which must be notified direct to the chief medical officer of the Ministry of Health.

In all cases (except food-poisoning), the notification of infectious disease is made on a prescribed form (supplied gratis by the local authorities), which in respect of a tuberculosis case must be sent in such a manner that *during its transmission its contents cannot be observed.* The fee payable by local authorities is 2s. 6d., except in relation to cases occurring in a hospital or institution or in buildings occupied for the purpose of defence services, when the fee is 1s., for which variation there seems little justification.

The doctor, in all cases except food-poisoning, must notify "as soon as he *is aware* that the patient . . . is suffering from the disease" (he must notify tuberculosis "as soon as he forms the opinion"); but he must notify food-poisoning "as soon as he becomes aware or *suspects* the patient is suffering from the disease." The difference is important.

The penalty for failure to notify is 40s.

The county district medical officer of health (in London the medical officer of health of the Common Council or of a Metropolitan borough) must send within twelve hours, if possible, and a maximum of forty-eight hours (twelve hours in London) a copy of every notification of infectious disease received by him to the corresponding county medical officer. The medical officer of health must report to the Registrar-General weekly the numbers of the different diseases notified; and the latter issues, weekly and quarterly to medical officers of health, a statement detailing this information collated for England and Wales. In some areas the medical officer of health regularly and informally tells the general practitioners about the occurrence of notifiable disease in the town or district. In regard to some of the most dangerous infectious diseases (smallpox, plague, typhus, relapsing fever, and malaria contracted in England) the medical officer of health is required to notify the Ministry at once that he has had a notification. The Ministry have in the past informally requested the immediate notification of pemphigus neonatorum and of outbreaks of gastro-enteritis in maternity homes, though these are not statutorily notifiable diseases.

STATUTORY NOTIFICATION BY OTHERS

As already indicated, others besides doctors have responsibilities clearly laid upon them in regard to notification.

Under the Public Health Acts the keeper of a common odging-house must notify to the medical officer of health the occurrence of infectious disease in an inmate.

Under the Milk and Dairies Regulations, 1949, every person having access to milk or to milk receptacles in registered dairy farms, cowsheds, milk shops, &c., as soon as he becomes aware that he or any other member of his household is suffering from any disease notifiable under the Public Health Act, or dysentery or gastroenteritis, must notify the occupier of the premises who must forthwith notify the medical officer of health. Conversely, if the information reaches the medical officer of health in any other way, he must notify the occupier.

Local Acts have given various local authorities extended powers in relation to infectious disease, including compulsory notification—e.g., by parents to the head teachers of schools and Sunday schools.

Every midwife and maternity nurse (except those in hospitals with at least 15 maternity beds, and a resident doctor) must under the Central Midwives Board's rules which are made under statutory powers, notify the local supervising authority (the county borough or county council) if she is liable to be a source of infection or if she has been exposed to any infective condition.

The master of a ship and the commander of an aircraft must report to the port or aerodrome medical officer all cases of suspected infectious disease aboard during the journey.

Veterinary surgeons attending animals suffering from anthrax or rabies or glanders or farcy must inform the medical officer of health.

Justification of Notification

Notification of disease can only be justified if it serves a demonstrably useful, and indeed necessary, purpose. Clearly, it gives information as to the incidence of disease, both in regard to the rate at which it is occurring, its age and sex distribution, the time of year in which it is prevalent, and the place in which it is found. Secondly, it is essential for the immediate local control, and also in the graver cases, national and international control, of those diseases in which control seems practicable. Thirdly, it ensures that appropriate care, including if necessary hospital care, is offered; but apart from cases of tuberculosis, this element is less significant now than it was before 1948, when the local authority itself provided treatment of these diseases; even so, the health authority has duties in relation to advice in the home, home nursing, home helps, and prevention. Finally, it may be of use as a means of providing a comprehensive list of cases which then become the basis of further study, either clinically (as in acute rheumatism) or in regard to ætiology or epidemiology, or in regard to the formulation of policies relating to their control. To be effective for control purposes, notification must be statutory: it should then be complete, but we know that in regard to some diseases it is far from comprehensive. Informal notification is almost necessarily incomplete, though in some instances in respect of what is attempted it is probably nearly complete—e.g., cancer cases treated in hospital are notified fairly comprehensively to some of the regional cancer bureaux. Who can doubt that more accurate information will be obtainable in Manchester, where german measles is notifiable, on the effect of this disease in pregnancy than will be obtained by the voluntary inquiry now being made in regard to this and other diseases by the Medical Research Council?

Notification a Prelude to Control

Infectious diseases may be made notifiable either because they are very dangerous or because, though not very dangerous, their spread can be limited, which is almost always desirable.

In many infectious diseases, knowledge is far from complete as to the way in which they are spread, and action designed for control is often taken empirically and sometimes on an insecure foundation of knowledge. It is obviously particularly difficult to control diseases which are spread by direct contact, especially in the incubation period. It is much harder to predict and to control human behaviour than to control an inanimate substance like water or food. The practice regarding contacts of disease varies greatly, but control by strict quarantine of contacts is quite impracticable even though some control of contacts in relation to occupation, school attendance, and so on, is still practised.

In regard to those diseases which are notifiable under the Public Health Act, 1936, certain legal controls apply; these deal with exposure of other persons to the disease, either by contact or through clothing, bedding, &c., not adequately disinfected; attendance at school; sending of infected articles to the laundry; carrying on trade; home work (textiles); selling rags; letting rooms; travelling by public conveyance; and the compulsory removal in certain circumstances of cases of notifiable disease to hospital and their retention in hospital and the compulsory removal in certain circumstances of tuberculous patients. Much the same apply in London. These sections of the Act do not apply to those diseases made notifiable by the Minister under regulations because he has applied to them only sections 144, 145, and 146 of the Act (the notification and not the control clauses). On the other hand, diseases made notifiable by local authorities under the Act do become subject to the same controls as the other notifiable diseases named in it. Although some of these clauses appear to be no longer necessary, it is valuable that the law does control the behaviour of persons suffering from the graver infectious disorders, and those in charge of them.

Some Suggested Variations of Notification Requirements

In considering any changes in notification the questions which should be borne in mind are:

1. Is the disease serious?
2. Is its natural history well understood?
3. Does it spread quickly?
4. Is its spread controllable?

No useful steps in regard to control are practicable in regard to acute primary pneumonia, which has now lost most of its terrors; it is time we abandoned its notification. Membranous croup is no longer diagnosed separately, and it should be left out of the list. Cholera, typhus, and true "relapsing fever" are now practically unknown in England, but as they are dangerous and subject to control they should be allowed to remain notifiable. Three others are so infectious that all the susceptible contacts are likely to get the disease—namely, measles, bacillary dysentery, and probably whooping-cough. The notification of the first case in the family in any one family outbreak would be sufficient to put the health department into touch with that family. (It must be admitted it is very difficult in epidemics to follow up adequately every family concerned.) In law, the health visitor cannot notify any subsequent case, though there may be no doubt about it; some arrangement for an acceptable record of these later cases should and could be worked out. Since, however, whooping-cough is likely to be made the subject of an immunisation campaign it may be thought necessary for assessment of the results to maintain notification of *all* cases, though it is believed that notification is even now very far from complete. A saving would be necessary in respect of dysentery—namely, that whenever the case is in a food worker or a home contact of a food worker, it should be notifiable, so that "assurance might be made doubly sure."

Scarlet fever poses particular difficulty whilst the other forms of streptococcal throat infection are not notifiable. But scarlet fever is a pretty definite clinical entity, whereas streptococcal sore throat may not be clinically distinguishable from other varieties of sore throats. The risk of spread of streptococcal infections to the community seems greatest when it occurs in milk workers, maternity-hospital workers, and institution staffs generally. Erysipelas is only a risk to the public health when it occurs in such a worker or a home contact of such a worker. Apart from these cases, which should be notifiable in every instance, it would be desirable and sufficient to notify only the first case of acute streptococcal sore throat as diagnosed clinically, or scarlet fever in a family, leaving the health department to follow up the family.

Puerperal pyrexia and ophthalmia neonatorum are conditions which may be due to infective causes, for they are incomplete diagnoses: notifications are useful if they point the way to improvements in standards of maternity care, and so affect the prospects of other mothers and infants. Many feel the present Puerperal Pyrexia Regulations are too stringent; possibly up to two-thirds of the cases notified would not have been notified under the older regulations. If the doctors would state the believed cause (and this should be required) and also if doctors would take swabs in all doubtful cases—a vaginal or eye swab can easily be taken by the midwife if so directed—preferably before or early in treatment, the accurate diagnosis, which is so important from the point of view of prophylaxis and control, would more certainly be reached; and this should be encouraged. Probably, both these conditions are substantially under-notified. Notification is said to be distasteful to general practitioners because it is followed by inquiry by the local health department; but how much would the medical officer of health be criticised, and how rightly, if notification led to no inquiry and no action; that would, indeed, be proof of its uselessness.

TUBERCULOSIS

Tuberculosis is probably better ascertained than ever before. Preliminary notification (on suspicion of the disease) has been applied in Northern Ireland to tuberculosis with, it is said, considerable success. But with increasing facilities for mass miniature radiography here, there seems little doubt that notification of tuberculosis is steadily becoming more and more complete. We must realise, as must the public, that the key to the control of tuberculosis lies not only in medical care, drugs, and surgery, but in the recognition of its infectious nature. There should be no doubt of the obligation on doctors in charge of mass miniature radiography units who should be required to notify cases suspected by them to be tuberculous. Regulations, quite reasonably, exclude from notification cases diagnosed solely on the tuberculin test. In America, a classification of cases based on the apparent activity of the lesions has been suggested, some being notifiable compulsorily, others optionally, others not at all—a method likely to lead to confusion. In England, it has been suggested that cases which are infectious or require treatment should be notifiable, but this has not been adopted legally. Simple pleural effusion of unexplained origin should be a notifiable disease in view of the frequency with which it is the primary sign of tuberculosis. The secrecy attaching to tuberculosis notifications is still preserved in the 1952 regulations though its degree is not explicitly laid down as formerly: it is wrong that a person in close and continuing contact with young children could, even though affected by open tuberculosis, continue to work amongst them; but the medical officer of health is not legally permitted to use his knowledge of the notification to intervene. This should be altered.

ACCURACY AND RISK

In regard to some of the diseases—notably malaria, acute primary pneumonia, acute influenzal pneumonia, typhus, relapsing fever, typhoid fever and dysentery in food-handlers, and notifiable disease and gastro-enteritis in milk workers—the medical officer of health is required at least to take action as prescribed in regulations, and is given certain specific powers; but generally he is left free to make such arrangements as he can for the control of the disease.

Speaking broadly, effective control depends on speedy, comprehensive, and accurate notification: reasonable accuracy and reasonable speed should not be regarded as antagonistic. Where the spread of infection is slow, notification should be based on reasonable certainty; but it is worth remembering that the patient who is mobile and infectious is a greater danger to the community than the one who is laid low by the disease.

There are two questions which any doctor seeing a case of infectious disease should ask himself, after he has made his provisional diagnosis and arranged treatment: (1) is this disease a serious risk to the community? and (2) are the circumstances here likely to make for spread? And one of the most important considerations is the occupation of the patient and his home contacts. Where the disease is a grave risk to the community, as in smallpox, poliomyelitis, typhoid, or when the circumstances are such that an explosive outbreak may occur (e.g., bacillary dysentery in a food worker or streptococcal infection in a milk worker) notification should be very prompt, and reasonable *suspicion* should be enough to justify it—certainty too often comes too late. Notification by telephone, as is increasingly practised by more progressive doctors and accepted by more progressive health departments, should be not only locally agreed, but sanctioned by the law, in regard to the cases and circumstances just referred to. Today, however, many practitioners will wait until the diagnosis is verified bacteriologically, which may take anything from one to three or four days, before they notify—a delay which makes efforts at control, or even investigations, completely ineffective.

The meaning of food-poisoning should be clarified; it is often used in reference to isolated cases of salmonella infection proved in the laboratory, but it should be reserved for illness usually intestinal or gastro-intestinal, occurring in two or more persons at or about the same time, who are known to have eaten the same foodstuff at or about the same time.

THE LABORATORY

Doctors in medical laboratories, whilst they do not make the diagnosis, do give confirmation or precision to a diagnosis, and often have information about cases of both the notifiable and the non-notifiable infectious diseases, such as glandular fever, virus diseases, leptospirosis, and possibly influenza, as well as acute streptococcal sore throat, various forms of meningitis, food-poisoning, typhoid, dysentery, meningococcal infection, and whooping-cough and tuberculosis. It would be invaluable if they were statutorily, or by direction of the Minister, required to inform the medical officer of health as soon as the bacteriological or serological or other laboratory identification is reasonably secure and points to infectious disease. This is almost self-evident in regard to the Public Health Laboratory Service, which has been set up to help to safeguard the public health, even though it is not responsible for the epidemiological control of disease; indeed, in some areas, and in part, the arrangement here suggested is already in operation. The same should be applied at least to hospital laboratories, now a part of the National Health Service, and which often have information about patients not in hospital as well as about those in hospital. These latter, if infectious, are a risk in the hospital, and possibly even to the community, and in any case should be investigated.

These proposals, if carried out, would do more than anything else to make it possible to study the natural history of all kinds of infections, where alone it can be properly studied, locally and in the home.

CARRIERS

Notification does not yet apply to persistent carriers, but only to *sufferers*. This is a serious defect in regard to salmonella and shigella carriers and should be remedied. At the present time, the regulations which govern the action of the medical officer of health and local authority in regard to enteric and dysentery are under revision, and it is probable the control of carriers will be made more effective, but not necessarily their notification. Notification is not required in regard to cases recognised long after the phase of acute illness is over, though in some instances, it should be—e.g., late recognised paralysis in poliomyelitis. It is not required of doctors who may know of the occurrence of an infectious disease but who are not in attendance or called in to visit the patient, and this is sound.

Notification is not required in regard to patients in hospitals in which persons suffering from infectious diseases are received—an exclusion which was, doubtless, due to the fact that at the time (1936) fever hospitals were owned by local authorities and administered through their medical officers of health; this is a weakness largely overcome in isolation hospitals by the close relations still existent between these hospitals and health departments, relations which may not, however, persist indefinitely. But although no-one would doubt the capacity of the staff to cope with the infections, the notification of a notifiable disease arising in an isolation hospital should now be a statutory requirement. This proposal is in line with, though it goes further than, the recent recommendation of the Central Health Services Council. Although doctors in general hospitals are not exempted from the duty of notifying, they are notoriously lax in doing so.

NON-NOTIFIABLE INFECTIONS

There are very many infectious diseases which are not statutorily notifiable, in particular, infective enteritis of infancy, gastro-enteritis of unknown origin and possibly viral, influenza, common cold, meningitis of various kinds, brucellosis, glandular fever, Bornholm disease, simple infectious jaundice, leptospiral jaundice, homologous serum jaundice, pemphigus neonatorum, and the venereal diseases. During the last war, notification of alleged causal cases of venereal disease was in certain circumstances permitted (Regulation 33B). Otherwise Parliament has always refused to require its formal notification. A certain amount of transference of information about defaulters and cases where contact tracing is important goes on between clinics and health departments which have the statutory duty of aftercare.

Influenza is a disease of which the diagnosis is by no means straightforward until an epidemic is clearly on the way, but it is at the beginning of an epidemic that it is most important to know that it is occurring. It is doubtful if the notification of clinical influenza is practicable. Occasionally, laboratories get blood samples and nasopharyngeal swabs and can make a bacteriological diagnosis. Colds are so frequent and, although serious in childhood, are generally so trivial that their notification would clearly neither be practicable nor justifiable. Presumably, the spread of the common cold can only be limited by keeping the sufferers at home.

Acute gastro-enteritis, or enteritis, may be an infectious disorder or not, but if we wait until the bacteriological diagnosis is established by laboratory investigation, we have waited too long for any hope of control. In food workers (including milk workers) this diagnosis alone should necessitate notification. Curiously, the milk worker with gastro-enteritis must notify his employer, who must notify the medical officer of health, but his doctor need not. When occurring in infants in an institution or in the staff of institutions (such as day or residential nurseries, maternity homes, or hospitals) it should also be notifiable.

Probably, glandular fever, which is said to be increasingly a serious disorder and replacing diphtheria in interest, even if, fortunately, it is rarely fatal, should be notifiable. Simple infectious jaundice, homologous serum jaundice, and leptospiral jaundice are all probably commoner than is realised, and some measure of control for them seems practicable: it would seem reasonable to make them notifiable. It is now exceedingly difficult to trace the origin of brucellosis, so control (apart from pasteurisation) is difficult.

It is impossible to make regulations covering indefinite infectious diseases and yet how valuable it would be if any explosive outbreak or clearly infectious process (even if not formally notifiable, or even not completely diagnosed) were to be reported voluntarily to the medical officer of health, a reasonable fee, say 5*s*., to be payable for informing him of the outbreak. The occurrence of family epidemics is recognised by every general practitioner and more painfully still perhaps by every doctor who has a family.

Notifiable Industrial Diseases

The notifiable industrial diseases include, by virtue of the Factories Act, 1937, poisoning by lead, phosphorus, arsenic, mercury, and anthrax; by the Lead Paint (Protection against Poisoning) Act, 1926, lead poisoning in painters of buildings; by various regulations (dates in parentheses), toxic jaundice (1915), chrome ulceration (1919), epitheliomatous ulceration due to tar, pitch or bitumen, mineral oil or paraffin (1919), carbon bisulphide, aniline, chronic benzene poisoning (all 1924), manganese poisoning (1936), compressed air illness (1938), and toxic anæmia (1942).

Any medical practitioner attending or called in to visit a patient whom he believes to be suffering from any of these diseases, contracted in any factory, must notify the Chief Inspector of Factories, London, for which he receives a fee of 2*s*. 6*d*. Failure to notify carries a penalty of 40*s*.

The occupier of a factory is required to notify the factory inspector and the appointed factory doctor of the occurrence of a notifiable industrial disease in his factory, and he can voluntarily notify industrial dermatitis.

Notification is obviously required in order to direct attention to any factory in which an industrial disease has occurred so that appropriate preventive measures can be taken. It is also important in relation to those cases that end fatally because a coroner's inquest is then desirable in regard to which the Factories Act, 1937, makes special provision. The question of compensation—there are 38 statutory compensable diseases—is not related to notification.

Since the toxic effects of poisons are usually insidious these cases do not present so dramatically as the infectious diseases; and Legge suggested that any symptoms necessitating absence from work and appeal to a doctor for treatment constitute sufficient grounds for notification. He also, however, said that in some of the diseases listed—e.g., mercury poisoning—for every declared case there may easily be twenty minor cases in the shop. Quite clearly, therefore, notification should be made on reasonable suspicion.

Other Non-infectious Disease

Notification is primarily used for control. Is it desirable to extend it to non-infectious diseases where controllable factors may be apparent, and to disease in which ætiological factors of social and environmental nature may be of real significance—for example, abortion, coronary vascular diseases, peptic ulceration, diabetes, cancer (some occupational cancer is already notifiable), and even mental illness? A great deal of mental disorder is already, in effect, notified to the medical officer of health and it would be unwise at this stage to go beyond that.

Clearly, requirements to notify must be kept within reasonable limits and morbidity returns and registration of sickness cannot be regarded properly as within the scope of a discussion on notification. Notification of non-infectious disease is a most difficult problem. My own view is that in selected areas it might be tried experimentally for a limited period in the first instance for one or more diseases—say for abortion, or diabetes—or even nationally for a single disease. Inquiry should be made along pre-selected lines and in conjunction and in collaboration with the general practitioners and hospital consultants. Abortion inquiries would have to be protected in some way from police intervention—a very difficult matter. But these disorders appear to be a real justification for such an inquiry and such notification. Unless the hospitals and the general practitioners are both concerned, any notification scheme must be incomplete.

All notifications should be made in the first place to the local medical officer of health so that there would be no gaps in his knowledge of the health of the community. The necessary transfer to the Registrar-General, to the Ministry of Health, or Factory Inspectorate, should follow in a way to be prescribed. He has, too, the best opportunities for making in the home detailed inquiries necessary in epidemiological research.

If hospital consultants and general practitioners and medical officers of health, the Medical Research Council and university departments of preventive medicine, collaborated adequately, the amount of information available would be enormous. Its reduction to statistical terms would be a considerable task; but we might reasonably hope that sooner or later, in some of the diseases, preventable factors would be shown. Without such an effort, the elusive factors will probably go on eluding us, making health the sport of fate.

Leave of Absence

On Oct. 1 Manchester City Council disapproved the decision of its establishment committee to refuse the application of two doctors in their employ for unpaid leave to attend a part-time two-year course for the diploma in public health (*Manchester Guardian*, Sept. 25 and Oct. 2). The course is the first of its kind to be held at the new department of social and preventive medicine at Manchester University. Manchester Regional Hospital Board has granted leave with full pay to the members of its staff who have enrolled for the course; Salford Corporation and Lancashire County Council have granted leave at a reduced salary.

The reversal of the committee's decision was moved by Dr. William Chadwick, chairman of the health committee, who pointed out that too few doctors had taken the D.P.H., which is an essential qualification for medical officers of health. It was to the ultimate benefit of the city and to the advantage of local government that junior medical officers should be allowed to take the course. Several councillors who agreed to the granting of leave in principle objected that 2½ days a week was too long. Alderman H. Quinney pointed out that a recent applicant for an appointment as school M.O. had been asked by the education committee to take the D.P.H. For Manchester to ask for the qualification and yet refuse facilities for obtaining it was unfair; other authorities had to allow facilities and then Manchester came along and took the finished product. He reminded the council that the doctors taking the course were sacrificing £300 a year to do so.

The growing number of calls on the time of senior officers of the council was also discussed. Alderman R. S. Harper pointed out that the M.O.H. spent an enormous amount of time [illegible] London; they had to protect him f[illegible]ms on his time. Councillor J. E. Pheasey, too, held that the absences of chief officers of the council were growing to alarming proportions; in 1950–51 one of them had been away for more than half the working days of the year. Councillor L. W. Biggs thought that, though it was to the credit of Manchester to have a chief officer whose services were in such demand, six months' absence in the year was too much.

As the *Manchester Guardian* points out editorially, an officer who is taking part in the deliberations of a public body may be serving his council in absence as well as when present, for these national bodies "are often the real policy-makers of local government."

L.C.C. Health Services

Figures given in the statistical report of the London County Council health committee for the quarter ended June 28, 1952, show that the number of home confinements in the county continues to fall. In the June quarter of 1950, 3641 London mothers were confined at home; in 1951 the total was 3381; and this year it is down to 2820. Expressed as a percentage of notified live and still births in each of the three quarters, the figures are 25·1, 22·7, and 20·0 respectively. The number of first attendances at the council's antenatal clinics during the quarter fell from 6242 in 1951 to 5306 this year. It is estimated that 38% of expectant mothers received some part of their antenatal care in the clinics, as compared with 45% in the previous quarter and 43% a year ago. First attendances at child-welfare centres were also less than in the corresponding quarter of 1951.

These figures represent a continuation of the national trends noted in the Ministry of Health's annual report, which is the subject of a special article in this issue.

Slum Clearance

In his report for 1951 Mr. F. Binns Hartley, chief sanitary inspector for Wolverhampton, says that if the present rate of allocation of new houses to families from clearance areas continues, it will take 40 years to clear the borough's 6000 substandard houses. So far only those houses which have become a positive danger to life and limb have been cleared; the best that seems possible in the near future is the demolition of the 200 worst houses, but at the present rate of clearance it will take 4 years to deal with these alone.

Infectious Diseases in England and Wales

Disease	Week ended September			
	6	13	20	27*
Diphtheria	23	26	21	15
Dysentery	132	100	103	123
Encephalitis:				
Infective	4	2	3	2
Postinfectious	1	—	1	1
Food-poisoning	200	105	160	137
Measles, excluding rubella	2937	2121	2597	3272
Meningococcal infection	28	26	30	21
Ophthalmia neonatorum	55	29	31	44
Paratyphoid fever	41	61	33	31
Pneumonia, primary or influenzal	228	210	261	316
Poliomyelitis:				
Paralytic	115	116	127	101
Non-paralytic	73	68	62	57
Puerperal pyrexia and fever	260	203	255	249
Scarlet fever	557	701	853	1164
Smallpox	—	—	—	—
Typhoid fever	7	0	5	3
Whooping-cough	1831	1187	1366	1258

* Not including late returns.

Special Articles

THE EXPANDING HEALTH SERVICE

The Ministry's Annual Report

THE report of the Ministry of Health,[1] published last week, tells of the steady expansion of the National Health Service in England and Wales—an expansion hampered by financial restrictions, but an expansion none the less. The limit of £400,000,000 set on health-service expenditure for the whole of Great Britain in 1951 meant that new developments and extensions of existing services could be achieved only by saving money elsewhere in the service; and the report describes some of the ways in which this was done.

The report covers the twenty-one months from April 1, 1950, to Dec. 31, 1951. These dates were chosen so that future reports could deal with calendar, rather than financial, years, thus bringing them into line with the reports of the Ministry's Chief Medical Officer and with most statistical records other than financial.

HOSPITAL AND SPECIALIST SERVICES

Though, as the report points out, figures for hospital waiting-lists must always be accepted with caution, the number of people waiting for admission fell by 27,000 in 1951—from 530,543 on Dec. 31, 1950, to 503,584 a year later—but the figure is still some 6000 higher than it was at the end of 1949. A more reliable sign of the improving situation is the increase in the number of available beds by nearly 14,000 in 1950 and 1951; the total rose from 448,057 in 1949 to 461,892 in 1951. The corresponding increase in the number of inpatients treated, as measured by discharges or deaths, was from 2,936,980 in 1949 to 3,259,214 in 1951; and there were about 150,000 more "new" outpatients in 1951 than in 1949. The report continues:

> "This development has to a considerable extent been achieved by better use of existing resources. . . . Former isolation beds are now used for tuberculosis, uneconomic units—those, for example, for the treatment of infectious diseases—have been aggregated so as to free staff and accommodation for the development of special departments, hospitals have been linked clinically as well as administratively, departments have been redistributed within individual hospitals and groups. Re-organisation within hospital groups leads to a better service and reduced costs—in some cases, for example, children's beds and maternity and gynæcological beds have been concentrated to good effect in single units. Other services, such as pharmacy, maintenance, supplies and laundry, have been re-organised on a more economical group basis. In general, the major feature of the period under review has been the better planning of the service so as to secure the fullest and most economical utilisation of all resources."

The consultant service has also grown: there were 1605 whole-time consultants in 1951, as against 1310 in 1949; and part-time consultants increased from 3879 to 4274 over the two years. The domiciliary consultant services, which help to reduce considerably the demand on beds, were called on more often; 129,538 patients were seen at home in 1949 and 171,193 in 1951.

The development of the hospital service was also shown by a rise of over 10,000 in the number of whole-time nursing and midwifery staff, and a steady increase in other professional staff—physiotherapists, occupational therapists, and so on.

Turning to the standard of treatment provided, the report remarks:

> "The developments in the service have been qualitative as well as quantitative—in other words, not only have more patients been enabled to receive treatment but individual patients have often been enabled to be treated better or more comfortably. The difference is perhaps most marked in the old hospitals where modern equipment has been installed, particularly the former public assistance institutions which have in the last two years become true hospitals with efficient consultant services and less forbidding appearance. Many of these hospitals were filled with bedridden people in 1949, but now many of the patients are being rehabilitated and made ambulant once more. These old institutions have changed their character and are recognised locally as real hospitals."

Voluntary Aid.—Gifts and legacies to hospitals increased from £1,700,000 in 1949–50 to about £3,000,000 in 1950–51, "and have helped materially to provide all kinds of amenities and in some cases equipment and services which could not otherwise have been provided from restricted budgets." The Hospitals Endowments Fund distributed over £600,000 to hospitals in 1950–51 and as much again in 1951–52.

Beds for the Chronic Sick.—The service is still in difficulties over providing enough room for the care and treatment of the chronic sick. Nearly 57,000 beds are now set aside for this purpose, but the waiting-list is still over 8800. The Ministry says:

> "The heavy demand for hospital beds for other classes of patients tends to limit the admission of chronic sick patients as the hospital service must have regard to the fact that the admission of one long-stay chronic sick patient will prevent the admission of a number of short-stay acute cases."

Suitable nursing staff are still lacking in some areas, and 3100 beds in chronic-sick wards are unoccupied for this reason.

Tuberculosis.—Beds for the treatment of respiratory tuberculosis are still scarce, mainly because of shortage of nursing staff, but the situation has much improved. Suitable blocks in general and isolation hospitals have been set aside for the treatment of tuberculosis, and closed beds have been brought into use again; by these means 3650 more beds became available between July, 1950, and December, 1951, bringing the total increase since the service began to over 6000. The waiting-list (which does not include those patients who are admitted within ten days of being put down for admission) fell from about 11,000 in December, 1949, to about 7000 in December, 1951; and moreover the length of time taken to find a bed for a patient on the list has on the average been much reduced.

Appliances.—In the twenty-one months, over a million new surgical and medical appliances were supplied, and over 117,000 were repaired through the Hospital Service. The output of hearing-aids was higher than ever before, but in spite of this the waiting-list fell by only 2000 (to 110,000) between November, 1950, and August, 1951; but by the end of February, 1952, it was down to 94,000.

MENTAL HEALTH SERVICES

There are still too few nurses and beds; and overcrowding, waiting-lists, and restrictions on the admission of voluntary patients persist. Nearly 5000 beds are unoccupied because of lack of staff. On the other hand, the beds that are in use are now showing a more rapid turnover than in pre-war years, and the number of admissions and discharges in 1949 was double the corresponding figure for 1939. The report gives two reasons:

> "In the first place, voluntary patients are coming forward to an ever-increasing extent, with the result that a higher proportion of cases are coming within reach of treatment in the early stages of illness when the prospects of successful treatment are, of course, better; secondly, there has been a notable increase in the development and application of curative treatments."

GENERAL MEDICAL SERVICES

The Ministry reports that a large number of visits made to general practitioners by members of the regional medical service have given "a general impression of increasing satisfaction with improvements which are taking place, despite inevitable complaints about some administrative matters." Where direct access to X-ray and pathological departments has been given to practitioners, they "have found added interest in their work and benefit both to patients and themselves." Such arrangements have not thrown any unnecessary burden on the special departments.

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[1] Report of the Ministry of Health covering the period April 1, 1950, to Dec. 31, 1951. Part I. (1) The National Health Service. (2) Welfare, Food and Drugs, Civil Defence. Cmd. 8655. H.M. Stationery Office. Pp. 166. 5s.

Large surgeries were still the rule; many doctors have found "that the appreciable seasonal remission in attendances is much less marked than before the start of the Health Service," and the number of patients attending with trivial ailments was a cause of general complaint. Though few practitioners had difficulty in securing hospital admission for patients who were acutely ill, many still found it very hard to get beds for the chronic sick.

By the end of 1951 there were about 18,000 doctors in the service, and their lists totalled over 43,000,000, though this is a somewhat inflated figure.

GENERAL DENTAL SERVICES

After the introduction of charges for dentures on May 21, 1951, there was a substantial decline in the demand for false teeth, but the amount of conservative treatment continued to increase gradually. The average cost to public funds of a course of dental treatment dropped from its peak figure of £5 16*s.* to £2 14*s.* by the end of 1951.

The number of dentists in the service rose from 9495 at the end of 1949 to 9694 two years later; this "slow rate of recruitment," says the report, "gives rise to some disquiet, particularly when the high average age of the profession is taken into consideration."

SUPPLEMENTARY OPHTHALMIC SERVICES

The demand for spectacles fell sharply after May 21, 1951, when charges amounting to roughly half the cost were introduced. Before this date spectacles were being supplied at the rate of about 7,500,000 pairs a year; in the second half of 1951 the rate was down to about 3,300,000. Arrears were cleared off by early 1951, and spectacles are now being supplied as quickly as in pre-war days.

PHARMACEUTICAL SERVICES

The number and cost of prescriptions increased steadily. The chemists dispensed 217,144,505 N.H.S. prescriptions in 1950; and in 1951 the total rose to 228,585,022. The average cost per prescription went up from a little over 3*s.* 1*d.* at the beginning of 1950 to a provisional figure of over 3*s.* 11*d.* at the end of 1951. The report says that the introduction of chloramphenicol into general practice, more prescribing of other expensive drugs, and the rise in the prices of certain drugs and dressings contributed to the higher cost.

LOCAL HEALTH AUTHORITY SERVICES

Fewer mothers were confined at home in 1951; the *domiciliary midwifery service* dealt with 253,035 confinements last year, as against 270,752 in 1950 and 299,372 in 1949. The decrease is attributed partly to the falling birth-rate and partly to the growing demand for institutional treatment. In 1950 gas and air analgesia was provided in 58% of domiciliary cases, compared with 53% in 1950 and 43% in 1949.

Attendance at *antenatal, postnatal, and child-welfare clinics* also declined. The number of women who went to antenatal and postnatal clinics in 1951 was 15% less than in 1949; and attendances at child-welfare clinics fell by about 2½% in the same time.

On the other hand, *health visitors* and *home nurses* had more work to do; and the *ambulance service* received more calls than ever, though the average mileage per patient continued to fall steadily.

GENERAL PRACTICE IN REVIEW

THE annual meeting of the Executive Councils' Association for England and Wales, held last week, and that of the Scottish association in the previous week, brought to light some interesting views on general practice and other branches of the National Health Service.

OPINIONS FROM SCOTLAND

Mr. G. G. C. BAIN, retiring president of the Scottish association, which met in Inverness, remarked[1] that new brooms, in sweeping clean, sometimes collected useful material which was also consigned to the scrap-heap. Thus at the start of the National Health Service some regional boards had based the staffing of hospitals on an entirely wrong conception: the general practitioner had been unceremoniously swept out of the way, and the loss in many cases had been considerable. Mr. Bain called for a more general use of the family doctor in hospitals, and for a much closer link in the radiological service between consultant and general practitioner.

Dr. E. R. C. WALKER, Scottish secretary of the British Medical Association, said[2] that in the National Health Service Scotland had its own distinct statute and administration; yet he doubted whether the wisdom—or even the existence—of this arrangement was always appreciated. There was an obvious danger that for the sake of uniformity changes might be made which were not required by natural and organic evolution—or, more important, that changes necessitated by such evolution might be prevented. Dr. Walker observed in particular that "a distinctive feature of Scottish hospitals—the medical superintendent—may before long disappear, not because of any proven demerit, but for extraneous and largely irrelevant reasons."

> "Developments since 1948 make it quite clear, I think, that the purely administrative superintendent will disappear as a feature of hospital management in England. It is the declared objective of the Ministry of Health to reduce to a minimum the time to be given by medical staff to administrative duties. . . . It is difficult to see what is happening in this regard in England as anything other than a comparatively humane form of liquidation of the administrative medical superintendent."

Dr. Walker criticised the attitude to any proposed change which found expression in the response: "But that would mean an amendment of the Act." In this, as in other social services, considerable legislative changes must be expected in the future.

Like Mr. Bain, Dr. Walker was concerned with the imperfect integration between general practice and the hospital service. The Scottish Health Services Council, discussing this problem, had said: "We think it right to record our view that unless a full measure of integration is achieved through the existing machinery, serious consideration will have to be given to changes in the administrative framework." The reference to "existing machinery" related, among those things, to the liaison or coördination committees set up under the Act.

> "I find it difficult to believe that this arrangement can effectively contribute to the 'full measure of integration' which the Health Services Council rightly calls for. Even supposing that it could and did, is this not rather a clumsy and cumbersome way of achieving the end in view? Would it not really be at once simpler and better to eliminate the need for coördination by the straightforward process of making one administration responsible for all the medical services?"

Dr. Walker also referred to the legal liabilities of doctors in contract with administrative bodies in the service.

> "From earliest times the relationship between a physician and his patient has always been regarded as an essentially personal one and, as a corollary to the strict confidentiality

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[1] *Glasgow Herald*, Sept. 26.
[2] *Scotsman*, Sept. 27.

thus involved, doctors have always accepted absolute responsibility for their actions. The Common Law provides safeguards against any dangers that may be inherent in this relationship. If this responsibility is now to be shifted to, or at least shared by, the administrative authority, does it not seem inevitable that this authority, which in effect means the State, will become a directly interested party in the doctor-patient relationship ? I feel quite sure that the vast majority of people in Scotland would not wish to see this come about. Moreover, I feel morally certain that it was not the intention either of the framers of the Act or of Parliament that it should. Yet the first steps in this direction have already been taken."

Mr. JAMES STUART, secretary of State for Scotland, said that last year the cost of the pharmaceutical service in Scotland was over £1 per head; the total of over £5 million was more than that paid to all the Scottish doctors. The immediate result of the charge on prescriptions had been a fairly substantial drop in the number of prescriptions dispensed, though this had been partly offset by the continued rise in the average cost of prescriptions. With regard to the dental services, it was still too early to say what savings could be expected from the new charges; but fully 40% of all patients now going to the dentist belonged to the priority classes—nursing and expectant mothers and young people under 21—who paid nothing for treatment. In the supplementary ophthalmic service the demand for sight tests seemed to be settling at a level where each year some 7½% of the population were having their eyes tested.

THE MEETING IN ENGLAND

At the meeting of the association for England and Wales, at Scarborough, Mr. IAIN MACLEOD, Minister of Health, suggested that the following trends should be encouraged:

1. Full coöperation between the general practitioner and the local authorities' domiciliary services, to relieve the pressure on beds by ensuring that patients did not spend time unnecessarily in hospital.

2. An increase in the number of partnerships and the development of practice by groups of doctors working together as teams.

3. A better distribution of doctors so as to avoid some having more patients than they could care for properly.

4. Closer association between family doctors and the hospitals, including contact with the doctor's own patients in hospital and direct access to X-ray and pathological departments.

5. The family doctor becoming the leader of a team comprising all the services provided by the local health authority according to the needs of the patient.

6. Closer coöperation between doctors, dentists, opticians, and chemists working under executive councils.

In Mr. Macleod's view hospitals should keep general practitioners in touch with their patients. Hospital staffs should be prepared to do what they could to let general practitioners have access to their patients in hospital, to keep them informed of progress and on discharge, and to discuss cases with them. General practitioners should have prompt notice of discharge and any necessary clinical details, which in cases requiring continuity of care should be given in advance. Hospitals could also help family doctors by inviting them to attend clinical meetings and by developing the already increasing provision for direct access to X-ray and pathological departments: "We shall not feel satisfied till all general practitioners have direct access to these departments." General practitioners in the smaller towns and in rural areas (and some others) in his opinion should be able to have charge of those of their own patients who did not need specialist care but needed admission to hospital; and selected general practitioners should hold specific part-time posts of various kinds.

Under the Danckwerts award, total remuneration would keep pace with the number of doctors. When a good distribution of practitioners had been secured, the Ministry and the profession would have to agree on the proper rate of entry into general practice, and arrangements would have to be made to link remuneration to that rate. "The Exchequer," said Mr. Macleod, "clearly cannot finance an unlimited increase in the number of doctors beyond the point at which the best practicable distribution can be secured consistent with the proportion of the national resources that can be devoted to this purpose."

Mr. H. C. BROWN, the president, pointed out [3] that no particular politicians or party could claim the National Health Service as their brain-child. "I think it is time that the scramble for credits ceased and that the politicians tacitly agreed that the health of our nation should be sacrosanct from party political jobbery."

DEFENDING DOCTOR AND DENTIST

THE two English medical defence societies have lately held their annual meetings, and have issued instructive and readable reports obtainable on application. The Medical Defence Union has its offices at Tavistock House South, Tavistock Square, London, W.C.1, and the Medical Protection Society at Victory House, Leicester Square, W.C.2.

Medical Defence Union

Presiding over the 67th annual general meeting on Sept. 16, Dr. S. COCHRANE SHANKS, the president, said that the council had taken a prominent part in professional affairs during the past year.

In collaboration with the British Dental Association, it had urged that under the new Dentists Act the proposed dental auxiliaries should not be allowed to undertake fillings or extractions of teeth. The Act, as passed, would allow auxiliaries to extract children's teeth; but, unless the new General Dental Council so decreed, there would be no dental auxiliaries.

With the British Medical Association it had been studying the procedure for investigating complaints from hospital patients. (Some proposals now being further considered are set out in the annual report.)

Ten years ago the Union had begun to press for measures which would prevent confusion of one kind of anæsthetic-gas cylinder with another, and considerable success had been attained. in conjunction with the Society of Anæsthetists and the Ministry of Health.[4]

> "We have reached full agreement with the U.S.A. and Canada about the colours of cylinders and non-interchangeable couplings, and at a conference to be held in Paris next month we hope to reach similar agreement with all European countries outside the Iron Curtain."

In warning members of the common hazards of practice, the President referred particularly to the hot-water-bottle burn, the diathermy burn, the too tight plaster-of-paris, and the injection of anæsthetics into an artery instead of a vein.

Membership of the Union stood at just over 37,000 on July 15 last, and 500 new members were elected in August. The accounts for 1951–52 showed a net surplus of £7630. Because of the very heavy litigation expenses incurred in 1948, the Union's indemnity policy with the Yorkshire Insurance Company has been revised. "In future the Union will be responsible for the first £40,000 in damages, opponents' costs, and settlements out of court. The Yorkshire has to take the next £40,000, and if that figure is exceeded we have to call on Lloyd's for £100,000. After that we would have to call on our own reserves, a contingency that is very remote."

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[3] *Manchester Guardian*, Oct. 4.

[4] See *Lancet*, July 5, 1952, p. 36.

Dr. Cochrane Shanks, who was re-elected president, concluded by paying a special tribute to Dr. Robert Forbes and Dr. P. H. Addison (secretary and assistant secretary) and the other members of the staff.

Medical Protection Society

Sir **Ernest Rock Carling**, in his presidential address on Oct. 1, said that the professions must face the fact that the word responsibility was now being used in two senses. Every doctor and every dentist had always accepted *medical* responsibility for the care he gave to his patients. But *legal* responsibility now seemed to include responsibility for everything done by anyone who assisted him—the house-surgeon, the nurse, or anyone else. Some means must be devised by which the doctor could delegate responsibility without penal sanctions: how could he be responsible for every action of a junior officer whom he might not even have been allowed to choose? Such a state of affairs was impossible, and could even lead to breakdown of the work of a hospital. Another and yet more serious development was the situation in which the hospital, in seeking to clear itself from a charge of negligence, might cast aspersions on members of its own staff. What would be the relations between board and staff if this sort of thing happened?

"To err is human," said Sir Ernest; "but I am bound to add that there is nothing about the law in our courts which is divine or forgiving." And, by taking more thought, mistakes and difficulties could sometimes be avoided.

Some dental surgeons, he felt, had a slightly casual attitude towards the casual (and even regular) patient. There should always be records, and where there had been some mishap a note should be made that the patient had been told about it. For surgeons and physicians careful records were equally important.

Whoever was making an injection ought to verify its nature by personally reading the label on the bottle or ampoule—even when he was presented with the fluid by someone else. Care must also be taken to see that ampoules taken out but not used were not put back in the wrong box. And before giving an intravenous injection one must be quite certain that the needle is in the vein.

Anæsthetists must recognise the extreme importance of ensuring that taps and valves were in order—neither too stiff nor too easily turned on—and of preventing a harmful drag on the arm of a patient under a relaxant drug.

Certain accidents of practice, such as a slip on the floor, might come under the heading of third-party risks; but, wherever there was doubt, members of the society could be sure they would get the benefit of it. "Let there be the slightest slur on the professional reputation of a member, and we shall deem it our business to defend him."

The 60th annual report shows that, for the sixth successive year, expenditure exceeded income; and Mr. W. M. **Mollison** held that the rise in subscription last January, from £1 to £2, was fully justified. With a membership of over 27,000 last December, the expenditure per member was £1 8*s.* 3½*d.* The society's financial resources amount to about £150,000, and it is reinsured with Lloyd's for any sum exceeding about £11,600 which it might have to pay by way of costs and damages in any year.

Sir Ernest Rock Carling, Mr. Mollison, and Dr. Alistair French were re-elected president, treasurer, and secretary, receiving in each case the very warm thanks of their colleagues.

> ". . . Whatever the method of improving humanity and of raising men to a higher position than they occupy today may be, and whenever and however the millennium may be reached, it is not to be reached by declaring in favour of class consciousness and class antagonism, hatred between one class and another. The problem we have to solve is an educational and moral problem. No political constitution can enfranchise a people, no possessions can enrich them, no rank or title can ennoble them, unless they have solid, manly character and wholesome honesty, as the granite rock upon which they are built."—Sir Edward Grey, 1910; quoted by Ann Bridge.

In England Now

A Running Commentary by Peripatetic Correspondents

In New Zealand we are conscious of our insularity, and one of the manifestations of our isolation is the way in which we pounce on every incomer and question him closely about his country of origin and his journeyings. In London we find that our appearance from the other side of the world is accepted as commonplace. Such acceptance is of course refreshing, but I wonder if those who greet the travellers so casually do not miss much of interest.

Lately we took advantage of a beautiful day to go by water to Greenwich, and we thoroughly enjoyed the sight and sound of so much that was deeply familiar though never before visited by us. As we sat on Greenwich Pier, working out our return plans from a bus map, a grubby little Cockney joined us. She proved adept at maps and soon we knew just where she lived, where Mother did the shopping, and where to find various aunts and uncles. As we were now good friends I thought she might be interested to tell her school mates that she had talked with folk from the ends of the earth; so I inquired if she knew the map of the world. "Oh yes, we've done it at school." "Do you know where New Zealand is?" "Down by Australia." "We have just come from there." "Have you?" and she hastened on to leave an uninteresting subject with, "Have you any more maps of London?"

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Your correspondent who was horrified by hearing his own recorded voice may be interested to hear that his dismay is often shared by professionals. Many of the actors and singers whom I have met in my laryngological practice admit surprise, pleasant or unpleasant, on hearing their own voices "played back." The reason is of course, that in real life we never hear ourselves as others hear us. But if allowance is made for microphone distortion, particularly at high pitches and great intensities, and if the singer or speaker has used his full voice—rather than murmuring into the microphone and relying on amplification to achieve volume—recording can enable us to hear ourselves for the first time. In the ordinary way we hear our own voices partly by bone conduction through our own skull and this usually increases the richness of timbre. For the same reason otosclerotics, with normal cochleæ, often speak in a quiet and gently modulated voice. The performer's voice may of course be further distorted by the acoustics of the hall or auditorium; the voice which is reflected back to him may differ in quality from the tones heard by the audience.

* * *

Many of us open-air types in the West Country are gravely concerned about the virtual disappearance of our English partridge. Where we used to get 15–20 brace on the first day out we now get only one or two. We guess at possible causes: lack of keepering, increase of vermin, the use of artificial manures, open trapping, "intensive" farming which repeatedly disturbs nesting pairs, destruction of eggs by tractors, and so forth. All these doubtless play their part and are largely inevitable. There is however another possibility about which I should like to have an authoritative opinion. Here the buzzard is a protected bird and its numbers have increased enormously. It is unusual in the course of an ordinary country round to see fewer than half a dozen of these handsome creatures either circling the sky or perched on telegraph poles. Are they perhaps wreaking havoc among the young broods? If so, is it not time that they were deprotected? Of course possibly the partridges don't mind either way.

* * *

I have been doing some research into the Smile Factor in hospital staffs. This was prompted by a remark of our maid that she liked the West African nurses at the local hospital "because they were always smiling," and was made possible by my own admission for a minor operation to one of our London teaching hospitals. During a stay of three nights, with one subsequent outpatient visit, I met 27 members of the hospital staff and noted the number who smiled at the first time of meeting (excluding 2 porters who put me on to the

the theatre trolley, as I was too sleepy to notice or record them). Of these 25, 12, or 48%, smiled the first time we met. Good, I thought; but perhaps not quite good enough? Of course a statistician would boggle—they are all born bogglers—at any comparison with other hospitals or groups; for they would claim that other factors were involved, such as whether the observer smiled first (an apprehensive and propitiatory grin seldom left my face); whether the patient was known to be a doctor—but which way would that work? —or even on the state of the weather. There is also the difficulty that a smile may *sometimes* be such a *frigid* and automatic grimace that it is less welcoming than a cheerful, friendly, but technically smile-less approach.

Breaking down the figures, I find that the percentage was higher in the older age-groups, showing perhaps that training is in the right direction. Hospital porters appear to be an exception to this, though the sample was small (3). More research is needed—haven't I heard that phrase before somewhere?—and the King Edward's Hospital Fund might offer a challenge cup.

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We know what the M.R.C. investigators say about their famous experiment on the Scottish island. *They* say that the *pedigree virus* they brought from Salisbury had grown too tame to bite, and that their susceptible volunteers would have remained quite healthy and happy if they hadn't chanced to catch a wild cold from a crofter on the mainland. That's what *they* say; but that's far from being the story told by the people on the Sutherland coast. What the inhabitants say is that when this experiment began they were a peaceful and contented community, tending their sheep, and stacking peat, and maybe catching a few cuddies or a sculloch off the rocks of an evening. And then suddenly the M.R.C. let loose from Eilean nan Ròn a cold so terrible that its memory will live in the minds of their children and their children's children. That's what the crofters say; and I know it's true, because that same cold has been travelling down through Scotland and England and I caught it myself last Saturday. Whatever may be averred about harmless domesticated viruses, I for my part shall always take care to gargle after meeting any member of the M.R.C.

* * *

Even advertisements are bigger and better in the States. Last month, for instance, a well-established American medical agency advertised for a medical man, skilled in surgery, "especially in appendectomy," with a wife, also medically qualified, experienced in obstetrics and gynæcology. They are wanted by a *mysterious foreign potentate* "in a far-off sultry land" to attend the royal household, location unspecified, which comprises four wives and a harem. Both doctors must be American-born graduates of a class-A medical school, and they will receive $50,000 annually, all expenses paid, free of U.S. income-tax, and live in the palace. The only snag stated is that water is so scarce that the ladies of the harem have to bathe in perfume. The potentate is said to be "enormously wealthy, and very American-minded." He has an American chauffeur and an American business adviser, and lives on American food. Perhaps that is why he needs someone at hand who is a dab at appendectomy.

Why can't we have jobs like this advertised in the "Miscellaneous" section at the back of THE LANCET? Who wants whales when he could have camels?

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"In the short time at my disposal I shall be unable to refer to the work which . . . or to those interesting . . . or even to . . ." How often have we heard a speaker waste a precious half-minute in so excusing himself for some unimportant omission. The alternative formula "the time allotted to me does not permit . . ." is usually accompanied by a hard and reproachful glance at the organising secretary. If every participant in a scientific meeting agreed to discard these almost invariably employed platitudes, there would be time on each programme for one more paper or for an additional ten minutes at that important coffee-bar where friendships are made and ideas exchanged. Speakers should follow the excellent advice of Lady Mendl: "Never complain, never explain."

Letters to the Editor

THE CRIMINAL AND THE INSANE

SIR,—It is one of the fundamentals of English law that no prisoner is tried if he cannot defend himself adequately, or at all, by virtue of mental disease or defect. Yet the same prisoner can be incarcerated as a criminal lunatic without having been convicted of any crime. There are said to be *many* inmates of Broadmoor who insist that they are innocent of any offence and who deeply resent their detention as criminal lunatics. Some of them have committed suicide, others might have preferred execution, but few would not have elected to stand their trial. What would they have had to lose?

A prisoner, without necessarily being mentally abnormal in the legal sense, often takes little or no part in his defence. The conduct of the case is left to legal experts, and legal assistance is provided for those who cannot afford it or would dispense with it. Would it not be more just, reasonable, practical, and humane therefore to allow all prisoners accused of murder to stand their trial? Their mental state and the degree of responsibility could be assessed after a verdict had been reached.

There are many lunatics who have no homicidal tendencies. Should not those who commit murder be executed? Generally speaking, crimes are not committed by lunatics but by criminals who are mad. As a psychiatrist I am naturally in favour of the treatment of lunatics, but I am not unmindful of the fact that there are good and bad lunatics. I have little sympathy for the criminal who is insane. He is a far greater menace than his mentally normal contemporary. Professionally I have encountered only two murderers who were, in my view, insane. The histories of both these men revealed criminal tendencies and behaviour long before there was any evidence of insanity. A case could certainly be made out for the execution of murderers who are mad. My professional conscience is more concerned with the prevention of further loss of innocent lives than it is with the survival of a homicidal lunatic.

Many murderers in their early twenties have been executed. Some of them had no previous criminal record, yet there was no question of attempting to convert them into useful citizens. Why then do we expend time, energy, brains, and money in efforts to cure criminal lunatics? If this was done solely in the interests of science, it would be sound and practical; but it is nothing of the kind. Murderers who are found to be insane are not executed, because we are civilised and humane—but we are not humane enough to abolish capital punishment or attempt the regeneration of mentally normal murderers.

Enemies of society should be used for the benefit of society. Endeavour to cure them by all means, or experiment on them if you like; but the execution of the normal and the reprieve of the lunatic constitutes an inconsistency which is devoid of all intelligence and humanitarianism.

London, W.1. ELLIS STUNGO.

SIR,—After over twenty years' experience in psychiatry, including six years with the Industrial Neurosis Unit at Belmont Hospital, I feel that something must be done to safeguard the community from the menace of the aggressive psychopath.

I am prompted to write this letter by the fact that during the past few months a number of aggressive psychopaths, either after discharge from hospital or while out of hospital for a few hours, have been charged with murder or attempted murder. On reading the records of the offenders, when apprehended, it is clear that many if not all of them are aggressive psychopaths.

Of the patients admitted to the Industrial Neurosis Unit at Belmont Hospital 75% are psychopaths, and many of these are of the aggressive type. Their histories for the most part show many points in common. They are often illegitimate or come from broken homes (the main factors in the production of psychopathy being, in my opinion, lack of the security and affection to which all children are entitled); they are brought up in orphanages, become delinquent in childhood (often with sadistic practices), and thereafter graduate through approved schools and Borstal to prison.

I am one of those who hold that psychopaths are made by their early environment, and I do not regard the hereditary aspect as important. I believe that if these children could be placed in reasonable foster-homes, where they could have security and affection, psychopathy could in many cases be avoided. I am also convinced that once a psychopath always a psychopath, and that when their antisocial characteristics have become ingrained only prolonged treatment may remove these deep-seated habits. They are embittered, refuse to work, and prefer to maintain themselves by criminal means, resorting to violence if necessary to achieve their ends. But as they are not psychotic, they cannot be certified; and punishment in prison or elsewhere has little or no deterrent effect on their antisocial propensities. Intellectually they show no impairment; indeed their level of intelligence may be quite high.

Dr. Maxwell Jones has been attempting in the Industrial Unit to resocialise these psychopaths by group therapy. The whole unit, consisting of 100 patients, exists as a therapeutic community, and the patients and staff live as an integral group. They share their daily activities, and work out their tensions and difficult situations; and in this way the patients may gain insight, acquire a social conscience, and realise their duty to the community. But although in some cases the results are promising, in many the outlook is hopeless. One reason for the lack of success is the fact that the patient will not remain in hospital long enough for resocialisation. Hence many aggressive psychopaths are again turned loose on society and continue their lives of crime and violence.

We know that terms of imprisonment do not help in the least: they only embitter these people further and make them if possible more antisocial in their behaviour. We have to admit, too, that as things stand, the psychiatrist can seldom help such patients. I would like, therefore, to suggest an alteration in the law relating to them.

In Holland and Denmark for some time it has been the practice to send criminal psychopaths, under a court order, to an institution where they remain for life if necessary and which they are unable to leave unless they are held to have recovered from their illness. It would surely be to the advantage of society if such a colony were set up in this country to which criminal psychopaths (after being diagnosed as such by a panel of responsible psychiatrists) could be sent and where an attempt could be made, under more hopeful circumstances, to resocialise them by group therapy and community life. I would suggest that, though the patients would be sent there on an order of the court, the institution should be run more on the lines of a hospital than on those of a prison and that the staff should consist of psychiatrists interested in social aspects of their specialty, with nurses and social workers trained in the same sphere, while ancillary workers such as psychologists, occupational therapists, and trade instructors would also be employed. Also the colony should be largely self-supporting, for many of its departments could be staffed by the patients.

So long as these psychopaths are free agents, and can leave hospital whenever they want to do so, the chances of resocialising them are small. Legislation under which they could be detained would be of benefit both to society and to the psychopaths themselves.

Belmont Hospital,
Sutton, Surrey. LOUIS MINSKI.

** Denmark's experience with a prison for criminal psychopaths has been described in these columns by Dr. Stephen Taylor (*Lancet*, 1949, i, 32).—ED. L.

REPORTS FROM CONSULTANTS

SIR,—While I agree that unnecessarily large numbers of patients are referred to hospitals, it is nevertheless disconcerting, to say the least, if patients turn up at the surgery a week or more after their discharge from hospital, and the doctor has not received a report on their condition or the result of the investigation. Moreover, some reports simply recapitulate, with certain refinements, the patient's symptoms, and then conclude by stating that a certain line of investigation has proved negative.

May I quote two letters on a patient, a young woman, who has had flatulence, frequent loose motions, and loss of weight for about a year?

(1) "I think this patient has a chronic alimentary tract infection and I will treat her in my clinic for a while and report to you again."

(2) "I saw this patient again yesterday afternoon and I think she is beginning to respond to treatment."

London, N.W.6. W. LEVY.

CURE OF TOBACCO-SMOKING

SIR,—Life is indeed simple for Dr. Lennox Johnston. Tobacco-smoking is an addiction; addictions are bad; therefore tobacco-smoking ought to be abolished. Undoubtedly it is the duty of the individual practitioner to point out the disadvantages of smoking to the individual patient when occasion demands, but before committing the medical profession to a wholesale condemnation of smoking we must attempt to answer two questions: (1) What is the cause of mass addictions? (2) What is the balance of the good and evil effects of such addictions and of tobacco-smoking in particular?

Dr. Lennox Johnston provides the clue to an answer in his observation that smoking is not enjoyable until addiction has become established. In other words a strong need is artificially created, and the means for satisfying it are kept within easy reach.

The existence of civilised society is only possible through the constant control and abnegation of individual urges, and civilised life from birth onwards is a continuous chain of sacrifice of immediate satisfactions in order to qualify for, and make possible, the enjoyment of the advantages of organised social existence. Mass drug addiction is a highly successful artifice which grants the individual the repeated feeling of immediate gratification of urgent desires without bringing him into conflict with the codes and purposes of society. Before tampering with such a tremendous safety-valve we should consider the alternative. The activities of abstemious fanatics in various periods of history do not make a very reassuring study, and it may moreover be doubted whether a policy of freedom from all addiction and its equivalents could be successfully imposed for any length of time upon the majority of a civilised community. A fiscal or medical policy designed to eradicate tobacco-smoking would have to provide an acceptable and less injurious alternative or accept the moral responsibility for the consequences. Surely the tobacco addiction of the 20th century is preferable to the alcohol addiction of the 19th as being considerably less disruptive to the physical, moral, and economic health of the community. It might be wiser to concentrate on the question of how smoking can be made even safer than to tamper with a complex mass psychological phenomenon which in this century has found a fairly acceptable outlet. Even if smoking increases the chance of a man developing cancer of the lung from 1 in 10,000 to 1 in 1000, it remains questionable whether community or individual have anything to gain from the abolition of smoking. The chances of drowning increase even more steeply with the acquisition of the ability to swim, and it may after all be better to be a smoker than a swimmer. I do not assert that this is so; but nobody, and certainly not Dr. Lennox Johnston, has tried to draw up a correct balance.

It might be argued that we should strive to remedy the imperfections of society which render mass addictions necessary; but I believe that the need for such addiction is not primarily caused by faults in the social system but is of the very essence of civilised existence with its inevitable tension between the short-term urges of the individual and the long-term objectives of society. The medical profession must act upon human nature as it is and not as it might be.

There will always be cases in which smoking has to be discouraged. But there are many non-smokers to whom the best advice that a doctor can give is that they should get a pipe and dissolve some of their soul- and body-destroying frustrations into blue smoke.

Edinburgh. ERICH GEIRINGER.

SIR,—Gluttony, one of the seven deadly sins, is now, like most of the other six, excused by psychologists and encouraged by advertisers. Dr. Lennox Johnston would have us classify smoking among the vices of addiction. But addiction to food does as much to fill the graveyards; and, although it does not dissipate scarce dollars as smoke, it preserves calories bought with hard currency as massive subcutaneous monuments to uninhibited alimentary lusts.

The surgeon who has to fight his way into the peritoneal cavity is justified in wishing that his patient had eaten less and smoked more. Would Dr. Johnston now use his considerable talent for polemic in the cure of addiction to eating?

Chelsea. AUBREY LEACOCK.

SIR,—There is no great difficulty in stopping smoking provided one applies ordinary common sense.

(1) The patient must have a real desire to stop smoking.

(2) This is often effective after an illness.

(3) Having decided to stop, fix a date five days hence—four days is not long enough, six days is too long. Make the patient realise that on the fixed date all forms of smoking must cease. In the meantime get him to carry out the following breathing exercises: inhale slowly and fully, pause for five seconds, then exhale forcibly; repeat six times. The pause will ensure that CO_2 will produce the same effect as smoking—increased CO_2 tension in the alveolar air. This exercise can be repeated as often as desired. Breathing should be entirely nasal, unless there is some obstruction. At the same time concentrate on the date fixed. This treatment should suffice for patients of ordinary intelligence.

But most cases one has to treat individually, and either direct or indirect methods must be applied. For example, a direct method would be used when a patient comes in with a glossitis or leucoplakia. "This condition is not serious in itself, but in a smoker it may lead to something serious." If necessary, produce some literature from a reliable source: quote Fourier of Paris and Kelly of Baltimore as arriving at the same conclusion that the condition was not of any great importance unless there was a collaborator—and that collaborator was tobacco.

The indirect method can be tried on a patient interested in sport or in his personal appearance. A golfer can be told that his putting has deteriorated because of smoking: quote Bishop Harman, and, if necessary, show him the book about the deterioration of vision and irregular formation of writing produced by smoking. "Stop the puffs and slot the putts."

Again, women patients may like to smoke and also remain attractive. Well, they just cannot have both. Advise them to visit a few women's bridge clubs, where they will always see one or two excellent examples of nicotinism. Tense expressions, faces the colour of a spade guinea, trying desperately to augment their incomes, or at any rate trying to avoid losing.

I am an ex-chain-smoker who used to average 40 cigarettes a day. Seventeen years ago I stopped as the result of a challenge by a drug addict. I stopped smoking at once and have never smoked since. I am glad to say that I am still friendly with many hundreds of ex-smokers whom I helped to give up the habit. I have lost a number of patients through refusing any treatment unless they stopped smoking. "Do you think my catarrh has anything to do with smoking, doctor?" "Yes." "Can't you give me something to stop this cough unless I give up smoking?" "No." But I must avoid getting too involved in the subject, for I know well that any attack on the tobacco-smoking habit is always followed by a counter-attack with a definite purpose.

PRACTITIONER.

OCCUPATIONAL ADAPTATION OF MENTAL DEFECTIVES

SIR,—The research on this subject was both interesting and useful, and the report by Dr. Tizard and Dr. O'Connor (Sept. 27) should be studied by all concerned with mental deficiency. It is, therefore, a pity that they allow themselves conclusions on more general matters. Mental-deficiency hospitals are not maintained for the sole purpose of occupational training, but for the whole care of whole individuals of many types and with many needs. Thus, the authors' dislike of large hospitals, which is not necessarily justified even from the point of view of training the feeble-minded, takes no account of the whole problem, the small supply of trained staff, and the cost to the community, already in financial difficulties. It is unfortunate, also, that they should publish such sweeping criticisms without stating their evidence; and that they do not distinguish between the faults (or virtues) they see in policy and design, and those things which are due to the conditions of the time.

It is true that many more hostels are needed for the finishing stage of high-grade patients who are nearly ready for licence, and that such hostels can be run very cheaply. But this is offset to some extent by the increased cost of the parent institution which is left with a greater number of non-productive patients. After years of education by those in the service the authorities have begun to accept the principle of hostels, but most hostels have still to be found. New houses cannot be built, old ones do not always stand where they are wanted, and, as usual, there is no money. Again, the small number of social workers is not due to any failure of method or principle but to the inadequate birth-rate in the 1930s which provided too few girls for the increasing number of jobs which now need them. Commendation is given to the great increase in daily licence at Darenth, and it is mentioned that this is part of a general movement, which is true. But it is only in part due to a general improvement and liberalisation of policy within the hospitals: it is also due to the fact that it has now become easy to place patients in outside jobs which they could not have got before the war.

The statement "The *widely recognised shortcomings* of the mental-deficiency service formed the starting-point of the research" creates a moment of anxiety as to the absence of bias with which scientific research should be conducted. The anxiety is revived when one finds the questionable statement "*with very few exceptions* institutional *policy* has not been to return defectives to the community but to segregate them." The italics are mine. This is known to have been true of some places in the old days and it is believed to be still true of a few hospitals which have not moved with the times. It is certainly not true of some, and I should need facts before accepting the criticism with respect to others of which I know something.

I remember Douglas Turner, some 25 years ago, insisting that the patients in an institution were not to be likened to a stagnant pool but to a flowing stream. The flow is inevitably slow but, as Galileo said, "Eppur se muove." It is a pity to have spoiled a piece of good work by straying too far.

St. Albans. NOEL H. M. BURKE.

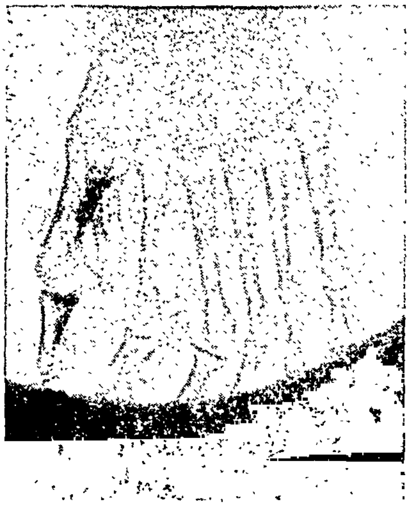
HÆMOPHILIA

SIR,—We are being asked by many doctors to collect in one centre all the relevant information on hæmophilia and allied subjects. We shall be very grateful, therefore, if authors would put the International Hæmophilia Society, 94, Southwark Bridge Road, London, S.E.1, on their mailing-list for reprints.

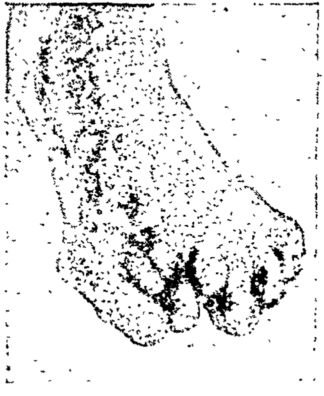
FRANK A. SMITH
President, International Hæmophilia Society.

CONGENITAL ABNORMALITY OF THE FOOT

SIR,—In a village in Gambia, British West Africa, a man aged about 25 years was examined whose left foot had nine formed toes and a small appendage on the dorsum, which had been present from birth.



His gait was normal and he stated that he was not inconvenienced in any way by the deformity. The posterior part of the foot appeared normal, but the anterior part was very broad and had a marked hallux valgus. The lateral part of the foot with the lateral four toes, and the great toe, were normal; but between the two were four extra toes (see figure).



Radiologically, the lateral four toes and metatarsals appeared normal as did the great toe and the first metatarsal. One of the abnormal toes had three tarsal bones and a normal metatarsal bone. Two of the other abnormal toes also had three tarsal bones, but had very short metatarsals. The fourth abnormal toe had only two tarsal bones, and associated with it there was a head of a metatarsal which tapered abruptly to a point posteriorly. The dorsal appendage had no osseous structure. The medial cuneiform was either greatly enlarged or there was a closely associated accessory bone lying between it and the intermediate cuneiform.

The right foot and both hands were normal clinically and radiologically.

Human Nutrition Research Unit,
Medical Research Council,
Field Research Station,
Fajara, Bathurst, Gambia. JAMES A. MCFADZEAN.

A CHEAP SURGEONS' CAP

SIR,—To have recourse to Authority, even to one as eminent as Sir Holburt Waring, in branding a new idea as bad never was a very convincing argument; and I feel that on this score the outright condemnation by Mr. Whittingdale last week of Mr. Howkins's fisherman's jersey bonnet (Sept. 27) must be viewed with suspicion.

On the other side must stand the host of surgeons whose eyebrows have stood exposed despite possible falls of dandruff, and without septic consequences. Drops of sweat indeed are usually a much more frequent dropping than flakes of dandruff, and in the solving of this problem Mr. Howkins's cap seems a reasonable suggestion.

In any case, is there any reason why Mr. Whittingdale should not introduce his own modification of the Howkins cap by pulling it over his eyebrows?

Ballochmyle Hospital,
Mauchline. IAN A. MCGREGOR.

MEGALOBLASTIC ANÆMIA

SIR,—Dr. Foy and his colleagues[1] have discussed the response to oral penicillin in four cases of megaloblastic anæmia. *Cases 1 and 2 were treated with 100,000–200,000* units per day, while cases 3 and 4 received 800,000 units daily. The first two cases had certain features which appear significant to me.

These are the visible icterus, the high blood-bilirubin level, the subnormal mean corpuscular hæmoglobin, and the reticulocyte-counts of 1 and 1·5%. In
are distinct enough to point to a
active megaloblastic hyperplasia wc
These may be described as case
hæmolytic anæmia," where the marrow is hyperplastic and the cells are of the normoblast or macroblast type; and, "even when deeply basophilic, primitive forms are found, they do not show the peculiar scroll-work type of nuclear chromatin which is characteristic of many of the nucleated red cells in the marrow of pernicious anæmia and related forms of macrocytic anæmias."[2] Therapeutically classified, they *belong to the group of anæmias which are amenable to* treatment with sulphonamides, antibiotics, or surgery.[3]

In the first two cases penicillin has halted the excessive peripheral blood destruction, with consequent remission in the anæmia as shown by the return of the findings to normal. It is likely that, in these two cases, the marrow contained cells which have been variously named "macroblasts," "macronormoblasts," "transitional megaloblasts," and "unfinished" or "precoctic" cells. Despite these varied names, I think they all describe the same cell. I consider that their presence in the marrow indicates a sustained and profound stress resulting in what may be called intermediate erythropoiesis, the significant cell being neither a megaloblast nor a normoblast in structure. In such cases the emphasis in treatment is on intercurrent pathology rather than on anti-anæmic measures. Sometimes anti-anæmic measures are not *necessary.*

The sole finding in case 3 indicative of a megaloblastic anæmia is the active megaloblastic marrow; for the peripheral blood is of the normocytic, normochromic type. I find this disparity difficult to explain.

Case 4 appears to be a true megaloblastic anæmia of the dyshæmopoietic type in the early stages of a *relapse.* Since the mean corpuscular hæmoglobin is on the increase, the visible icterus and the high bilirubin content of the blood should not be taken to indicate hæmolysis; these findings are made often enough in pernicious anæmia, so that it was once thought that pernicious anæmia had a hæmolytic origin.

It would be interesting to speculate on the response of cases 1 and 2 to the larger doses, and of cases 3 and 4 to the smaller ones. I feel the result would have been the same, and submit that Dr. Foy and his colleagues lost a very good opportunity of proving their point. They might have treated cases 3 and 4 on the small-dose scheme when the larger one proved futile.

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1. Foy, H., Kondi, A., Hargreaves, A., Lowry, J. *Lancet,* 1952, i, 1221.
2. Wintrobe, M. M. Clinical Hematology. London, 1951.
3. Sturgis, C. C. *J. Amer. med. Ass.* 1949, 141, 969.

Penicillin given by mouth is absorbed mostly from the duodenum, while in the lower reaches of the intestinal tract more is destroyed than is absorbed. The concentration of the antibiotic in the colon is negligible, while in the ileum the concentration may be a little higher. Can the drug, in such poor concentration, effect any far-reaching changes in the flora, either for good or ill ? It has been proved that antibiotics of wider spectra have a tendency, with long-continued administration, to produce symptoms attributable to intestinal sterilisation and vitamin deficiency. Can the same be said about penicillin, whether given by mouth or by the intramuscular route ?[4] In conditions like lung abscess and empyema, requiring prolonged administration of penicillin in large doses, these complications have not been evident, even when no vitamins were given.

On the question of a high-carbohydrate low-protein diet being responsible for the production of inimical microflora, I wish to observe that the Brahmins of South India commonly eat this type of diet; and I have come across only a very few cases of megaloblastic dyshæmopoietic anæmia in this community. The majority of them are strict vegetarians.

Trichinopoly, South India. M. S. NARAYANAN.

SALT-WATER BOILS

SIR,—Deep-sea fishermen suffer from a septic condition of the wrists and forearms known as " salt-water boils." It is due to friction of oilskin sleeves on forearms sodden with salt water. An additional abrasive element, especially in the case of bosuns, is sludge brought up with the catch from the sea bed. I am collecting information in order to obtain :

(a) Official recognition as an occupational disease in the schedule.

(b) Uniform medical certification in the interests of sufferers.

(c) Adequate treatment at sea in accordance with the Ministry of Transport's *Ship Captain's Medical Guide 1946*, amendment no. 4.

I shall be grateful if any doctors handling these cases would write to me.

4, Hamilton Terrace,
Milford Haven, Pembs. W. BURNETT EVANS.

CHROMATOPHOROTROPIC HORMONE

SIR,—Dr. Sulman [5] has lately given his opinion on the identity of the chromatophorotropic hormone. He assumes that A.C.T.H. contains several factors, one of them being chromatophorotropic.

The mechanism of the so-called Konsuloff reaction was discussed in a recent article.[6] In 1934 Konsuloff [7] suggested that the melanophore hormone in the urine could serve as a reliable pregnancy test; and this test, based on the colour change of the hypophysectomised frog (*Rana esculenta*) after injection of urine, has been widely adopted in the Netherlands. What is the substance in the urine of pregnant women that causes the frog's melanophores to expand ? Which organ, during pregnancy, produces this substance in excess—the hypophysis or the placenta ? Is the long-known hypophyseal chromatophorotropic hormone (C.H.) identical with the hormone in pregnancy urine ? Is the latter substance identical with choriongonadotrophin ?

The identity of C.H. from pregnancy urine with choriongonadotrophin (Ch) (which, in view of the close parallelism in excretion of C.H. and Ch had suggested itself very forcibly) was rejected in 1949, among other reasons because impure 'Pregnyl' (Organon), a Ch-containing preparation, had a lower minimal effective dose for C.H. activity than very pure pregnyl. Contamination of pregnyl by a substance with C.H. activity might explain this discrepancy. When at the beginning of 1951 a small quantity of A.C.T.H. ('Cortrophin,' Organon) was placed at our disposal, it became clear to us that with this preparation (which is not free of other hypophyseal factors) expansion of the frog's melanophores could be brought about. The contaminant of pregnyl might, then, be A.C.T.H. As we did not have at our disposal " crystalline " hypophyseal hormones we tried to determine the minimal effective dose of several hypophyseal gonadotropic preparations and that of A.C.T.H.[8]

For reasons that we are explaining elsewhere, the identity of C.H. with luteotrophin (Squibb) (prolactin) or luteinising hormone (L.H.) did not seem improbable. Therefore we determined the minimal effective dose of luteotrophin, cortrophin, and pregnyl (a very pure Ch put at our disposal by Messrs. Organon Ltd.). The results were as follows:

Preparation	*Strength*	*Minimal effective dose (µg.)*
Cortrophin	.. 50 I.U. (16 mg.)	0·2
Luteotrophin ..	.. 1000 I.U. (54 mg.)	5·4
Pregnyl	.. 20,000 I.U. (43 mg.)	4·0

This shows that the C.H. activity of the preparation containing prolactin (luteotrophin) might be due to contamination by 5–10% A.C.T.H. That the pregnyl used contained this amount of A.C.T.H., is disclaimed by the manufacturers, who say that at the most traces might be found.

Even more important was the observation, which had hitherto escaped our notice, that the type of colour change was different, according to whether A.C.T.H. or pregnyl was injected. After injection of A.C.T.H. the *whole* body of the frog becomes dark. After injection of pregnyl (Ch) the hind legs of the frogs become dark, in contrast with the upper part of the body, which remains bright. This colour pattern cannot be brought about by giving cortrophin. The same colour change is also obtained with urine and blood-serum of pregnant women, 'Gestyl' (Organon) (pregnant mare's serum), and a watery extract from the frog's hypophysis. 'Ambinon' (Organon) (thyrotrophic-gonadotrophic hormone), gonadotrophin (Squibb), and luteotrophin gave the colour change of the type given by A.C.T.H. That we were indeed dealing with two substances with C.H. activity in the two groups was furthermore proved by our finding that the C.H. activity of our substances giving a colour change of the pregnyl type disappeared after half an hour's boiling at pH7, whereas the C.H. activity of the group which gave the colour change of the A.C.T.H. type appeared to be proof against this treatment.

Konsuloff's pregnancy reaction, then, in our opinion, is based on the presence of choriongonadotrophin in pregnancy urine. The chromatophorotropic activity of the hypophysis may be caused by A.C.T.H. on the one hand, or on the other hand by a substance which we think must be identical with prolactin and/or luteinising hormone. Experiments in which hypophyseal preparations are stripped of C.H. activity of the A.C.T.H. type, while the C.H. activity of pregnyl (choriongonadotrophin) type is preserved have confirmed the existence of two substances with C.H. activity. Injections of deoxycortone acetate 1 mg. and of cortisone ('Cortone,' Merck) 0·25 and 1 mg. did not give any colour change. Deoxycortone *made the frogs ill.* In our opinion the physiological significance of the C.H. activity of A.C.T.H. is not yet fully understood.

Treatment of prolactin with alkali [9] destroys the A.C.T.H. We injected prolactin treated in this way in frogs, and we found a positive Konsuloff reaction and a negative Galli Mainini spermiation test. In our opinion this suggests that prolactin possesses chromatophorotropic activity.

Gynæcological Department,
State University of Utrecht,
The Netherlands.

L. A. M. STOLTE
J. H. J. BAKKER
E. VERBOOM
P. W. DAUVILLIER.

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4. Foy, H., Kondi, A., Hargreaves, A. *Brit. med. J.* 1951, i, 380; *Ibid*, p. 1108.
5. Sulman, P. G. *Lancet*, 1952, i, 1161.
6. Mighorst, J. C. A., Stolte, L. A. M., de Roo, P. H. M., Creutzberg, F. *Acta endocr., Copenhagen*, 1949, 2, 97.
7. Konsuloff, St. *Klin. Wschr.* 1934, 21, 776.
8. Stolte, L. A. M., Bakker, J. H. J., Verboom, E., Dauvillier, P. W. *Ned. Tijdschr. Geneesk.* 1952, 96, 2068.
9. Morris, C. J. O. R. *Lancet*, 1952, i, 1210.

Notes and News

DANISH HOSPITALITY

On Oct. 2 members of the National Association for the Prevention of Tuberculosis and of the Anglo-Danish Society met to hear a report on the first year's working of the scheme, made possible by the generosity of the society, whereby British children with tuberculosis are sent to Denmark to receive free treatment at Vordingborg Sanatorium. The children are selected by the medical committee of the N.A.P.T., and Dr. Harley Williams, the secretary-general, explained that the first 25 children who went to Denmark in March were drawn mostly from London, but another 25 who had just left for Denmark came from Cornwall, the Midlands, Wales, Scotland, and East Anglia. Of the first party 14 had now returned to their homes greatly restored in health. All the arrangements had worked smoothly and the parents were satisfied and enthusiastic about the scheme. Sir Michael Kroyer-Kielberg, chairman of the Anglo-Danish Society Fund, said that it was the intention of the fund to send an increasing number of children to Denmark in the next few years. Dr. Niels Sjorslev, medical director of the Danish National Association for the Fight against Tuberculosis, described Denmark's successful fight against tuberculosis from the opening in 1875 of a sanatorium for scrofulous children to present-day methods of control which include a country-wide network of chest clinics backed by B.C.G. vaccination. In proposing a vote of thanks to him Sir John Charles happily contrasted the war-like invasion of England by the Danes so many centuries ago with the smaller return invasion this year when British children were overwhelmed with kindness and hospitality by the warm-hearted Danes.

SPASTICS NEEDING HELP

In the last ten years children with cerebral palsy have been receiving some public attention; and not before it was time. The numbers of spastics (so called) in Great Britain have been variously estimated at 20,000 and 30,000, and some 10,000 of these are children; but there may well be more, *since, of course, the condition is not easy to diagnose in infancy.* Most children with cerebral palsy are normal mentally, and all of them can benefit from training, beginning in childhood (the earlier the better), in the use of their muscles; but so far the provision made for such training is very scanty.

In a film, *The Chance of Their Lives*, the National Spastics Society have tried to show how great the need is; and they have had the good luck to get Wilfred Pickles to tell the story. The film shows how badly these children are handicapped when among normal children; and how greatly they benefit from training in special schools such as St. Margaret's School at Croydon. There are, however, only six such schools in the country at the moment, and only one spastic child in ten can hope to get a place. To illustrate the usual fate of the untreated case the film shows a young man with a severe degree of cerebral palsy applying hopelessly for one job after another, and being turned down on his appearance alone. Spastic children outnumber blind and deaf children by about 2 to 1; yet almost all blind and deaf children are taught in special schools.

The film is intended for general showing, and all will wish it well. It reveals sympathetically and pleasantly what children born with cerebral palsy have to face, as well as what friendly and likeable children they generally are.

University of London

Dr. Arthur W. Proetz, professor of clinical otolaryngology in Washington University and president of the American Board of Otolaryngology, will deliver the Semon lecture at 5 P.M., on Thursday, Nov. 6, at 1, Wimpole Street, W.1. He will speak on Clinical Aspects of Respiratory Air Currents.

Whitley Councils

The following have been nominated as members of the staff side of Committee C of the Medical Whitley Council for the session *1952–53*:

W. G. Clark, J. Cottrell, H. K. Cowan, Doris A. Craigmile, J. M. Gibson, C. E. E. Herington, E. Catherine Morris Jones, A. Macrae, B. R. Nisbet, J. Riddell, J. A. Stirling, J. A. Struthers, J. B. Tilley.

The following deputy members have also been nominated:

H. D. Chalke, H. M. Cohen, I. G. Davies, G. Matthew Fyfe, J. Kelman, J. Sharpe, Gladys Stableforth, H. C. Maurice Williams, R. C. Wofinden.

Royal College of Physicians of London

On Nov. 6, Dr. R. R. Bomford will deliver the Bradshaw lecture at the college, Pall Mall East, S.W.1. He will speak on Changing Concepts of Health and Disease, with Particular Reference to "Psychosomatic Medicine." Prof. A. A. Moncrieff will deliver the Charles West lecture on Tuesday, Nov. 11, on Infection in the Newborn Baby. Both lectures are at 5 P.M.

Royal College of Surgeons of England

Faculty of Dental Surgery.—Sir William Kelsey Fry has been re-elected dean.

British Postgraduate Travelling Fellowships

The British Postgraduate Medical Federation invites applications from doctors and dentists for these fellowships, which have been set up to enable graduates who are in the course of training as specialists in one of the preclinical or clinical branches of medicine, surgery, or dentistry, to obtain experience of the methods of practice, education, and research at universities or other centres in the United Kingdom and abroad. Further particulars will be found in our advertisement columns.

Society of Apothecaries of London

A course of postgraduate lectures on Modern Methods in Treatment is to be held in the hall of the society, Black Friars Lane, Queen Victoria Street, E.C.4, at 3.30 and 5 P.M., from Nov. 3 to 6. The speakers will be: Mr. T. Holmes Sellors, Sir Geoffrey Todd, Sir William Gilliatt, Dr. Kenneth Harris, Sir Horace Evans, Mr. A. Dickson Wright, Dr. Robert Forbes, and Dr. R. Hale-White. Admission is free, without ticket.

Heberden Society

On Saturday, Oct. 25, at 10 A.M., at B.M.A. House, Tavistock Square, London, W.C.1, Lord Horder, the president-elect of the society, will deliver the Heberden oration for 1952. He is to speak on Rheumatism—a National Problem.

University College, London

Sir Geoffrey Jefferson, F.R.S., will deliver the Rickman Godlee lecture at the college, Gower Street, W.C.1, on Oct. 23, at 5.30 P.M. He is to speak on the Prodromes to Cortical Localisation.

London's New Health Centre

On Tuesday, Oct. 14, at 3 P.M., Mr. Somerville Hastings is to open London County Council's first comprehensive health centre at Woodberry Hall, 218, Green Lanes, N.4.

Manchester Royal Infirmary Old Residents

More than three hundred members attended a dinner of the M.R.I. Old Residents Club held on Oct. 4 at Manchester under the presidency of Prof. John Morley. Prof. L. J. Witts, in proposing the toast of The Hospital and its Historian, Dr. William Brockbank, claimed for himself the distinction of having been described as "the finest student that Manchester ever turned out." Dr. Brockbank replied with a whirlwind of facts and figures about the infirmary and old residents. Dr. E. J. Foulds proposed the health of The President, and Professor Morley replied. The meeting had been moved forward a year so that it could coincide with the hospital's bicentenary year, and during the evening comparisons were inevitable but not odious. Today, for instance, there are so many resident posts that there is a net increase of about 15 a year in the membership of the club. Both of the country's surgical peers are members, and 2% of the members hold professorial chairs.

Association of Clinical Pathologists

At the annual general meeting held at Westminster Medical School on Oct. 2 Prof. R. J. V. Pulvertaft was elected president, Prof. Dorothy Russell vice-president, and Dr. Cuthbert Dukes chairman of the council. The annual dinner held next day commemorated the founding of the association 25 years ago, and eight founder members were present—A. Renshaw, E. N. Davey, S. C. Dyke, G. Hadfield, S. G. Platts, A. G. Shera, A. F. S. Sladden, and C. J. Young. The toast to The Founder Members was proposed by Dr. Dukes, and Dr. S. C. Dyke replied. Dr. W. H. McMenemey proposed the health of The Guests and Mr. Iain Macleod, Minister of Health responded. On Oct. 1 at the Constitutional Club, members of the council had given a dinner and a memento to Dr. Dyke at the conclusion of his ten years' tenure of office as chairman. Dr. McMenemey presided.

ety of Chemical Industry

a meeting of the fine chemicals group to be held at the on School of Hygiene, Keppel Street, W.C.1, on Monday, 13, at 7 P.M., Prof. F. E. King, D.SC., will deliver a lecture ie Synthesis of Simple Peptides.

criptions in August

ie Ministry of Health reports that in England and Wales ıg the month of August the declared number of National th Service prescriptions submitted was 14,075,256 :ease of 6·64% on August, 1951). The declared number of s submitted was 8,224,987 (decrease of 13·5% on August,). The ratio of prescriptions to forms was 1·71 (1·59 in ıst, 1951).

istry of Health Films

ıe Ministry has revised its list of sound films which may be hired from the Central Film Library. The films on th may be shown to lay audiences, those on medicine and ery only to medical and other professional audiences. :her particulars may be had from the library, Government ding, Bromyard Avenue, London, W.3.

idlesex Hospital Dinner

residing over the annual dinner of the Middlesex Hospital ical School on Oct. 3, Mr. David Patey said that the dlesex owed its special privileged position to being a hing hospital with university connections, responsible for graduate work. It was recognised that teaching neces- :es research, and in the present evolution of the health ice "we are splendidly poised for making advances in icine." With its established scientific institutes and its ɔwment fund (whose preservation and increase should a major concern) the hospital had a special duty and ortunity. From the standpoint of the patient, a teaching pital had its inconveniences, but the public should be ıght to understand that the special advantages they ive from being at a teaching hospital stem directly from fact that it *is* a teaching hospital. At the same time rything possible should be done to preserve the dignity the patient as an individual, by privacy or otherwise: Patey welcomed particularly the establishment of the hard Davis waiting-room for the relatives of patients who dangerously ill, and he would like to see further develop- nts in the architecture of the wards. Looking at the :ld more broadly, "all that has been regarded as civilisa- ı, from Marathon and Bethlehem, is in danger," he said, f being submerged in a new wave of barbarism; and we ı profession have a part to play in the intellectual refutation this barbarism as a necessary prelude to its physical ıtation." Sir Harold Boldero, the dean, spoke of the xiety many students had felt about the new Medical Act ıuiring them to hold 2 six-month house-appointments :ore registration. Long before the Act, however, the :rage number of house-appointments held by Middlesex n was $1^1/_2$; and there should be no hardship except :haps for men with families, whose case is now being ısidered. The hospital was proud to know that two dis- guished men were coming to continue their researches :re: Mr. V. E. Negus was to work in the Ferens Institute d Prof. S. P. Bedson, F.R.S., had been invited to the Bland- tton Institute. Perhaps the most important of all the velopments of the past 10–15 years, in Sir Harold's view, ıs the Institute of Clinical Research, which would be pported substantially from the endowment fund; and ıen the new extensions were opened, members of the staff ɔuld have modern facilities for pursuing ideas arising out their clinical work. Dr. P. A. J. Ball, senior Broderip holar, said that two students had represented the school well as Britain in the Olympic Games, and had all but ɔn a gold medal. For the first time, the majority of house- en were now married; and most of the others were engaged. ıis he regarded as a natural effect of the insecurity following e war; but older people seemed inclined to put it down a natural lack of forethought in the young and too much curity in the N.H.S.! The dean was reported to have said at it would of course mean the end of all social life. Mr. ichard Handley, proposing The Chairman, described r. Patey as the most honest man in London, and spoke his inquiring mind, his courage, his kindness, and his ımour. His recent nautical experiments, Mr. Handley id, had been particularly striking—perhaps the most ıportant being his demonstration (unfortunately uncon- olled) that steam does not always give way to sail.

Casualties in Korea

A recent casualty-list includes the name of Captain T. S. Hart, R.A.M.C., who has been wounded in action in Korea.

New York Academy of Medicine

Dr. Harry D. Kruse has been appointed secretary to the committee on public health relations of the academy in succession to Dr. E. H. L. Corwin, who has retired.

Lasker Awards

Among six recipients of Lasker awards from the American Public Health Association are Sir Macfarlane Burnet, F.R.S., director of the Walter and Eliza Hall Institute, Melbourne, and Dr. Brock Chisholm, director-general of the World Health Organisation.

Conference on Medical Photography

The medical group of the Institute of British Photographers is holding its third annual conference at the Royal Hotel, Woburn Place, London, W.C.1, from Oct. 10 to 12. Further particulars may be had from the secretary of the group, I.B.P. 49, Gordon Square, W.C.1.

Medical Congress at Evian

The second International Congress of Hippocratic Medicine will be held at Evian from Sept. 3 to 6 next year under the presidency of Professor Laignel-Lavastine. Prof. P. Delore, who is the secretary-general of the congress, may be addressed at 13 rue Jarente, Lyons, France.

British Standard for Cot Mattresses

A new British standard (B.S. 1819, part 2) has been issued for spring-interior cot mattresses (hospital type) to fit the standard hospital-type children's cots, as specified in B.S. 1694. Copies (price 2*s.* 6*d.*) may be obtained from the British Standards Institution, Sales Branch, 24, Victoria Street, London, S.W.1.

Union of St. Luke for Medical Practitioners of the Church of England

A service of commemoration of St. Luke's day will be held on Saturday, Oct. 18, at St. Stephen's Church, Rochester Row, London, S.W.1, at 3.15 P.M. After the service, at 4.15 P.M., there will be a meeting at the National Society, Great Peter Street, S.W.1, when Dr. P. C. Gibson will be in the chair and the Rev. F. S. Sinker, M.B., will speak on Coöperation Between Doctors and Clergy.

Dr. L. Guttmann, director of the Ministry of Pensions' Spinal Injuries Centre, Stoke Mandeville Hospital, and consultant to the Oxford Regional Hospital Board, is to deliver the first Fred H. Albee lecture at a conference on rehabilitation in paraplegia, to be held at the Kessler Institute for Rehabilitation, West Orange, New Jersey, on Oct. 10.

Births, Marriages, and Deaths

BIRTHS

FAWKNER-CORBETT.—On Oct. 1, at Lawn Edge, Meadowlands, Havant, Hants, to Phyllis (née Brumfit), wife of Dr. P. J. Fawkner-Corbett—a son.

HARRIS.—On Sept. 28, at Edgware General Hospital, to Sonia (née Bilmes), wife of Dr. Wallace C. Harris—a son.

HOGARTH.—On Oct. 2, at The Clinic, London, to Harriette Ruth (née Lewis), wife of Dr. J. C. Hogarth—a son.

LUNT.—On Sept. 29, to Penelope, wife of Mr. Randle Lunt, M.CH. ORTH.—a daughter.

PARKINSON.—On Sept. 29, at King's College Hospital, to Helen (née Overton), wife of Dr. Charles F. C. Parkinson—a daughter.

MARRIAGES

BOWSHER—REID.—On Sept. 27, at Liverpool, David Richard Bowsher, M.B., to Anna Meryl Reid.

PADDON—FORTESCUE.—On Sept. 20, at North West River, Labrador, William Anthony Paddon, M.D., to Sheila Mary Fortescue.

ROCKLEY—MATTOCKS.—On Sept. 20, Gerald Joseph Rockley, M.B., to Elisabeth Mary Mattocks.

RUGG-GUNN—COWAN.—On Oct. 1, at Salcombe Regis, Devon, Mark Andrew Rugg-Gunn, M.D., surgeon commander R.N., to Patricia Mary Elizabeth Cowan.

DEATHS

AITKEN.—On Oct. 2, at 'Clodiagh,' Stanmore, James Aitken, M.A., M.B. Edin.

HENDERSON.—On Sept. 29, at Ridgeway, Orchard Hill, Bideford, Devon, George Pouncey Henderson, M.D. Edin., aged 78.

LINDSAY.—On Oct. 3, at Shortfurrows, 65, Whyteleafe Road, Caterham, Surrey, Thomas Lindsay, M.D., F.R.C.S.E.

MATTHEWS.—On Oct. 3, Edgar William Matthews, M.B. Lond., D.P.H., of Oakingham, Bramber Road, Seaford, Sussex, aged 72.

SHAW.—On Sept. 29, William Samuel Jagoe Shaw, M.D. Belf., lieut.-colonel, I.M.S., retd., of Calcote House, Sandecotes Road, Parkstone, Dorset, aged 81.

Diary of the Week

OCT. 12 TO 18

Monday, 13th

Royal College of Surgeons, Lincoln's Inn Fields, W.C.2
5.15 P.M. Mr. E. G. Tuckwell: *Surgery of the Sympathetic Nervous System.*
6.30 P.M. Mr. O. J. Vaughan-Jackson: Fracture of Neck of Femur in Aged.
University College, Gower Street, W.C.1
4.45 P.M. Prof. Adrien Albert, D.SC. (Australian National University): Ionisation and Biological Activity. (First of three lectures.)
University of London
5.30 P.M. (King's College, Strand, W.C.2.) Prof. E. M. Landis (Harvard): Movement of Fluid and Dissolved Substances through the Capillary Wall. (First of three lectures.)
Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Dr. W. C. Osman Hill: Links Between Comparative Pathology and Pædiatrics.
Institute of Psychiatry, Maudsley Hospital, Denmark Hill, S.E.5
4.30 P.M. Dr. E. Stengel: Psychiatry [illegible]
Medical Society of London, 11, Chand[illegible]
8.45 P.M. Dr. Cuthbert Dukes: Your Ge[illegible] address.)
University of Edinburgh
5 P.M. (University New Buildings.) Prof. E. I. Evans (Virginia): Physiologic Disturbances Accompanying Severe Thermal Injury in Man. (First of three Macarthur lectures.)

Tuesday, 14th

Royal College of Surgeons
5.15 P.M. Sir Arthur Porritt: Surgery of Peptic Ulceration.
6.30 P.M. Mr. B. N. Brooke: Development of Surgery for Ulcerative Colitis.
British Postgraduate Medical Federation
5.30 P.M. (London School of Hygiene.) Dr. W. S. Feldberg, F.R.S.: *Physiology of the Autonomic Nervous System.*
Royal Society of Medicine, 1, Wimpole Street, W.1
8 P.M. *Section of Psychiatry.* Dr. W. S. Maclay: Deaths Due to *Treatment. (Presidential address.)*
Institute of Dermatology, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Prof. C. A. Keele: *Sweat.*
Chelsea Clinical Society
8.30 P.M. (South Kensington Hotel, 41, Queen's Gate Terrace, S.W.7.) Sir David Kelly: Russia.
Manchester Medical Society
5 P.M. (University of Manchester.) *Section of Surgery.* Mr. R. L. Newell: *Progress in Surgery. (Presidential address.)*

Wednesday, 15th

Royal College of Surgeons
5.15 P.M. Mr. Brian McN. Truscott: Alimentary Diverticulæ.
University of London
5.30 P.M. Professor Landis: Movement of Fluid and Dissolved Substances through the Capillary Wall. (Second of three lectures.)
Royal Eye Hospital, St. George's Circus, Southwark, S.E.1
5.30 P.M. Mr. J. F. P. Deller: Some Optical Aberrations of the Eye.
Royal Society of Medicine
5 P.M. *Section of Comparative Medicine.* Dr. C. L. Oakley: Sites of Production of Antibodies. (Presidential address.)
8.15 P.M. *Section of General Practice.* Dr. J. D. Simpson: Diagnosis in General Practice. (Valedictory address.)
Royal Institute of Public Health and Hygiene, 28, Portland Place, W.1
4.30 P.M. Dr. W. D. M. Paton: Uses of the Methonium Compounds. (Bengué lecture.)
Institute of Dermatology
5.30 P.M. Dr. J. O. Oliver: Bacteriology of Skin Diseases.
University of Edinburgh
5 P.M. Professor Evans: Clinical Management of Burn Shock. (Second of three Macarthur lectures.)
University of Glasgow
8 P.M. (Department of Ophthalmology.) Embryology of the Eye. (Instructional talking film.)

Thursday, 16th

Royal College of Surgeons
5.15 P.M. Mr. Geoffrey Keynes: Thymus.
6.30 P.M. Mr. J. C. Ainsworth-Davis: Surgery of the Prostate.
British Postgraduate Medical Federation
5.30 P.M. Dr. Paton: Principles of Ganglionic Block.
Royal Army Medical College, Millbank, S.W.1
5 P.M. Captain M. P. Ward: Mount Everest Reconnaissance.
St. George's Hospital Medical School, Hyde Park Corner, S.W.1
5 P.M. Dr. Desmond Curran: Psychiatry lecture-demonstration.
Royal Eye Hospital
5.30 P.M. Miss J. M. Dollar: Iridocyclitis and Choroiditis and its Differential Diagnosis.
British Institute of Radiology, 32, Welbeck Street, W.1
8 P.M. Dr. J. W. McLaren: Soft Tissue Radiography. (Presidential address.)
Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, W.1
7.30 P.M. Prof. A. [illegible] Gastro-intestinal Function and [illegible] Sprue, Cœliac Disease, and [illegible]
University of St. Andrews
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. Leonard Colebrook, F.R.S.: Burns and Scalds.
University of Birmingham
4 P.M. (Medical School.) Sir James Spence: Poliomyelitis. (First of two Ingleby lectures.)

Friday, 17th

Royal College of Physicians, Pall Mall East, S.W.1
3 P.M. *Lord Moran: Into the Past.* (Harveian Oration.)
University of London
5.30 P.M. Professor Landis: Movement of Fluid and Dissolved Substances through the Capillary Wall. (Last of three lectures.)
Royal Socie[illegible]
4.30 P.M. [illegible] *Preventive Medicine* [illegible] Prof [illegible] Illsley: Environment and [illegible] of Social Medicine [illegible] Research in Obstetrics.
8.15 P.M. *Section of Radiology.* Dr. E. R. Cullinan, Dr. R. Kemp Harper: Scleroderma.
Institute of Dermatology
5.30 P.M. Dr. M. S. Thomson: Lichen Planus.
Faculty of Radiologists
2.15 P.M. (Royal College of Surgeons.) Mr. C. E. Drew: Intrathoracic Fibroma. Dr. G. Simon: Tuberculous Bronchitis and Bronchiectasis. Dr. Neville Oswald: X-ray Appearances of Honeycomb Lung.
University of Edinburgh
5 P.M. Professor Evans: Clinical Management of the Burn Wound. (Last of three Macarthur lectures.)
University of Birmingham
4 P.M. Sir James Spence: Poliomyelitis. (Second of two Ingleby lectures.)

Appointments

Ballantyne, J. L., M.R.C.S.: appointed factory doctor, Coventry West, Warwickshire.
Ferguson, J. H. L., M.B.E., M.A., M.B. Camb., F.R.C.S.: asst. general [illegible] [illegible]ital, London.
Mac[illegible] [illegible]B. Edin.: appointed factory doctor.
Milne, D. G., M.B. Aberd., D.P.H.: asst. county M.O., Hertfordshire.
Temple, J. Ll., M.B. Lond., F.R.C.S.: consultant surgeon, Bristol clinical area, Weston-super-Mare.

Birmingham Regional Hospital Board:

Browne, R. A., M.B. Belf., D.P.M.: consultant psychiatrist and deputy medical superintendent, Coleshill Hall Hospital.
Lane, O. G., M.D. Lond.: part-time consultant pathologist, Dudley and Stourbridge group of hospitals.
Merry, Edith, M.B. Lond., D.A.: part-time consultant anæsthetist, Coventry group of hospitals.
Stephenson, S. F., M.B. Lond., F.R.C.S.: consultant thoracic surgeon, Birmingham and Mid-Worcestershire groups of hospitals.

Leeds Regional Hospital Board:

Allison, Rhoda, M.B. Leeds: *asst. pathologist* (S.H.M.O.), Huddersfield [illegible]
[illegible] [illegible]., M.R.C.P.E., D.P.H.: consultant in chest [illegible] and Dewsbury area.
Wilson, J. E., M.D., F.R.C.S.: consultant in thoracic surgery, Castle Hill Hospital, Cottingham.

Newcastle Regional Hospital Board:

Bell, R. C., M.B. Lond., F.R.C.S.: consultant plastic surgeon (asst.), Newcastle H.M.C. group and N.W. Durham H.M.C. group.
Browarski, W. J., M.B. Polish School of Medicine, Edin., D.P.M.: resident asst. psychiatrist (S.H.M.O.), St. Luke's Hospital, Middlesbrough.
Duggan-Keen, G. E., M.R.C.S., D.P.M.: deputy superintendent, Winterton Hospital, Sedgefield.
Edmunds, A. W. B., M.B. Edin., M.R.C.P.: consultant physician (asst.), Northallerton and Darlington H.M.C. group.
Gillis, Aaron, M.B., B.SC. Durh., M.R.C.P.E., D.P.M.: consultant psychiatrist, Cherry Knowle Hospital, Ryhope, near [illegible]
[illegible] Durh., F.R.C.S.: consultant plastic surgeon [illegible] H.M.C. group and the N.W. Durham H.M.C. group.
Inglis, Alexander, M.B. St. And.: consultant pathologist, hospitals in *Cumberland and N.* Westmorland.
Noble, T. C., M.D. Edin., M.R.C.P.E.: consultant pædiatrician (asst.), Sunderland H.M.C. group.
Potter, John, M.B. *Durh.*, F.R.C.S.E.: *consultant plastic surgeon,* Teesdale and Northallerton H.M.C. groups.
Potts, R. E., M.B. Glasg.: consultant pathologist (asst.), Teesside H.M.C. group.
Prinsley, D. M., M.D. Durh.: asst. chest physician (S.H.M.O.), Gateshead H.M.C. group.
Salfield, [illegible] consultant psychiatrist, Wintert[illegible]
Strang, Chr[illegible] consultant physician (asst.), [illegible] and Berwick groups of hospitals.
Szutowicz, Stanislaw, M.B. Polish School of Medicine, Edin.: *asst. pathologist,* hospitals in Cumberland and N. Westmorland.
Zinovieff, An[illegible] D.PHYS.MED.: director of physical medicine [illegible]nd N.W. Durham H.M.C. groups an[illegible] Centre, *Chester-le-street.*

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

SPECIALISATION, STRATIFICATION, AND RESEARCH*

Sir HAROLD HIMSWORTH
K.C.B., M.D. Lond., F.R.C.P.
SECRETARY OF THE MEDICAL RESEARCH COUNCIL

It is commonly said that, because of the breadth and complexity of modern knowledge, specialisation has now become a necessity; and it is customary to continue by expressing regret that such is the case. Quite apart from the fact that no man—not even a specialist—cares to be regarded as a regrettable necessity, there are other grounds for objecting to this statement. It is undoubtedly true that the limitations of human capacity render inevitable some degree of specialisation among members of highly developed professions like medicine. But implicit in the statement are two assumptions which, if allowed to pass unquestioned, can have far-reaching consequences. The first is that specialisation arises as a reluctant, conscious response to a recognised, practical necessity; the second, that the specialisations which have now achieved sanctification as Special Subjects represent an inevitable and permanent differentiation of function within the body of medical knowledge. If these two assumptions are correct, then there is nothing to be done about the present situation but to accept it. But a consideration of the evolution of medical specialisation suggests that they may not be; and, in that case, it should be permissible to modify the boundaries and organisation of specialties as need arises.

EVOLUTION OF A SPECIALTY

Generally speaking, we can distinguish two influences tending to specialisation—research and technique. To a greater or less extent both participate in the evolution of every medical specialty, but the part played by each varies from subject to subject. Let us first consider the evolution of a clinical specialty whose characteristic is a body of specialised knowledge rather than a specialised technique.

The founders of such a specialty were general clinicians with a special interest in a system and its diseases. The incentive for them to develop this interest—to do research—was curiosity, not a reluctant realisation of their intellectual limitations; and they remained well-founded in medicine and could draw fruitfully on their general experience. In the course of time the pioneers were succeeded by another generation, but such were the opportunities in the particular field that it continued to yield a rich harvest from within its original boundaries. With each succeeding generation, however, specialisation became more intense and the links with the general body of medicine more tenuous, while, at the same time, the virgin soil, susceptible to the now traditional approach shrank.

It is not difficult to foresee the outcome of this process. As Roger Bacon said, seven hundred years ago:

> "All sciences are connected; they lend each other material aid as parts of one great whole. . . . As an eye torn out or a foot cut off, so it is with the different departments of knowledge; none can attain its proper result separately, since all are part of one and the same complete wisdom."

To counteract the inherent, and potentially fatal, tendency of specialisation to isolation is no easy task; and it is particularly difficult in regard to the clinical specialties. With the passage of time there arises, not only a body of specialised knowledge, but a system of specialised practice. What began as a convenience becomes an established institution. As such it acquires an organisation which, however favourable to its perpetuation in the original form, may not necessarily be conducive to its further development.

This consideration applies with particular force to those specialties which are bound up with a particular technique. Consider the evolution of your own specialty, ophthalmology. Serious intellectual curiosity manifesting itself as systematic scientific research hardly existed until the time of Thomas Young and did not gather impetus until the work of Helmholz. But from time immemorial empirical techniques had been practised, both by itinerant oculists and by more regular members of the medical profession. In the 19th century the intellectual and technical streams came together, but at a time when, fortuitously, circumstances favoured developments on the technical side. Anæsthesia and antisepsis were discovered and provided the opportunity for technical development. The next fifty years were, understandably, preoccupied with a search for means to exploit the opportunity thus provided. Such success attended these efforts that ophthalmology emerged at the end of this time with an exacting technical discipline which exerted, and still exerts, a determining influence upon the form of your specialty.

But what has this led to; what is the position today? Should I be far wrong if I had said the ophthalmologists now recognise that not all conditions in their specialty are likely to yield to the surgical approach; that it is the others which now constitute the major challenge to research in their field; and that they are giving anxious thought on how to deal with this situation? For dealt with it must be if ophthalmology is not to degenerate into a mere technology.

I realise that in detailing the dangers of specialisation to you I have largely been preaching to the converted; for what is the Institute of Ophthalmology but an attempt to deal with these dangers? Here you have gathered together clinicians, pathologists, physiologists, biochemists, and physicists to work in association together. This is a major step in the right direction. But I am venturing to suggest to you that such an association alone is not enough. There is, in my opinion, still an important step to be taken. We have so far been considering the dangers inherent in specialisation but I think there is another development which carries at least equal dangers. I refer to the tendency, so marked in British medicine today, which one may call stratification.

STRATIFICATION

By *stratification* I mean the confining of interests within one of the major divisions of medicine to the exclusion of appreciation of relevant happenings in others. Despite repeated criticism of the medical curriculum as artificial, it does appear that medical knowledge tends to accumulate in layers roughly corresponding to the order in which the subjects succeed each other in the medical course. Along each traditional layer communications are relatively free, and important accessions to knowledge are unlikely to remain unknown. But between those in the different layers communications leave much to be desired. Thus, although a biochemist is usually soon aware of advances in chemistry relevant to his particular interest, he often does not know of equally relevant advances in histology, in pathology, or in the clinical field. Similarly much highly relevant knowledge in pathology and clinical research remains unknown to the physiologist. Despite the importance of bacteriology, immunology, and biochemistry to pædiatrics, few pædiatricians are competent to be their own bacteriologist, immunologist, or biochemist. And how many ophthalmologists have the necessary knowledge of functional pathology and applied physiology to undertake themselves comprehensive research into those conditions of the eye associated with general rather than local changes ?

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* An opening address delivered at the Institute of Ophthalmology on Sept. 30, 1952.

A NEW TYPE OF SPECIALIST ?

It may seem that I am denying that necessity for specialisation which I had already conceded inevitable. On the contrary I am pleading for the recognition of a further, and new, type of specialist—a specialist whose function is, not segregation, but integration. Let these men contract their interests within the particular stratum of medicine in which they find themselves—biochemistry, physiology, pathology, clinical medicine, or even a large specialty such as ophthalmology—in order to penetrate deeply into the strata on either side. Let us have, for example, clinicians who by contracting their clinical interests have liberated themselves to be competent biochemists, or pathologists, or physiologists. Such men can never supplant the clinicians, pathologists, physiologists, biochemists, and physicists proper. But that is not their rôle. They are to be complementary to these and their object is to nail together the different strata of medicine.

Let us apply these considerations specifically to ophthalmology. As a first step I suggest that two or three clinical research posts for ophthalmic physicians should be created. Many of the unsolved problems of ophthalmology are such that a man with the training, background, and outlook of a research physician would be attuned to them. Such men would in no way replace the general physicians now on the staffs of ophthalmic hospitals. Their interests would be much narrower to the end that they would be free to penetrate deeper into relevant studies in applied physiology, functional pathology, and clinical chemistry. The types of subject that I see them attacking are, for example, the degenerations of the eye (often with a hereditary basis) which develop during life, the mechanism of the retinopathies associated with metabolic disorders, and the functional changes in the eye following disorders in other systems. And quite apart from these direct contributions to ophthalmological research they would constitute a most valuable link in the chain of research-workers which stretches from the ophthalmologist proper to the basic sciences.

But do not underrate the difficulty of what I am suggesting. I am proposing, not simply that such ophthalmic research physicians be given all necessary facilities for laboratory work, both investigational and experimental, but also that they be given full staff status as clinicians with charge of research beds and responsibility for the patients under their care. Clinical research cannot be done by permission on other people's cases; nor can a practising clinician properly take responsibility for research work carried out by others on his patients.

CONTINUOUS ADAPTATION

I have chosen to take my example of the new type of specialist from the clinical field because the creation of such raises the greatest practical difficulties. But I could equally well have taken the example from the preclinical field. Both the strata and specialties of medical science are constantly tending to solidify from the crystallisation of career structures. The difficulty, and the necessity, is to keep the situation fluid so that it may be kept adapted to the opportunities of the present rather than to those of the past.

The essential thesis that I have been trying to defend is that specialisation, although a necessity in principle, is essentially an expedient in detail; that its boundaries at any particular period of time are a matter of temporary convenience; and that the condition of its healthy development is to prevent those boundaries becoming fixed and exclusive. To observe these requirements when a specialty has become embodied in a particular organisation is no light matter. But the difficulties, at least in the clinical field, are probably less now than they may be in the near future. In the precisely prescribed requirements which are now being proposed, with the best of intentions, for the training of consultants and specialists we see embodied those very dangers against which medicine, if it is to develop, must ever be on its guard; for the progress, and ultimate health, of any branch of knowledge depends upon the success with which, by preserving the elasticity of its organisation and adapting itself to new needs as they arise, it succeeds in counteracting its inherent and inevitable tendency to isolation.

INFLAMMATION AND ITS CONTROL*

A BIOCHEMICAL APPROACH

GEORGES UNGAR
M.D., D.Sc. Paris

RESEARCH ASSOCIATE, RHEUMATIC-FEVER RESEARCH INSTITUTE, NORTH-WESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILLINOIS

INFLAMMATION, the commonest local reaction of animal tissues to environmental change, has been one of the basic concepts of pathology since the beginnings of medicine. However, because of its very traditional nature, the concept of inflammation remains vague and poorly understood. Morphological study of inflamed tissues, intensively pursued by generations of pathologists and histologists, has only filled in the details of the first description given by Celsus nearly two thousand years ago. During the last few decades the inflammatory reaction became an object of study for the physiologist and biochemist, and it now appears possible to formulate a working hypothesis of the mechanism by which the reaction is brought about. I present here such a hypothesis and the evidence on which it is based.

BASIC PATTERN OF INFLAMMATION

When an environmental change, whether physical (mechanical trauma, temperature, radiations, &c.), chemical ("irritant" substances), or biological (bacterial infection, toxin, venom, antigen-antibody reaction), stimulates or injures a tissue, the following reaction will develop: dilatation of the blood-vessels, increase in the permeability of the capillary walls, and migration of leucocytes toward the site of the stimulation. The result will be an initial increase in blood-flow throughout the area, followed by a gradual slowing down of the circulation at its centre, associated with the clumping of blood-cells and the formation of microthrombi. At the height of inflammation increased arterial flow and capillary stasis will coexist in what Ricker (1924) called "peristatic hyperæmia." The passage of fluid and cells across the capillary wall causes swelling of the tissue and pain, both constant manifestations of acute inflammation. The vascular reaction induces changes in other structures, particularly the connective tissue. There seems, however, to be little doubt that the blood-vessels are the site of the primary disturbance.

It is essential to distinguish the inflammatory reaction from the direct physical or chemical effects of the stimulation on the tissue. When, for example, extreme heat is applied to a tissue, several direct effects will result: loss of water, coagulation of proteins, inactivation of enzymes, loss of structure, &c. Inflammation, however, is not the sum of these changes; it is the response of the tissue to the stimulus and to its effects. This response is non-specific, and its basic pattern is the same, irrespective of the nature of the original stimulus. Quantitatively, however, the reaction may vary with the intensity of the stimulation and the tissue concerned. One component of the reaction may also predominate at the expense of others, but all are present in different proportions.

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* Some of the work summarised here was supported by the Walter P. Murphy Foundation and by a U.S. Public Health Service grant.

To keep the concept of inflammation clear it is also essential to recognise the distinction between the inflammatory reaction and its possible sequelæ—e.g., necrosis, suppuration, formation of granulation tissue, and sclerosis.

CHEMICAL MEDIATION OF TISSUE REACTIONS

Systematic study of the mechanism of tissue reactions began about thirty years ago with the work of Krogh (1929), Ebbecke (1923), and Lewis (1927), who showed that certain types of response to mechanical, thermal, and chemical stimuli are associated with the local release of a substance (" H-substance ") similar to histamine. The introduction of histamine into the tissues was shown to reproduce some of the features of the response. Later work (Dragstedt 1941, Feldberg 1941, Ungar 1937) has shown that histamine is also involved in the anaphylactic and anaphylactoid reactions and may play a part in the allergic or hyperergic type of inflammation. These early studies introduced the concept of a biochemical process underlying the inflammatory reaction. The concept subsequently gained wide acceptance. Opinions conflict only about the relative importance of the substances involved and the nature of the reactions by which they are released.

It soon became apparent that histamine alone cannot be responsible for all the components of the basic inflammatory response; and, in addition to the H-substance, liberation of a less diffusible " H-colloid " (Krogh 1929) or of a " slow-reacting substance " (Feldberg 1941) was postulated under certain conditions of tissue stimulation. In recent years polypeptides have been extracted from tissues or from inflammatory exudates. These, when injected into normal tissue, reproduced certain features of the inflammatory reaction (Duthie and Chain 1939, Menkin 1940a, Rocha e Silva et al. 1949, Spector 1951). Although the causal relationship between these peptides and inflammation is not clearly established, the reported observations suggest that one of the intermediate steps between tissue stimulation and inflammation is the breakdown of some protein molecules.

There is also evidence that histamine may be released as a result of protein breakdown. Although final proof of this proteolytic theory is still lacking, there is strong circumstantial evidence in its favour: (1) proteolytic enzymes can liberate histamine from cells in vitro as well as in vivo (Rocha e Silva 1946); (2) proteolytic activity can be detected in blood and tissues under conditions in which histamine is liberated (Ungar 1937, 1944, 1947a, Ungar and Mist 1949); and (3) agents which inhibit proteolytic activity also inhibit the release of histamine (Ungar 1944, Ungar and Damgaard 1951, Ungar et al. 1951a). The so-called protease inhibitors, however, do not prevent the release of histamine in vitro (McIntire et al. 1950).

An alternative mechanism has been proposed for the release of histamine (McIntire et al. 1951). It is based on the observation that histamine can be liberated in vitro and in vivo by several comparatively simple amines or more complex alkaloids (McIntire et al. 1951, MacIntosh and Paton 1949, Feldberg and Paton 1951). This was interpreted as the competitive displacement of histamine from a loose combination. However, one cannot exclude the possibility that these "histamine liberators" act through a proteolytic enzyme system, since this mechanism is compatible with the kinetics of the reaction when it takes place in the presence of an enzyme inhibitor (McIntire et al. 1951.) Preliminary experiments show that histamine-liberating amines —e.g., octadecylamine—and alkaloids—e.g., morphine—do activate profibrinolysin when added to guineapig serum in vitro.

FIBRINOLYTIC SYSTEM IN INFLAMMATION

Evidence has been accumulating for some years that the so-called fibrinolytic system may be involved in shock and inflammation (Macfarlane and Biggs 1948). This system includes a precursor, profibrinolysin, which, when acted on by a fibrinokinase, is converted into an active protease, fibrinolysin. The enzyme thus released is inactivated by an inhibitor, antifibrinolysin.†

Profibrinolysin is a normal constituent of blood-serum (Christensen and MacLeod 1945, Loomis et al. 1947). The first kinases known to promote its conversion into fibrinolysin were the bacterial toxins streptokinase and staphylokinase (Garner and Tillett 1934, Milstone 1941). The rôle of these bacteriofibrinokinases is clearly limited to bacterial infection by strains able to produce the toxin. The range of activity of cytofibrinokinase is much wider; this kinase is present in various tissue cells and is liberated when the cells are injured (Astrup and Permin 1948). It is non-diffusible and can be recovered from the microsomic layer of cell debris (Tagnon and Palade 1950). A third type of kinase, serofibrinokinase, is present in serum in an inactive form, which is activated by the antigen-antibody reaction as well as by certain anaphylactoid stimuli. The kinase thus activated converts profibrinolysin into fibrinolysin (Ungar and Mist 1949, Geiger 1952).

The kinetics of profibrinolysin activation differ according to the type of kinase: activation is slow and progressive with bacteriokinases and cytokinase (Milstone 1941, Astrup and Permin 1948), and sudden and explosive with serokinase (Ungar and Mist 1949).

Fibrinolysin, formed by the activation of profibrinolysin, is different from other animal proteases (Christensen and MacLeod 1945). In addition to fibrinogen and fibrin, it attacks such usual protease substrates as casein, gelatin, hæmoglobin, &c. Its activity has often been measured by semi-quantitative methods (Loomis et al. 1947, Seegers 1950), but more precise enzymological methods can be used in its study to definite advantage (Christensen and MacLeod 1945, Ungar et al. 1951a).

Inactivation by antifibrinolysin begins as soon as fibrinolysin is released. Antifibrinolysin inactivates not only fibrinolysin but also trypsin, chymotrypsin, the leucoproteases, and probably other proteolytic enzymes (Grob 1946). Its existence in serum was reported by Hildebrandt (1893) and has been widely studied, usually through its inhibitory action on trypsin. There are, however, distinct disadvantages in using trypsin for this study, because this enzyme is not present in blood and there is a considerable difference in the rates of inactivation of trypsin and fibrinolysin (Christensen and MacLeod 1945). *Antifibrinolysin inactivates fibrinolysin much more slowly than trypsin* (Guest et al. 1948). The peculiar kinetic behaviour of the fibrinolysin-antifibrinolysin reaction is a very important point. Recognition of its significance is essential for understanding the whole fibrinolytic mechanism.

In the active interval between the release of fibrinolysin and its inactivation the enzyme is free to act on proteins

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† The terms fibrinolysin and anti[illegible] are also used sometimes to designate [illegible] tococcal fibrinokinase (Garner and Tillett [illegible] ly at present usually referred to as streptokinase and antistreptokinase (Milstone 1941). To avoid confusion some workers have adopt[illegible] [illegible] term 'fibrinolysin' has been retained for the enzyme by most workers mainly because it was first described under this name by Dastre (1893).

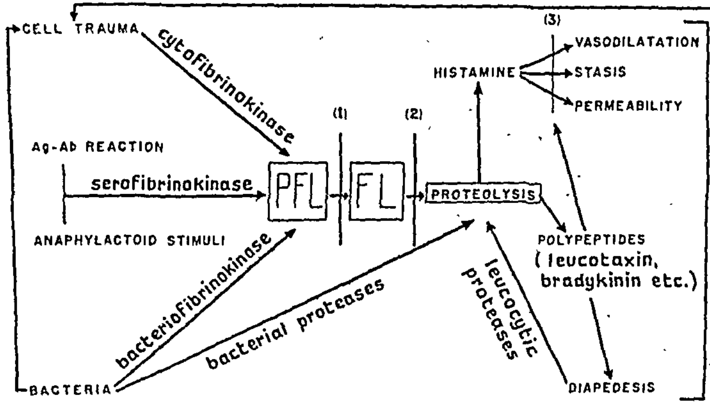

Fig. 1—Fibrinolytic hypothesis of inflammation: PFL, profibrinolysin; FL, fibrinolysin; 1, 2, and 3, points at which mechanism can be blocked.

and to release histamine and other substances, which in turn give rise to the various components of the inflammatory reaction: vasodilatation, increase in capillary permeability, stasis, and diapedesis. Proteases other than fibrinolysin *can no doubt initiate the same process, and* this may happen when tissues are infected by protease-producing bacteria. Leucocytic proteases may also contribute to the proteolytic process when white cells are disintegrating in the inflammatory focus. A vicious circle is established when more and more cells are injured under the influence of capillary stasis and anoxia, and when the cycle is constantly renewed by liberation of cytofibrinokinase. However, the fibrinolytic system is delicately balanced, and in a normal organism inflammation is self-limiting.

The hypothesis of a fibrinolytic mechanism of inflammation is summarised in fig. 1. The validity of this hypothesis can be tested by determining whether there is a correlation between the effects of certain conditions on the fibrinolytic system on the one hand and on the inflammatory reaction on the other. Fig. 1 indicates that, according to the present hypothesis, inflammation can be prevented (1) by blocking the conversion of profibrinolysin into fibrinolysin, (2) by inhibiting fibrinolysin, and (3) by inactivating histamine and other vaso-active substances.

For example, heparin at high concentrations is known to block profibrinolysin activation (Ungar and Mist 1949), as shown in fig. 1, point 1, and it is also known that heparin can prevent certain types of inflammatory reaction, especially *the Arthus phenomenon* (Grégoire 1946).

The action of histamine is inhibited (fig. 1, point 3) by anti-histamine drugs, whose main clinical use is to block allergic inflammation.

Inactivation of fibrinolysin (fig. 1, point 2) seems to take place spontaneously in the fibrinolytic system by antifibrinolysin. However, by virtue of the kinetics of the fibrinolysin-antifibrinolysin reaction there is an "active interval" sufficient to allow fibrinolysin to initiate the inflammatory response. This can be blocked either by an agent which exerts a rapid inhibitory action on fibrinolysin or under conditions which accelerate the inactivation of fibrinolysin by its natural inhibitor. Experimental evidence will now be given to show that both these actions may be exerted by two different types of agents.

FIBRINOLYSIN INHIBITION BY ANTIPHLOGISTIC DRUGS

Salicylates are among the oldest and most widely used antiphlogistics. Recent experimental findings show that sodium salicylate inhibits fibrinolysin in vitro. The inhibition takes place at concentrations similar to the blood level of salicylate required for therapeutic activity (Ungar et al. 1952). This observation prompted a systematic inquiry into a possible correlation between in-vitro inhibition of fibrinolysin and in-vivo antiphlogistic effect.

Table I shows that, for most of the drugs tested, there is a definite correlation between the two effects. Substances which inhibit fibrinolysin in vitro also reduce the Arthus phenomenon and are known to be clinically active in certain types of inflammation (group A). On the other hand, substances which have no demonstrable antiphlogistic activity, although they are structurally related to salicylic acid, were found inactive on fibrinolysin in vitro (group B). The only discrepancy (group C) is shown by drugs which are known to be converted in the body into other substances before exerting their action. It is known that acetylsalicylic acid is converted into salicylic acid (Smith et al. 1946), the dihydroxybenzoic acids (gentisic and γ-resorcylic) into the corresponding quinones (Meyer and Ragan 1948, Ungar et al. 1952), and the two last members of the group into *p*-amino-phenol (Michel et al. 1937).

The foregoing observations are compatible with the possibility that certain antiphlogistic drugs—such as those which owe their action to an *o*-hydroxy group in benzoic acid, the pyrazolone, *p*-aminophenol, and *cinchoninic-acid derivatives—act by inhibiting* fibrinolysin and blocking the fibrinolytic system at point 2 of fig. 1.

ENDOCRINE CONTROL OF INFLAMMATION

The discovery of the striking clinical effects of pituitary adrenocorticotropic hormone (A.C.T.H.) and cortisone (Hench et al. 1949) raised the problem of the mechanism of their action. Failure to explain the clinical effects by either the metabolic action of these hormones or their influence on antibody production led to the concept of a non-specific antiphlogistic action exerted by A.C.T.H. and cortisone (Dougherty and Schnaebeli 1950). Even before the discovery of the clinical effect of these hormones it was known that adrenocortical extracts prevented the increase in capillary permeability induced by tissue *injury* (Menkin 1940b, Ungar 1947b) and inhibited the release of histamine from blood-cells (Ungar 1944). These observations prompted an inquiry into the possibility of an action of the pituitary and adreno-

TABLE I—CORRELATION BETWEEN ACTIONS OF DRUGS ON FIBRINOLYSIN IN VITRO AND ON INFLAMMATION IN VIVO

Drug	Fibrinolysin inhibition*	Antiphlogistic action†
Group A:		
Salicylic (*o*-hydroxybenzoic) acid	+	+
Antipyrine (phenyl-dimethylpyrazolone)	+	+
Aminopyrine (4-dimethylamino-antipyrine)	+	+
3-Hydroxy-2-phenylcinchoninic acid	+	+
p-Aminophenol	+	+
Group B:		
Benzoic acid	−	−
m-Hydroxybenzoic acid	−	−
p-Hydroxybenzoic acid	−	−
Group C:		
Acetylsalicylic acid	−	+
Gentisic (2, 5-dihydroxybenzoic) acid	−	+
γ-Resorcylic (2, 6-dihydroxy-benzoic) acid	−	+
Acetanilide	−	+
Phenacetine (*p*-ethoxyacetanilide)	−	+

* Each drug was tested between the concentrations of 5 × 10^{-4} and 5 × 10^{-3}M.

† Assessed according to clinical action recorded in published reports and tested experimentally on the Arthus phenomenon (Ungar et al. 1951b).

TABLE II—CORRELATION BETWEEN INFLAMMATION AND ANTIFIBRINOLYTIC ACTION OF SERUM IN ANIMALS TREATED WITH VARIOUS HORMONES

—	Antifibrinolysin *	Inflammation †
Control	100	100
A.C.T.H. 15 mg.	124	38
Cortisone 5 mg.	129	21
Deoxycortone acetate 5 mg.	99	91
11-Desoxycortisone 5 mg.	102	81
Deoxycortone acetate 5 mg. eight days	50	164
Thyroid-stimulating hormone 5 mg. four days	26	173
Growth hormone 5 mg. four days	47	162

The figures are percentage values compared to the controls. All the figures are averages of results obtained in groups of 5–20 guineapigs. The probability that the means are not different from the controls is smaller than the conventional limit of 0·05.

* Amount of fibrinolysin inhibited by 1 ml. of serum in 5 min. (Ungar et al. 1951a).

† Measured by the "swelling index" (Ungar et al. 1951b).

cortical hormones on the fibrinolytic system (Ungar and Damgaard 1951). Treatment of laboratory animals with A.C.T.H. or with cortisone did not prevent the conversion of profibrinolysin in their serum. It was found, however, that the serum of animals treated with the hormones inhibited fibrinolysin more quickly than did the serum of untreated animals. This observation led to a systematic investigation of the fibrinolysin-antifibrinolysin reaction in the serum of guineapigs and rats treated with various hormones (Ungar et al. 1951a). Antifibrinolytic activity was determined after five minutes' contact between the serum and the enzyme, thus measuring not the total antifibrinolysin but the rapidly available fraction of it. It is believed that this indicates the rate of the fibrinolysin-antifibrinolysin reaction. Since, however, the kinetics of the reaction are not well known, it is not clear whether a change in the rate is controlled by some catalyst or by the relative concentration of the two reagents. Results of kinetic studies of the fibrinolysin-antifibrinolysin reaction now being made in this laboratory seem to indicate that the rate depends on the presence of accelerating or retarding substances in the serum.

The effect of the same hormones was studied simultaneously in experimental inflammation (anaphylactic arthritis) (Ungar et al. 1951b). The intensity of the reaction was measured as a function of the swelling of the inflamed area. This was done not because it is believed that œdema is the most important component of inflammation but purely for expediency, since swelling is the most easily measurable manifestation of the inflammatory reaction.

Table II summarises some of the results and shows the correlation between antifibrinolytic activity of serum and the modification of the inflammatory reaction. It is seen that both A.C.T.H. and cortisone reduce the swelling and increase antifibrinolytic activity. Deoxycortone acetate and desoxycortisone (Compound S) given in a single injection have no significant effect on the swelling or on antifibrinolysin. Table II also shows that certain hormones (prolonged administration of deoxycortone and pituitary thyroid-stimulating and growth hormones) increase inflammatory œdema beyond control levels, and that the sera of the animals treated with these hormones have a low antifibrinolytic activity.

The observation that the inflammatory response is increased by repeated injections of deoxycortone or of pituitary growth hormone agrees with the findings of Selye (1950, 1951)—i.e., that prolonged administration of either of these substances induces a type of tissue injury similar to allergic inflammation. The theory of diseases of adaptation requires the assumption that when the general adaptation syndrome, operating through A.C.T.H and cortisone (see upper part of fig. 2), is exhausted its place is taken by a mechanism harmful to the organism and operating through the production of growth hormone and 11-desoxysteroids. Recent observations (Ungar et al. 1951a and b) suggest, however, a different sequence of events for this second mechanism (see lower part of fig. 2). Conditions which increase the concentration of circulating thyroid-stimulating hormone of the pituitary—e.g., thyroidectomy and overdosage of thyroxine (Rawson and Money 1949)—decrease antifibrinolytic activity in the serum and increase the inflammatory reaction. This seems to implicate thyroid-stimulating hormone to the same extent as growth hormone.‡ There is also evidence that both these pituitary hormones are still active after adrenalectomy. This indicates that their action is not mediated by the 11-desoxysteroids. Present data suggest rather that the presence of the pituitary gland is necessary to the inflammation-promoting action of deoxycortone.

Fig. 2 summarises the endocrine control of inflammation as it may operate through the fibrinolytic system. A given aggression which elicits an inflammatory response also stimulates the pituitary through either the central nervous system or the metabolites of the tissue reaction. This stimulation sets in motion two opposite mechanisms: (1) release of A.C.T.H. stimulation of the adrenal cortex, which in turn releases Compound F or cortisone; and acceleration of the inactivation of fibrinolysin and inhibition of inflammation (see upper part of fig. 2); and (2) release of growth hormone or thyroid-stimulating hormone, slower inactivation of fibrinolysin, and augmentation of the inflammatory reaction (see lower part of fig. 2).§

The question marks on fig. 2 indicate some of the many problems raised by these observations: are the two endocrine mechanisms set in motion simultaneously, one of them predominating quantitatively, or do they succeed each other in time? Are the endocrine actions

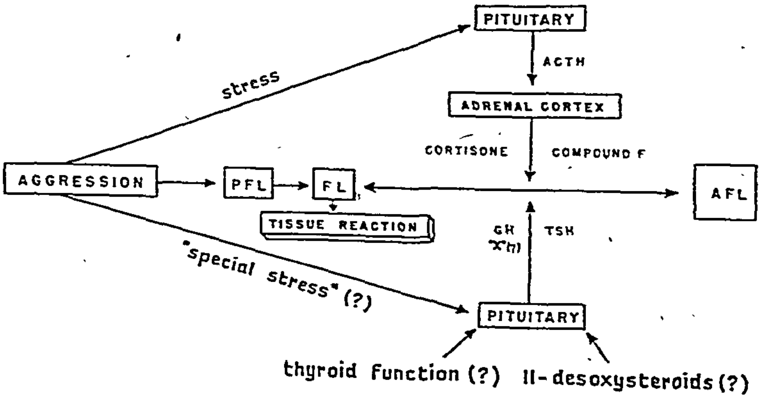

Fig. 2—Endocrine control of fibrinolytic system: PFL, profibrinolysin; FL, fibrinolysin; AFL, antifibrinolysin; GH, growth hormone; TSH, thyroid-stimulating hormone.

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‡ Since no pure preparation of either hormone is available, it is impossible to decide, simply by injecting them into animals, whether the effects here described are due to growth hormone, thyroid-stimulating hormone, or a third and unknown substance present as an impurity in the preparations.

§ There is a great deal of evidence (Ungar 1945, 1947b, Ungar and Damgaard 1951, Ungar et al. 1951a and b) that the spleen may play a part in the antiphlogistic action of the pituitary and adrenal cortex: cortisone does not reduce inflammatory œdema and does not accelerate the fibrinolysin-antifibrinolysin reaction in splenectomised animals; and a substance produced by the spleen (splenin A) can reproduce both these effects of cortisone. The spleen and the bone-marrow may also play a part in the inflammation-promoting action of the pituitary hormones through the release of another substance (splenin B). These observations, however, still await confirmation or denial from other laboratories.

different according to the nature of the stress, the inflammation-promoting mechanism resulting from some "special" stress? Can the balance of the two types of pituitary hormones be influenced by functional disturbances of the thyroid or the adrenal cortex?

There is a strong indication that this balance between A.C.T.H. on the one side and thyrotrophic and growth hormones on the other is the main factor in determining whether inflammation is self-limited, as happens in normal organisms, or becomes a self-perpetuating, chronic, or repetitive process.

MEANING OF INFLAMMATION

Inflammation has been considered as a defence mechanism ever since John Hunter suggested that it might serve a useful purpose. Recent evidence lends support to this view by showing that inhibition of the inflammatory response by corticotrophic hormone or cortisone facilitates the penetration of micro-organisms into the blood-stream and their dissemination (Mogabgab and Thomas 1950). However, the introduction of the question of purpose into the problem of inflammation, instead of helping to solve it, tends to confuse the issues. Inflammation is useful when it fulfils what, from a strictly pragmatic point of view, can be called its purpose: fixation of the aggressive agent and, consequently, protection of the rest of the organism. Quite as often, however, inflammation serves no detectable purpose and can even be harmful. Neither of the two mechanisms of endocrine control can therefore be called unreservedly good or bad.

From an objective biological point of view inflammation is the result of a complex chain of biochemical reactions controlled by the endocrine system. Since inflammation is the normal response of animal tissues to environmental changes it definitely has some survival value. It seems, however, that when the same sequence of biochemical reactions occurs at the systemic level, instead of being limited to a tissue, the resulting response, termed the shock syndrome (Moon 1938), is undoubtedly purposeless and harmful. This seems to suggest that the same mechanism can have adaptive value at a local level and no homeostatic significance whatever when it operates at the level of the organism as a whole.

Whatever the biological significance of inflammation, maybe better understanding of its mechanism would mean a considerable advance in our knowledge of disease processes. The hypotheses presented here will be either verified or eliminated by further experimentation. Meanwhile they can be justified if they fulfil the words of Claude Bernard: "Hypotheses and theories, even if mistaken, are useful in leading to discoveries" (Bernard 1865).

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THE EMERGENCY OBSTETRICAL SERVICE

A REVIEW OF 489 CASES IN THE MANCHESTER AREA

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It is a tragic event in childbirth when a mother bleeds to death. Fortunately it is a rare event nowadays, the number of maternal deaths from this cause having declined in common with those from other causes. Nevertheless in maternal mortality, hæmorrhage ranks a close second to toxæmia of pregnancy as a cause of loss of life. Moreover, the decrease in the number of deaths from hæmorrhage probably owes more to the efficiency of the blood-transfusion service and to the wider use of obstetric emergency units ("flying squads") than to improved management of the third stage of labour or reduction in its complications.

The good results which have followed extension throughout the country of the flying-squad services have been shown for the Newcastle region by Stabler (1947) and for other centres by Lloyd (1949), Shotton (1949), Shaw (1949a), and others. In the Manchester region, since 1936, the Emergency Maternity Service has been available for complications of the third stage of labour. Between September, 1947, and December, 1950, during which time I was connected with this service, 489 patients were treated. The calls were taken mainly by 12 doctors of registrar status, but sometimes by doctors not normally in the service. It was felt that an analysis of these cases might not only give additional information on the value of the service as at present constituted but would also show how our treatment of the third stage of labour and its complications might be improved, and how deaths from hæmorrhage might be prevented. The present paper comprises the results of this analysis.

COMPOSITION AND SCOPE OF EMERGENCY UNIT

The emergency team consists of a registrar and a sister, who are always readily available. A sufficient number of calls are received weekly for this to be possible. The efficiency of the service is greatly increased if valuable time is not lost searching for personnel to attend the call. This is an argument in favour of a single emergency unit serving a relatively large area, rather than two or more units which would be used much less frequently. In this respect it is important also that equipment is used sufficiently often for the sterility of the contents of the drums to be assured. Two complete sets of equipment are constantly ready, and drums are re-packed and re-sterilised immediately on completion of the case.

A detailed list of requisite articles of equipment has been given previously by Shotten (1949) and will not be repeated here. The materials used by the Manchester unit are almost identical. Any emergency obstetrical procedure can be performed without inconvenience other than that caused by the confined space of many of the patients' homes.

On receipt of a call the registrar on duty speaks to the practitioner or midwife. If the case is suitable, a car is at once loaded while the address is being located on the map. Blood, which is always rhesus-negative group O, is checked by the registrar or sister before setting out. The area served is wide, and calls may be received from thirty miles away or farther. Most of them, however, are to patients within ten miles of the hospital, who can normally be reached without serious loss of time.

Any case of complication of the third stage of labour is accepted and attended. In addition, as table I shows, other conditions where bleeding may be severe are sometimes seen, such as abortion, antepartum hæmorrhage, and secondary postpartum hæmorrhage. An additional duty which the flying squad has performed since 1947 has been to attend eclamptics in their homes, transferring them to hospital only after adequate initial treatment has been given. As has been pointed out by Shaw (1949), it is not part of the flying squad's duties to attend most of the antepartum and intrapartum obstetrical emergencies; such patients are better transported to hospital and dealt with there.

TABLE I—NUMBERS AND TYPES OF CASES TREATED

Type of case	No. of cases
Retained placenta	245
Postpartum hæmorrhage and shock	143
Abortion	33
Eclampsia	23
Antepartum hæmorrhage	9
Secondary postpartum hæmorrhage	9
Other conditions	27
Total	489

Nearly all the calls are for complications of the third stage of labour or of the immediate postpartum period, and it is on such cases that emphasis is laid here.

TREATMENT

Retained Placenta

The practitioner is asked to give his patient intramuscular ergometrine 0·5 mg., if he has not already done so, to limit the amount of bleeding while the squad is on its way. Experience of this over the last three years has seemed to confirm the original impression of Shaw (1949b) that the firm uterine contraction which results prevents further hæmorrhage.

On arrival a rapid history is taken and the patient is examined. Where shock is moderate, the blood-pressure, the pulse-rate, and the patient's general condition will indicate whether blood is needed or not. In cases of extreme shock we have often given a blood-transfusion at once without waiting to read the blood-pressure.

For the transfusion rhesus-negative group-O blood is always used, because the patient's rhesus group is seldom known for certain. If there is time, a direct compatibility test is made before any blood is given, but in a case of great urgency this may be dispensed with. Blood may be given if necessary under pressure.

On abdominal examination it is occasionally evident that the placenta has separated and is lying in the lower uterine segment or in the vagina. It is in this type of case, with the patient shocked by blood-loss and perhaps by repeated attempts at placental expression, that cord traction to deliver the placenta is most valuable, because it permits gentler handling of the uterus. But, as has been emphasised before (Dewhurst and Bevis 1951), this is a dangerous practice unless the operator is *certain* that the placenta has separated and is awaiting delivery, and that the uterus is firmly contracted.

Bleeding has usually ceased either because of the uterine contraction induced by ergometrine or because of the fall in blood-pressure. Sometimes, however, the uterus is full of blood, although there is no continuing external bleeding. The fundus will then be found well above the level of the umbilicus or even as high as the costal margin. In this type of case considerable benefit to the patient results from the gentle expulsion of this retained blood by fundal pressure, and obvious improvement in the patient's condition may be noted before the blood-transfusion could have been responsible, or indeed before the drip has been set up. While the attendants at the confinement are awaiting the arrival of the flying squad, someone must keep a hand constantly on the uterus to detect any rise in the level as the relaxed organ fills with blood. This should be done even when ergometrine has been given.

Attention is next paid to removing the placenta as simply and as safely as possible. The question of whether or not an attempt should be made to express the placenta by abdominal manipulation—usually squeezing and thrusting the uterus downwards—is debatable. Stabler (1947) suggested that one attempt should be made and not repeated. Repeated attempts have probably been made already, from which shock may have resulted. If the patient is extremely shocked, it is probably safer to proceed directly to manual removal. In this series most of the placentæ were removed manually.

The placenta is usually removed under inhalation anæsthesia induced by the patient's own doctor. Latterly thiopentone was used from time to time with good results. As a rule only a very small amount was needed to obtain adequate relaxation. Dangers arising from open fires in the room are also thus avoided.

The time of removal of the placenta is very important. This should be as soon as the patient shows signs of improvement, usually after 15–30 minutes, when $^{1}/_{2}$–1 pint of blood has been given. To wait longer in the hope of getting the patient's blood-pressure much above 80 mm. Hg is undesirable; bleeding is likely to begin again, the blood-pressure will fall again, and all that has been gained may be lost.

I am confident that the sooner the placenta is removed and the patient's blood-pressure comes back permanently towards normal, the better—and the change in management of these cases in recent years in Manchester supports this view. It is a mistake to think that these patients will not stand the anæsthetic while the blood-pressure is still well below 100 mm. Hg. They will do so readily, they will require very little anæsthetic, and they will often be found to be improved when the placenta has been removed, before the anæsthetic has been discontinued. These facts have been stated before (Stabler 1947, Shotten 1949) but they are worth stating again.

After the removal of the placenta, recovery is usually rapid; further active treatment is unnecessary beyond the transfusion of a second pint of blood in some cases.

In a few cases, however, under certain conditions (see below) it is advisable to transfer the patient to hospital for further observation and treatment.

Postpartum Hæmorrhage and Collapse after Delivery of Placenta

As these patients are suffering from blood-loss, transfusion is the most effective treatment. In the straightforward type of case excellent results are obtained from this simple treatment, more than two pints of blood being seldom needed.

The recovery after transfusion of the healthy patient shocked from blood-loss alone is dramatic. Hence, if a rapid response is not obtained to transfusion, a careful assessment of the case must be made lest a more serious abnormality (e.g., rupture or inversion of the uterus) which requires urgent treatment has been overlooked. Even in the absence of such severe accidents as these the patient will be found occasionally to be more shocked than the blood-loss alone would account for. Repeated traumatic attempts to express a retained placenta may be to blame; so also may the injection of pituitary extract. Retained blood—sometimes in large amounts—may be found in the uterus, and should be expelled at once.

These conditions should be remembered as a cause of delay in recovery (see below).

Abortion, Antepartum Hæmorrhage, and Secondary Postpartum Hæmorrhage

The majority of these cases do not require the services of the emergency unit. It is occasionally necessary to resuscitate a patient before she is fit to undertake the journey, and it may even be necessary to transport her to hospital with the blood-drip in place. Rarely will it be possible to deal effectively with any of these complications in the patient's home, and the wisest course is transfer to hospital. More than half the cases of abortion which the squad attended required no preliminary treatment before removal to hospital, and, of course, for only a small fraction of the number of abortions admitted to the hospital were the services of the flying squad ever requested.

Eclampsia

The flying squad has dealt with eclampsia to avoid long journeys with the patient inadequately sedated and to ensure that the patient is attended constantly by medical personnel in an attempt to limit further fits. Doctors requesting admission of an eclamptic patient are asked to give the patient morphine at once and to remain with her until the arrival of the unit. Morphine and paraldehyde have been the drugs mainly used for the initial sedation before transfer of the patient to hospital. If the first injection of morphine has been given by the doctor, a further injection of gr. $^1/_4$ is given on arrival of the squad, followed shortly by paraldehyde either 5–10 ml. intramuscularly or drachms 6 in oil by rectal instillation. Some time later, when the attendant is satisfied that the level of sedation is satisfactory, the patient is removed to hospital in the ambulance. Everything which may be required in the event of a further fit is at hand during the ambulance ride. Magnesium sulphate is sometimes given in the early stages if the blood-pressure is very high; 10 ml. of a 20% solution being injected intravenously. It was rare for the patient to have further fits under this régime.

Obstetric examinations are reduced to a minimum, and no examination per vaginam is made unless the patient is thought to be in labour with the cervix nearing full dilatation. On two occasions, when the patient was in the second stage of labour, she was delivered at home before removal to hospital.

TABLE II—RETAINED PLACENTA

Total no. of cases	245
Placenta :	
Delivered on arrival	15 (*6·1%*)
Removed manually	175 (*71·4%*)
Expressed	55 (*22·4%*)
Shock :	
Present	156 (*63·7%*)
Absent	89 (*36·3%*)
Transfusion	179 (*73·1%*)
Parity :	
1	74 (*30·2%*)
2–5	149 (*60·8%*)
6 +	22 (*8·9%*)
Delivery :	
Normal vertex	219 (*89·3%*)
Forceps	17 (*6·9%*)
Breech, &c.	9 (*3·6%*)
Maternal deaths	2 (*0·8%*)

TABLE III—POSTPARTUM HÆMORRHAGE AND COLLAPSE

Total no. of cases	143
Parity :	
1	54 (*37·7%*)
2–5	82 (*57·3%*)
6 +	7 (*4·9%*)
Delivery :	
Natural forces	115 (*50·4%*)
Forceps	28 (*19·6%*)
Shock present	104 (*72·7%*)
Shock present but delayed	40 (*27·9%*)
Transfused	107 (*74·8%*)
Inversion of uterus	3 (*2·1%*)
Rupture of uterus	1 (*0·7%*)
Maternal deaths	5 (*3·5%*)

DISCUSSION

The value of the emergency obstetrical service is evident from examination of the results obtained (tables II and III). As will be seen from table II, of 245 patients with retained placenta 156 were shocked, many severely so. The placenta was successfully removed manually in 175 cases; 179 patients received a blood-transfusion with great benefit. When it is remembered that some of these patients were situated twenty, thirty, or more miles from hospital, 2 maternal deaths does not seem a high figure. The alternative treatment of transfer of these patients to hospital—even after transfusion—would almost certainly have led to a much higher mortality.

Two comments must be made on table II which reflect upon the general conduct of the third stage of labour. The first is to note with approval that in a third of the cases blood-transfusion was not required, and the general condition of the patient had not been allowed to suffer despite the third-stage abnormality. Probably this proportion can be increased further. Bleeding during the third stage before any other sign of placental separation is apparent often indicates the presence of an abnormality. If the placenta is not separating normally and cannot be expressed with one attempt, and manual removal is deemed inadvisable, the attendant should try to prevent shock by refraining from any further expression, to limit the blood-loss by giving ergometrine, and to control the fundus until assistance has arrived.

The second comment is on the fact that the flying squad was called to 17 patients with retained placenta after the practitioner had delivered the patient with forceps. It is surely a criticism of our medical teaching that doctors will embark on a forceps extraction but will not undertake manual removal of the placenta while the patient is still anæsthetised. As Stabler (1947) has pointed out, this is no doubt due to the old teaching that manual removal is the most dangerous operation in obstetrics. He emphasises that it is a life-saving operation and is easier and less dangerous than a forceps extraction. The flying squad once travelled thirty miles to find a woman, extremely shocked, who had been delivered with forceps two hours previously; she required a blood-transfusion, a second anæsthetic, and a manual removal of the placenta, which could have been done safely and easily very soon after the delivery when it became apparent that the placenta was not coming away.

The first of the 2 maternal deaths in this group illustrates this point.

Case 1.—A primigravida had been 48 hours in the first stage of labour. After 10 hours in the second stage she was given 0·5 ml. of 'Pituitrin.' Delivery did not follow; so she was delivered with low forceps under chloroform anæsthesia. After a further $2^{1}/_{4}$ hours the placenta was still not delivered and the flying squad was called. Resuscitation was started, followed by manual removal of the placenta $4^{1}/_{2}$ hours after delivery. The patient's general condition then seemed good, and she was left, only for the emergency service to be recalled $1^{1}/_{2}$ hours later because of a deterioration in her condition. Despite further treatment she died 4 hours later.

There are, of course, other factors here which no doubt contributed to a fatal result apart from the failure to remove the placenta until $4^{1}/_{2}$ hours after delivery. The dangers of whole-pituitary extract are discussed below. Cases 1 and 2 indicate that recovery is not always the rule, despite resuscitation and successful removal of the placenta.

The second death also shows how serious is such hæmorrhage in the woman who has borne many children.

Case 2.—A 9-para was delivered easily and normally. After $1^{1}/_{4}$ hours, as the placenta had still not separated, she was given 5 units of 'Pitocin.' She became shocked almost at once. The flying squad arrived $2^{1}/_{2}$ hours after delivery, to find the patient in extreme shock. She was given blood, and the placenta was removed manually. After 6 hours her blood-pressure was still only 60 mm. Hg, and after 8 hours she had improved to 100/60 mm. Hg, and shortly afterwards she was left in the charge of her own doctor and midwife. The improvement, however, was not maintained, and she died 12 hours later.

It has not been the practice to transfer patients to hospital after the placenta has been removed. Of 245 patients fewer than 10 have been moved. It can be argued, however, that the lives of both of these patients who died might have been saved if they had been transferred to hospital shortly after the improvement became established. Probably transfer is occasionally desirable—for example, where recovery is slow, or where two anæsthetics have been given, or where the patient has borne many children, or where supervision is impossible at home. The possible need for further treatment in such cases should be remembered.

In describing the routine treatment of postpartum hæmorrhage the comment was made that the recovery of these patients was often dramatic. And yet, despite this, 5 mothers died in this group, 4 of them from hæmorrhage alone (table III).

The danger of overlooking a uterine inversion or rupture has already been mentioned. There were 3 cases of uterine inversion, in 2 of which the diagnosis was confirmed on a routine vaginal examination as soon as it was seen that the patient was not improving satisfactorily from the transfusion. The diagnosis of this abnormality is difficult on abdominal examination alone if the inversion is incomplete, but it should be recognised at once if a vaginal examination is made. In all 3 cases, after preliminary resuscitation, the uterus was successfully replaced, in 2 cases by the hydrostatic method (O'Sullivan 1945) and in the 3rd manually. The patients were transferred to hospital afterwards, and each made an uneventful recovery. The cases have been described in greater detail elsewhere (Dewhurst and Bevis 1951).

One case of uterine rupture occurred which forms the first maternal death in this group.

Case 3.—A primipara, aged 35, collapsed towards the end of the second stage of labour. The delivery of the child was normal, and the placenta was expelled normally. Bleeding up to two pints took place during the third stage. Despite blood-transfusion from the flying squad there was no improvement, and a rapid examination per vaginam disclosed a rupture in the posterior wall of the lower uterine segment. The patient's general condition was so poor that she could not be moved for this to be dealt with, and she died shortly afterwards.

Mention has already been made of the dangers of pituitary extract. Of 140 cases of postpartum hæmorrhage crude pituitary extract was given in 28. These patients were among the most shocked of all. There can be little doubt that the injection of whole-pituitary extract to a patient suffering from blood-loss is dangerous. Cardiac irregularities and blood-pressure effects which might follow its injection in a healthy patient are far more serious if they occur in a patient already suffering from blood-loss. This effect cannot be entirely prevented by using purified oxytocic factor, especially if this drug is given intravenously. Intravenous or intramuscular ergometrine is just as effective and far safer.

What has been said previously about the relaxed uterus filling up with blood is no less important here, and the value of expressing the blood is equally evident. The presence of a relatively small amount of blood distending the uterus seems to have a greater effect on the condition of the patient than a similar amount lost externally. Just as the uterus with the placenta retained can fill with blood while the attendants are waiting for the flying squad, so it can fill up even after the third stage is complete. This type of postpartum collapse is most distressing because it is the most easily preventable. In 40 out of the 104 patients, more than half an hour, and sometimes many hours, had elapsed after the *completion* of the third stage before the patient was seen to be in poor condition. Blood had been allowed to accumulate in the uterus, and the level of the fundus had risen unnoticed. As no bleeding was seen externally, no abnormality was suspected; either the fundus was not palpated or, if it was, the significance of the rise in the level was not recognised. It is sufficient only to palpate the uterus from the time following delivery to prevent this type of delayed bleeding and collapse. Should the level be rising, the retained blood should be gently expelled by fundal pressure to allow the uterus to contract vigorously on the empty cavity. Blood allowed to accumulate slowly will effectively prevent this contraction and permit further bleeding. Case 4 shows what disastrous effects this can have.

Case 4.—A 2-para was delivered normally at term. The placenta did not separate, and there was some bleeding; so her doctor removed the placenta manually. Afterwards pituitrin 5 units and ergometrine 0·5 mg. were given intramuscularly, and the patient was thought to be well. Two hours later, however, she was found to be collapsed, and the flying squad was summoned. Despite resuscitation and expulsion of the retained blood in her uterus the patient was too far gone, and died in $1^{1}/_{2}$ hours.

The third maternal death took place in almost exactly similar circumstances in a primipara.

The increased liability to complications of the third stage of labour, when the patient has been delivered with forceps or by other means under general anæsthesia, is obvious from an examination of these figures. 28 patients were delivered with forceps or by breech extraction in this way—an incidence of nearly 20%, which is a very high figure in general practice. It is necessary to add that, when the patient has been delivered under general anæsthesia, precautions are required to overcome the uterine atony and postpartum hæmorrhage which is likely to take place. How effective is the use of ergometrine given when the body of the child is being delivered has been shown by Shaw (1949b).

The last 2 maternal deaths in this group illustrate again the greatly increased danger of postpartum hæmorrhage in the multipara who has borne many children. What has been said about the rapid recovery from hæmorrhage of the healthy patient does not apply to the patient whose general condition before labour is poor.

Many multiparous patients, of course, fall into this group. Gross deficiencies in diet may produce a dangerous state of chronic anæmia, which may be very difficult to detect. Hæmoglobin percentages of 40 or lower are not uncommon in the Manchester area. When postpartum hæmorrhage occurs in these patients, their lives are in jeopardy; death may be too rapid for treatment even to be started.

Case 5.—A 5-para was booked by a midwife a few days before term. She had received no antenatal care because she had travelled round the country throughout her pregnancy. The midwife, recognising her poor state of health, arranged for her to attend a clinic for advice. Labour began, however, before this was done; delivery was rapid, and the patient began to bleed as soon as the baby was born. The placenta was expressed, but heavy bleeding continued. The patient at once became extremely shocked, and died before the arrival of the flying squad, although the delivery took place not more than a mile from the hospital.

Case 6.—A 10-para bled profusely after a premature delivery. Efforts to preserve her life before the arrival of the squad were of no avail, and she died before it could reach her.

These 2 deaths took place in the group of only 7 patients whose parity was more than 5. It is hard to overemphasise the dangers of postpartum hæmorrhage in this type of patient. In all, there were only 27 patients in both groups who had had more than 5 children, and in this small number 3 maternal deaths took place. These facts speak for themselves.

One last type of dangerous patient must be mentioned—namely, the patient who has previously had an abnormality of the third stage of labour. It has been quite common among the cases described here to encounter patients with retained placenta or postpartum hæmorrhage who have had the same complication in a previous pregnancy. When the third stage of labour has once been abnormal in this manner, there is an increased likelihood of recurrence of the abnormality, and it is inadvisable for these patients to be confined outside hospital if this can be avoided.

There is no need to discuss here the cases of abortion and of antepartum and postpartum hæmorrhage. All the patients were transferred to hospital and treated there successfully, without mortality.

Discussion of the subsequent treatment of the cases of eclampsia is not within the scope of this paper, and results will only be given briefly. Four patients ultimately died: 1 from subarachnoid hæmorrhage which was finally decided to have been the primary lesion, the patient not therefore being properly included in these figures; 1 had a cerebral hæmorrhage in the region of the brain stem; 1 had extensive hepatic necrosis and pituitary hæmorrhage; and the 4th had hepatic necrosis with evidence of old chronic pyelonephritis. Although these figures are not good, it is unlikely that they would have been better had the flying squad not attended the patients. It is thought that this is a development of the flying squad which could, with benefit, be put to more widespread use. The excellent results of Dewar and Morris (1947) in Scotland are good evidence of the value of this form of treatment.

Miscellaneous Conditions

Little need be said about this group, which includes such cases as hæmorrhage at cæsarean section done in a nursing-home, 1 case of blood-loss into a large vaginal hæmatoma, 1 ectopic pregnancy, several cases of menopausal bleeding, and even 1 hæmorrhage following tonsillectomy.

CONCLUSIONS

Hæmorrhage in childbirth still constitutes a serious threat to the life of the patient. So long as domiciliary midwifery continues, the need will arise for the treatment of patients bleeding in their own homes. A method of dealing with these emergencies by an obstetrical flying squad staffed at the registrar/senior-registrar level is outlined in this paper. It is submitted that the results obtained provide additional evidence of the value of this type of service and demonstrate that treatment without the routine transfer of a shocked patient to hospital is satisfactory. It is important to the efficiency of the emergency unit that the personnel on duty be immediately available at all times.

If the services of the emergency unit are required, the attendants at the case have an important duty to perform in preserving the patient's general condition while the unit is on its way. To do this, simple measures only are indicated—the prevention of further bleeding by the use of ergometrine, the control of the fundus, and simple measures for the treatment of shock. Repeated attempts at placental expression, and permitting the relaxed uterus to fill up with blood, will increase the degree of shock present; so also will the use of whole-pituitary extract, the use of which is to be deprecated at all times.

The value of blood-transfusion for the patient suffering from blood-loss needs no emphasis. If blood is given to a patient with a retained placenta, the placenta is best removed at an early stage as soon as the patient's condition begins to improve. When a transfusion is given to a patient suffering from postpartum hæmorrhage, if rapid improvement in the patient's condition is not seen, the possibility should be remembered of a further complication which may have been overlooked, such as uterine inversion or rupture.

It does not seem to be sufficiently realised that there is an increased incidence of complications of the third stage of labour when the patient is delivered under general anæsthesia. The services of the flying squad are still requested for retained placenta after the patient has been delivered with forceps. It must be concluded that practitioners, prepared to embark on a forceps extraction, are not all willing to carry out a manual removal of the placenta. This is a simple procedure with which the practitioner should be familiar. The evidence in this report of 175 manual removals indicates that this is not the difficult and dangerous procedure it was formerly believed.

There are some patients in whom the risk of hæmorrhage is increased, making delivery outside hospital dangerous. In this category are those patients who have previously had an abnormality of the third stage of labour, perhaps with a blood-transfusion and a manual removal of placenta. Similarly, multiparæ with many previous pregnancies are often in considerable danger, particularly so if the dangerous state of anæmia so common in this class of patient is present. It is carrying obstetric practice beyond the bounds of safety to confine these dangerous patients at home.

Although most of these patients can be treated completely at home, a few of them should be transferred to hospital after treatment for further observation.

One last point may be emphasised. With the maternal mortality-rate standing at less than 1 per 1000 live births, death of the mother is no longer an adequate yardstick from which to judge the safety of our obstetric practice. Many of the patients mentioned here were near to death—so near in fact as to cause the gravest concern to even the most experienced of the flying squad. There is a natural tendency to recall fatal cases and to forget the others. We should remember them, and profit by the lessons they teach.

SUMMARY

The results are presented of 489 cases treated by the Manchester Emergency Maternity Unit from September, 1947, to December, 1950.

Most of the calls were to cases of retained placenta or of postpartum hæmorrhage, which together totalled

388. In these two groups there were 7 maternal deaths.

The routine methods of treatment used by the Emergency Unit are outlined, and the difficulties and dangers likely to be encountered in the two main classes of patient are discussed.

The maternal deaths are analysed in an attempt to show how similar deaths can be avoided.

My thanks are due to my colleagues on the flying-squad staff of St. Mary's Hospitals, Manchester, who have treated so many of these patients, and also to the nursing staff who have given such able assistance at all times. In particular, I would like to thank Miss C. B. Gott, S.R.N., S.C.M., for assistance in the preparation of these figures. Prof. C. Scott Russell has given me much help in the writing of this paper, and I am indebted to the board of St. Mary's Hospitals, Manchester, for permission to publish these results.

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THE SURGICAL TREATMENT OF MALIGNANT RECTAL POLYPS

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As is well known, benign epithelial tumours of the mucosa of the large bowel are frequent precursors of cancer. From this it follows that they require treatment, whether or not they are causing symptoms. The majority of such tumours are in the rectum or lower pelvic colon and can usually be seen and removed through a sigmoidoscope, the method of removal depending on the site and the presence or absence of a stalk. For tumours higher in the colon laparotomy and colotomy are commonly used.

All tumours removed in this way should be examined microscopically. If the polyp appeared clinically to be benign, and this is confirmed by the microscopical examination, further treatment will probably not be required. Sometimes, however, though the polyp appeared to be benign, microscopy reveals malignancy. The surgeon is then faced with a difficult decision: can he rely on the removal by local excision, or should he advise excision of the rectum and its field of lymphatic drainage? This problem would be simpler if he could be certain that local recurrence in the bowel would precede dissemination: then a policy of "watch and wait" could safely be advised. But there is doubt as to whether lymphatic metastasis has already taken place, or may do so in the absence of local recurrence or before the latter can be detected. In short, delay may deprive the patient of his only hope of permanent cure.

The purpose of this paper is to try to give some guidance to surgeons faced with the unexpected discovery of carcinoma in a pedunculated rectal tumour which appeared clinically benign and was removed by local excision. Through the courtesy of our colleagues we have had access to all their cases, and we review here a series of such cases treated and carefully followed up at St. Mark's Hospital.

Pathology of Malignant Rectal Polyps

The significance of the discovery of malignancy in a rectal polyp varies greatly according to the extent of the carcinoma and its histological grade of malignancy. To show the importance of the extent of spread, we illustrate in figs. 1–6 the different phases in the evolution of a malignant polyp:

Fig. 1 represents a simple non-malignant pedunculated adenoma in a quiescent state.

In fig. 2 several zones of more active epithelial proliferation, still of a non-malignant character, are represented by darker outlines to some of the mucus-secreting glands.

A further stage in development is represented in fig. 3, in which microscopic foci of carcinoma are represented by black spots. This may be described as "carcinoma in situ"—i.e., the initial stage of malignancy when there is not yet any evidence of infiltration or invasion. Since there is often an element of doubt about the malignancy of a lesion described as "carcinoma in situ," these have not been classified as cancer cases but only as doubtful or suspicious lesions.

The further growth and fusion of foci of "carcinoma in situ" results in a larger lesion, which now is definitely malignant though still almost completely confined to the region of the mucosa. We have illustrated this in fig. 4 as "focal" carcinoma.

When there is evidence of further spread into the stroma of the polyp or into the submucosa of the bowel we describe this as "invasive" carcinoma, which may be further subdivided into cases in which there appears to be an ample free margin below (fig. 5) and those in which there is no apparent free margin (fig. 6).

The histological grading of malignant tumours is now a routine procedure in the examination and classification of many varieties of cancer. The system which has been in use at St. Mark's Hospital for many years is to divide malignant tumours on the basis of the degree of differentiation of the neoplastic cells into "low," "average," and "high" grades of malignancy. A histological classification on similar lines is adopted by most pathologists when reporting on adenocarcinomata. For the grading system in use at St. Mark's Hospital see Gabriel (1948).

Material

In 1933–49 about 2500 cases of rectal cancer were treated surgically at St. Mark's Hospital—47 of them by what was described as local excision. The term

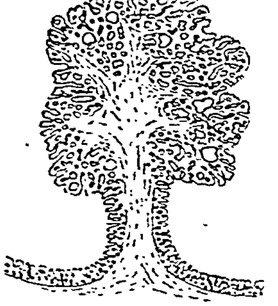

Fig. 1—Mucus-secreting adenoma.

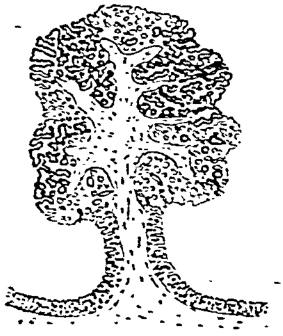

Fig. 2—Proliferation in adenoma.

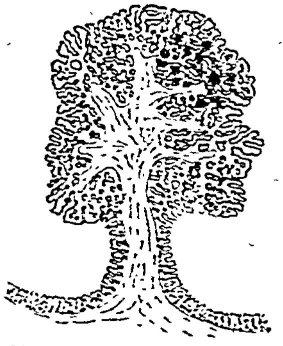

Fig. 3—Carcinoma "in situ."

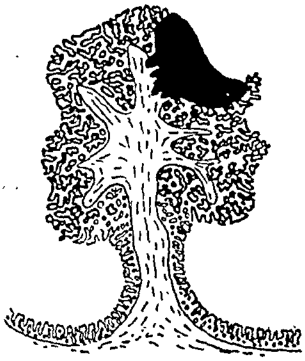
Fig. 4—" Focal " carcinoma.

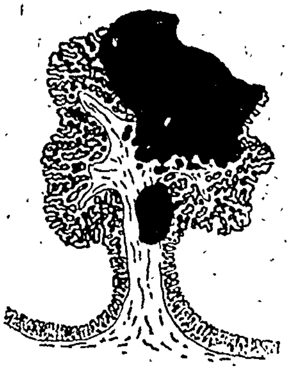
Fig. 5—" Invasive " carcinoma with free margin.

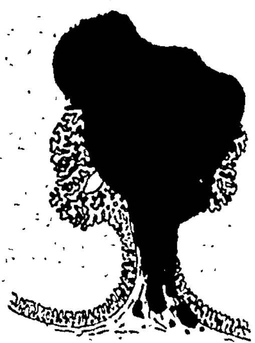
Fig. 6—" Invasive " carcinoma without free margin.

" local excision " has been used to describe any operation in which only the tumour itself was removed, sometimes perhaps with a cuff of surrounding tissue, but with no attempt to remove lymph-glands ; and any tumour in which definite malignancy was found has always been classified as cancer in the records and has thus been available for analysis. These 47 tumours were all malignant, in whole or in part, and the series does not include any tumour of doubtful malignancy or " carcinoma in situ " only.

The tumours varied greatly in size and shape. Some were pedunculated polyps ; others were small semi-pedunculated villous tumours ; others again were small nodular tumours. Most of them were clinically benign tumours in which the malignancy was only discovered on microscopy, but in others the malignancy was known or suspected before treatment was undertaken. These latter were mostly small mobile tumours in which it was felt that local excision might well be curative. It seemed to us that the inclusion of these latter cases was justified because, although malignancy was known or suspected, the method of treatment was that normally applied to a benign tumour.

These 47 tumours were all solitary, arising from the mucosa of the rectum, and were all treated by local excision only ; but we found that during the period under review 18 other tumours of a closely similar character had been treated for various reasons by more radical measures—e.g., combined excision, perineal excision, and restorative resection. In these 18 cases the lymph-glands were also removed, and the pathological reports on these cases have revealed how far the disease had spread. We found it instructive to compare these cases with the 47 treated by local excision, because, apart from the operation performed, the two series were in all respects comparable.

All these tumours—both the 47 removed by local excision and the 18 removed by radical excision—have been reviewed and classified as " focal " or " invasive " and according to their grade of malignancy. We have also attempted to decide, in the cases treated by local excision, whether that excision had apparently been clear of tumour tissue or not—i.e., whether there was an " apparent free margin " or only a " doubtful free margin."

The method of removal varied. Most of the pedunculated polyps were removed with the diathermy snare, whereas the villous tumours and those in which malignancy was clinically suspected were removed by an excision through the full thickness of the bowel wall.

Results

IN " FOCAL " CARCINOMA

(See figs. 4 and 7)

The end-results of treatment of early rectal cancer vary greatly with the stage of development of the disease. In the cases classified as " focal " carcinoma—i.e., carcinoma limited to the mucosa—the results of local excision were completely satisfactory. There were 17 such tumours among the 47 removed by local excision. One patient died from heart-disease four months after operation, but the other 16 are all alive, with no sign of recurrence. The period of observation has varied, but 14 patients have been under observation for more than three years, and 8 for more than five years. One of the 16 patients developed another polyp in another part of the rectum after eight years ; this also showed focal carcinoma on section, but he has remained well since his second operation.

All these 17 cases of focal carcinoma were classified as being of low or average grade of malignancy. It is not surprising that there was no example of high-grade malignancy in this group, because it is well known that undifferentiated or anaplastic carcinomas of the rectum grow rapidly and so would pass quickly from the stage of focal to that

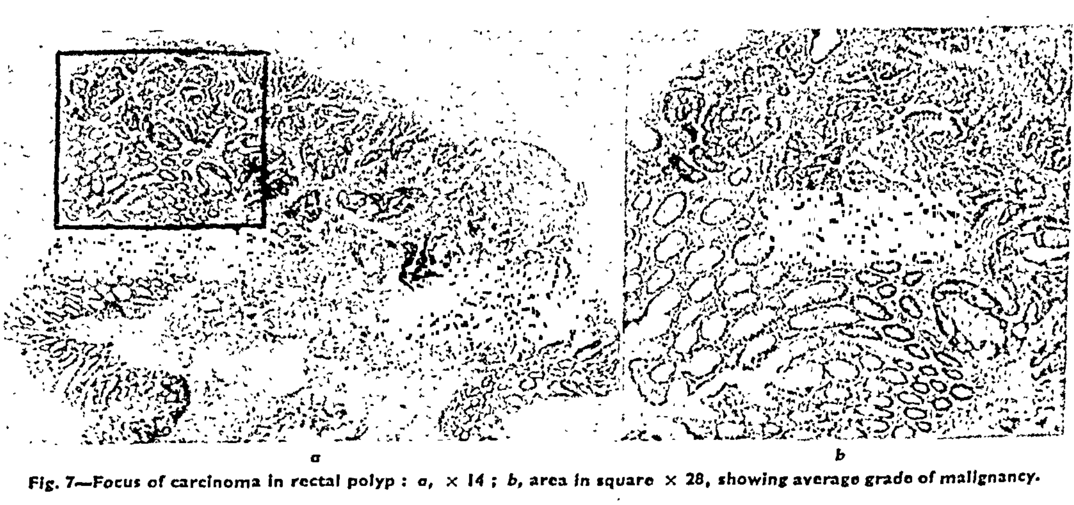

Fig. 7—Focus of carcinoma in rectal polyp : a, × 14 ; b, area in square × 28, showing average grade of malignancy.

of invasive carcinoma. If a carcinoma of high-grade malignancy were found to be still at the stage which we have described as focal, we are by no means sure that it would be safe to rely on local excision alone. So we may sum up our experience of focal carcinoma by saying that local excision certainly seems to be adequate for tumours classified as of low or average malignancy, but we doubt if this would be adequate for undifferentiated carcinomas classified as of a high grade of malignancy, which we think should always be treated radically.

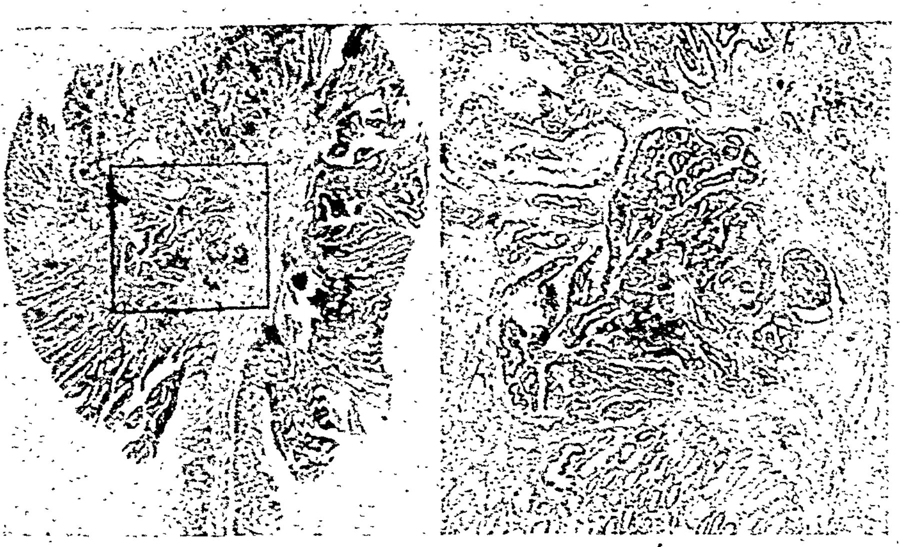

Fig. 8—Early stage of invasive carcinoma arising in pedunculated adenoma: *a*, × 5; *b*, area in square × 16.

IN "INVASIVE" CARCINOMA

(See figs. 5, 6, and 8)

It is in these cases that the grade of malignancy is of special importance in relation to prognosis after local excision. We therefore present the results according to their histological grading and compare them with the findings in the 18 similar tumours treated by radical excision, all of which were considered to be "invasive."

Tumours of Low-grade Malignancy

Of the "invasive" tumours in the series removed by local excision, 7 were considered to be of low-grade malignancy.

One patient had previously had a malignant polyp removed by snare at another hospital, and was referred to St. Mark's for opinion. As the polyp had shown complete replacement by low-grade adenocarcinoma, and had been at a sufficiently high level for a restorative operation, this was done; careful microscopy of the specimen failed to show any residual malignant cells, either at the primary site or in the glands.

The 6 other patients were treated primarily at St. Mark's and have all remained well: 2 for five years, 3 for three years, and 1 for two years.

In 4 of these cases there was an apparent free margin of normal tissue round the tumour, even though the growth had extended into the submucosa of the bowel wall; but in the 2 others there was little if any free margin, yet these patients also are free from evidence of disease two years and three years from the time of treatment. This period of observation is too short for final conclusions, because the natural development of low-grade tumours should be measured in years rather than in months, but it is encouraging that there has so far been no evidence of recurrence or metastasis.

The question of unsuspected metastasis naturally arises here, and in this connection it is instructive to examine the extent of spread in the 18 similar cases of rectal cancer which had been treated by radical excision, 14 of which were considered to be of low-grade malignancy. Examination of the operation specimens showed, in each of these 14 cases, that the growth had not extended beyond the rectum (A cases) and there were no lymphatic metastases.

Tumours of High-grade Malignancy

Of the 47 cases, 3 were classified as of high-grade malignancy, and recurrence took place in each of them.

One of these 3 patients was found to have local induration three months after removal of the polyp. Combined excision was undertaken without delay, and one gland was found to have been replaced by carcinoma; this patient is alive four years later.

The second patient was found, six months after removal of the polyp, to have a small nodule at the previous site. Again combined excision was advised, but it was refused for a further six months, by which time nine glands were found to be involved, though the local manifestations were still slight (see fig. 9). The patient died of metastases six months later, eighteen months after the local excision.

The third case is of particular interest in that on sigmoidoscopy the patient was found to be normal five months after a malignant polyp had been removed. When he was re-examined three months later, a small malignant ulcer was seen at the previous site, and a combined excision was undertaken. The operation specimen showed that five glands were by then involved. The patient died of chest complications a few days after the operation.

A carcinoma of high-grade malignancy was found in only 1 of the 18 similar cases treated by radical excision:

A woman, aged 42, under the care of Mr. Naunton Morgan, complained of rectal bleeding. After several negative X-ray and sigmoidoscopic examinations a polyp was finally seen 18 cm. from the anus, and laparotomy was advised. The colon was opened with a view to local excision of the tumour; but, as it felt hard in one part, the bowel was closed and resection with primary anastomosis was done instead. The operation specimen showed a pedunculated polyp partly replaced by carcinoma of high-grade malignancy invading the stalk, and four lymph-glands contained metastases (C2 case).

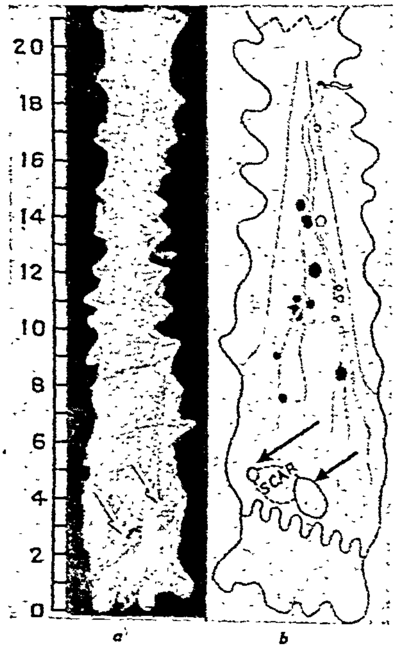

Fig. 9—Recurrence after local removal of rectal polyp containing carcinoma of high-grade malignancy: *a*, operation specimen obtained from synchronous combined excision by Mr. E. T. C. Milligan a year after local removal of polyp; *b*, sites of lymphatic metastases. Arrows indicate sites of recurrence. (Scale in inches.)

It is apparent from these 4 cases that in these tumours of high-grade malignancy lymphatic metastasis occurs early, and that, though local recurrence is likely, extrarectal lymphatic spread may precede any local manifestation.

Tumours of Average-grade Malignancy

These form the largest single group in the series removed by local excision, 20 of the 47 tumours being so classified. Only 6 of the patients have remained well, 4 having been under observation for five years, 1 for six years, and 1 for nine years; 5 others have died from unrelated causes, 4 of them within two years of treatment, but 1 after four years, during which there was no evidence of recurrence.

No fewer than 9, or nearly half, have had further disease. In 2 of them we are ignorant about the first manifestation of recurrence: 1 died of rectal cancer two and a half years after treatment; and the other now, five years after treatment, is reported to have an inoperable rectal growth. Of the other 7 patients 4 showed a localised nodule at the site of former excision as the first sign of recurrence two months, five months, thirteen months, and three years after treatment. They were all treated by combined excision, and in 1 of them a nearby lymph-gland contained a metastasis, though the local recurrence in this case was confined to the mucosa. In the 3 others lymphatic metastasis was the *first* sign of recurrence. In 2 this was in the inguinal glands, the primary having been at the ano-rectal junction, whereas in the 3rd the glands in the mesorectum became palpable through the posterior rectal wall. In none of these 3 cases was there clinically detectable recurrence at the primary site.

Of the 18 tumours removed by radical excision, only 3 were of average-grade malignancy. In 1 of these the malignant change was confined to the pedunculated tumour, but in the 2 others it had extended to the muscle coat, and in 1 of these a nearby gland contained a metastasis. Thus it is apparent that in these tumours of average-grade malignancy early metastasis is not uncommon, even though the tumour may be small and still pedunculated.

It is in the further analysis of this group of cases that we believe the assessment of the margin of clearance may be of value. Excluding the patients who died from unrelated causes, we found that of the 5 cases with an "apparent free margin" only 1 recurred, whereas of the 10 cases with a "doubtful free margin" 8 recurred. Undoubtedly detailed information about the margin of free tissue round a tumour is likely to be of considerable help to the surgeon in deciding future treatment.

Discussion

The discovery of a small unsuspected focus of malignancy in a rectal polyp is not rare, but the literature reveals considerable difference of opinion as to what is the best treatment. Bacon et al. (1951) say that, if definite malignancy is found in a benign tumour, even if the change is only "in situ," a radical excision should be done forthwith. Swinton (1948) reports 22 cases with "early malignant change" treated by local excision and followed up for seven years without recurrence, and is therefore more conservative in his attitude towards treatment. McLanahan et al. (1949) subdivide their cases into "non-invasive" and "invasive" tumours, using much the same criteria as set out above, and show that a third of the "invasive" tumours recurred, an incidence very similar to that found by us (see table). Marino (1948) also emphasises the difference between "invasive" and "in-situ" carcinoma, though neither term is defined.

Most of these workers agree on the importance of removing the whole polyp for careful microscopy, an opinion which we fully endorse, and which has been well expressed by deVeer, cited by Marino (1948): "The method of removal should be, if possible, the one that least interferes with histologic examination." It is only when the pathologist has the whole tumour for examination that he is in a position to give a fully valid opinion, and we are therefore opposed to the method of removal sometimes practised, whereby a ligature is tied tightly round the pedicle of a tumour, which is then left to slough away. Though it is certainly true that the detection of an "invasive" tumour is of the greatest importance, we believe that, for the most accurate prognosis, three factors should be taken into account: (1) the extent of spread of the malignant process (i.e., whether it remains "in situ," or is "focal," or has become "invasive"); (2) the grade of malignancy; and (3) the pathologist's assessment as to whether the excision has apparently allowed an adequate free margin of normal tissue round the tumour. There may be occasions when the pathologist will be reluctant to express a definite opinion, but nevertheless we believe that an attempt at assessment along the lines we have suggested will be of great value to the surgeon in deciding the best course for the patient.

MALIGNANT CHANGE IN RECTAL POLYPS

Type of carcinoma	No. of cases	No. of recurrences
Focal	17	Nil
Invasive:		
Low-grade malignancy ..	7	Nil
Average-grade malignancy ..	20	9
High-grade malignancy ..	3	3

From the material presented in this paper we have formed certain opinions about the policy to be pursued when a malignant polyp has been removed. In our series there were 17 "focal" carcinomata, and in none of these patients has recurrence been observed. If the malignant disease is still at the stage of focal carcinoma, local excision is, we believe, sufficient to eradicate the disease. In the case of pedunculated tumours the diathermy snare is probably the most effective method of removal, but for villous tumours the removal of the whole tumour by full-thickness excision, where feasible, is more satisfactory, as advocated by Coffey and Brinig (1950).

It is logical to conclude that, if "focal" carcinomata have done so well after local excision, malignant tumours at an earlier stage of development should have an equally good prognosis. We are accordingly of the opinion that local excision is adequate for cases of carcinoma "in situ." This opinion is at variance with that expressed by Bacon et al. (1951) but in agreement with most other authors.

Where the tumour is definitely "invasive," cure by local excision is less certain, but it is in these cases that we regard histological grading as of value. Of the 4 tumours of high-grade malignancy in our two series, all had lymphatic metastases; so it is obviously unwise to temporise. From our knowledge of the behaviour of rectal cancers of high-grade malignancy and their bad prognosis, it seems that, if any area of high-grade malignancy is reported in a removed polyp, it is wisest to proceed without delay to radical surgery as giving the patient the best chance of survival.

In none of the 7 tumours of low-grade malignancy in our series of local excisions, however, has recurrence been observed; nor were there any lymphatic metastases in the 14 similar cases treated by radical excision. That such tumours can recur is not doubted; but, in view of the low malignancy and lack of tendency to early metastasis, it is safe to assume that evidence of recurrence would become apparent locally before lymphatic spread took place; and, provided that these patients are kept under close observation, the fear of metastasis need not deter the surgeon from pursuing a conservative policy in the first instance. We think it safe to defer radical surgery in these cases, unless there is evidence of recurrence.

The "invasive" tumours of average-grade malignancy are the most common and pose the most difficult problem. In our series 9 out of 20 recurred, and in at least 4 of these lymphatic metastasis was also observed.

In view of these unsatisfactory results from local excision there can be little doubt that the greatest safety for the patient lies in immediate radical surgery: certainly we feel that excision of the rectum should be advised if there is microscopical evidence of spread into the bowel wall, or if the local removal has only left a small and inadequate margin of normal tissue round the malignant tumour. In cases where the malignancy is still confined to the pedunculated tumour, and where the margin of clearance has been good, it is probably safe to defer radical surgery, provided that the patient can be re-examined frequently. Such a policy would, of course, be safer where the lower rectum is involved, because here the earliest sign of recurrence could be detected by palpation, probably before any abnormality became apparent to visual examination. Every case should be most carefully assessed, and the closest collaboration between surgeon and pathologist is needed.

It is appreciated that, when any procedure other than a radical excision is done for a tumour in which malignancy is found, careful and frequent re-examination is essential for the patient's safety. Such frequent re-examination is, however, advisable in any patient from whom a rectal polyp has been removed, even though it may prove histologically to be entirely benign. This has been appreciated for many years (Lockhart-Mummery 1934), and is surely a small price to pay if the rectum can be safely preserved.

Welch (1951) points out the difficulty of detecting recurrence of tumours beyond the reach of the sigmoidoscope, and states that, of 70 polyps in the colon thought to be benign, 11 contained carcinoma. He therefore advised that resection should take the place of colotomy and local excision in dealing with polyps in the colon. The results presented here indicate that recurrence and metastasis are to be expected in many of these polyps after local removal only; nor is it possible to predict without full pathological examination which polyps are likely to recur. In view of the present low mortality associated with uncomplicated colonic resection, it is doubtful if this operation now carries any greater risk than colotomy, and we agree with the views expressed by Welch.

Although it has been shown by the results presented here that certain types of very early focal and low-grade carcinomata have been cured by local excision, this should not be interpreted as advocacy of conservative surgery for established rectal cancer. We still believe that, when a clinical diagnosis of rectal cancer is made, radical excision offers the patient the best chance of survival.

Summary

An attempt is made to give guidance to a surgeon faced with the unexpected discovery of malignancy in a rectal polyp.

A description is given of the early stages in the development of carcinoma, and it is suggested that, when examining a malignant polyp, the pathologist should pay special attention to the extent of local spread of the carcinoma, the histological grade of malignancy, and the presence or absence of a free margin.

The results obtained by local excision in 47 such cases are reported and compared with those obtained by radical excision in 18 similar cases.

It is concluded that local excision of the malignant polyp only is all that is required for most cases at the stage of carcinoma in situ or focal carcinoma, the only exception being anaplastic carcinoma of high-grade malignancy, which always calls for the widest possible removal.

When invasive carcinoma is found in a polyp, the decision as to treatment is much more difficult, and must depend on many factors, of which the two most important seem to be the histological grade of malignancy and the presence or absence of a free margin.

ADDENDUM

Since this paper was written, Fisher and Turnbull (1952) have reported a similar investigation. They have used a classification for malignant polyps based on principles similar to those we have adopted, but differing slightly in details of terminology.

We are grateful to Mr. H. J. R. Bussey, B.SC., of the research department of St. Mark's Hospital, for help in tracing patients and for drawing figs. 1–6. Some of the expenses involved in this work were met by a grant from the British Empire Cancer Campaign, and the follow-up department was assisted by a grant from the Medical Research Council. To both these we offer our thanks.

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PRINTERS' ASTHMA

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THIS paper reviews 32 cases of asthma in printers. These men developed asthma after exposure to a spray, made of gum-acacia and isopropyl alcohol, which is used in colour-printing. This spray is thrown over each sheet and forms a barrier between successive sheets on which the colour-print is still wet. Colour from one sheet is thus prevented from passing on to the back of the next sheet added to the pile. With many spray machines working, the mist can be seen spreading from one printing-machine to the next.

Gums have come into increasing use in industry, and, in the various reports on sensitivity to different gums, acacia, Karaya gum, and tragacanth have been the three most common allergens, in the order listed (Brown and Crepea 1947). Bohner et al. (1941) in America were the first to describe a group of printers with asthma due to sensitivity to gum-acacia. They reported 10 cases and reviewed the literature of isolated reports of sensitivity to inhaled acacia. In Canada Sprague (1942) reported a further case of asthma in a printer sensitive to inhaled acacia. The disease has not been described in printers in this country.

Bohner et al. (1941) showed conclusively by passive transfer tests that the printers who developed asthma were sensitive to the gum-acacia in the spray fluid.

MATERIAL

The first patient attended a general medical outpatients department complaining of asthma which he believed was due to the spray fluid to which he was exposed at work. A few weeks later 31 further printers were examined. They came in response to a letter sent to London printing chapels asking members who thought they were affected by the spray fluid to attend for examination.

TABLE I—EFFECT OF INHALED GUM-ACACIA ON 63 PRINTERS

Reaction to inhaled acacia	No. of printers complaining of symptoms	No. of printers employed by one firm and routinely examined	Total
No symptoms attributable to spray fluid	4	13	17
Early symptoms of sensitisation to gum-acacia	2	12	14
Asthma resulting from exposure to gum-acacia ..	26	6	32
Total	32	31	63

Finally another 31 printers, comprising the staff of a firm engaged largely on colour-printing, were examined. In this firm 2 men were on holiday and not seen.

The effect of inhaled acacia on these 63 printers is shown in table I.

After the clinical picture of the 32 florid cases of asthma had been established, it became clear that 14 other printers had typical early symptoms of asthma although the full clinical picture had not developed.

PAST HISTORY AND FAMILY HISTORY OF ALLERGY

In 26 of the 32 printers with asthma there was no past history or family history of allergy preceding exposure to the spray fluid.

One man gave a previous history of bronchial asthma. He had suffered from infancy with eczema and bronchial asthma. He had lost no schooling from his attacks, which were mild and ceased at the age of 14. Now aged 22, he had been a printer for five years and exposed during this period to the spray fluid. For the last two years he had had attacks of asthma an hour after exposure.

A second man had a sister with bronchial asthma, and had himself had hay-fever since childhood.

A third man had a son, aged 5 years, who had had eczema of the face at the age of 1 year, followed by flexural eczema and asthma.

Two other men had had attacks of hay-fever every spring since childhood.

The grandfather of a sixth man had asthma.

DURATION OF EXPOSURE BEFORE SENSITISATION

The average duration of exposure before asthma *developed in these 32 printers was 4·8 years.*

In 4 cases exposure to spray fluid had lasted for ten years or more before symptoms developed (see table II).

TABLE II—DURATION OF EXPOSURE BEFORE SENSITISATION IN 32 PRINTERS WITH ASTHMA

Duration of exposure	Less than 1 yr.	1–2 yr.	3–4 yr.	5–10 yr.	More than 10 yr.
No. of cases ..	2	11	8	7	4

In 2 the exposures had for long periods been slight. In the other 2 there had been heavy and prolonged exposure. The period of exposure before symptoms developed could not be related to the amount of spray to which they were exposed. The concentration of spray fluid could only be estimated roughly. Most of the men had been exposed to increasingly heavy concentrations through the last few years because additional spray machines had been added to the printing-presses.

In the 6 printers with a past or family history of allergy the average duration of exposure before symptoms developed was 2·4 years. In the remaining 26 the corresponding figure was 5·3 years.

CLINICAL PICTURE

The onset was gradual in 28 cases and abrupt in 4.

The printer first notices that the nose becomes blocked and the throat feels constricted at the end of a day when there has been a heavy concentration of spray. Sneezing and an irritating cough are common early symptoms. "Colds," which have previously lasted a few days, continue for weeks.

The earliest evidence of asthma is a wheezing in the *chest noticed by the printer, at first only when he has a* "cold." Later he may experience wheezing on first rising in the morning but is free from symptoms on Sunday and Monday. Over a few weeks or months attacks of bronchial asthma increase in severity, and the man becomes incapacitated after exposure to the spray fluid.

ILLUSTRATIVE CASES

Case 1.—A man, aged 37, had been a printer for twenty-three years and exposed to spray fluid for six years. For the first five years' exposure to spray fluid he remained well. He then noticed the gradual onset at work of symptoms referable to the upper respiratory tract. He sneezed frequently at the end of the day. His nose became blocked and his throat felt tight. An irritating cough troubled him. Over a period of six months these symptoms increased and he began to have attacks of asthma three or four hours after being exposed to spray fluid. The attacks persisted all evening, but he was free *from symptoms on waking next morning.*

There was no past history of serious illness, and before his present symptoms he had never had asthma, hay-fever, or urticaria. There was no history of allergy among his parents and eight siblings.

He looked fit and was an intelligent and reliable witness. Loud expiratory rhonchi, typical of bronchial asthma, were heard over both lung fields. The remainder of the physical examination was negative.

TABLE III—DURATION OF IMMEDIATE EXPOSURE BEFORE ASTHMA DEVELOPS

Time	Less than 1 hr.	1–3 hr.	4–7 hr.	8 hr. or more	Variable (see text)
No. of cases	3	12	9	5	3

Radiography of the chest showed clear lung fields. A skin sensitivity test with the spray fluid gave a strongly positive reaction.

The patient was forced to change his job to avoid the spray fluid, and immediately lost all his symptoms. When examined a week after exposure to spray fluid had ceased, no adventitious sounds were heard in the lungs.

Although the onset is usually gradual, in 4 cases the *onset of asthma was abrupt. The following* is an example.

Case 2.—A man was exposed to spray fluid for three years. The first year he noticed no symptoms on exposure to the spray. One Friday evening he started to cough and became breathless. Bronchitis was diagnosed, and he remained off work for three weeks. On the day he returned to work he felt *well until the afternoon,* when he suddenly developed an attack of asthma. He has since invariably had asthma five or six hours after any heavy exposure. The attacks subside two hours after leaving the spray fluid.

Asthma usually develops some hours after exposure to the spray fluid (see table III).

Three printers gave histories which suggested that the length of exposure each day before the onset of symptoms depended on the exposure during the days immediately before.

Case 3.—A man noticed symptoms at 3·30 P.M. on Monday after a weekend away from work. The attacks would develop *an hour earlier on Tuesday. By Thursday* the symptoms often started at 10 A.M. and persisted to the next day. This printer has avoided spray fluid for two years and remained free from symptoms.

Case 4.—A man developed asthma starting each week at 4.30 P.M. on Monday. *By Friday* the attacks would begin at noon. Since avoiding the spray he has remained well.

Case 5.—A man, working at night, found that with a five-night week the attacks of asthma would come on earlier and more severely as the week progressed. By working a four-night week with a break in mid-week he is little troubled by his attacks of asthma.

TABLE IV—TIME TAKEN FOR SYMPTOMS TO SUBSIDE AFTER CESSATION OF EXPOSURE

Time	Less than 1 hr.	1–2 hr.	3–5 hr.	6 hr. or more	Indefinite
Persons	6	6	4	11	5

All 32 printers thought that the severity of the asthma varied with the amount of spray fluid they inhaled.

The time taken for symptoms to subside after the men ceased to be exposed to spray fluid varied considerably (see table IV).

DISCUSSION

In the London printing industry about 500 printers are exposed to the spray fluid. The work is highly skilled, and printers are loth to change to the less remunerative black-and-white printing. For this reason it was unlikely that all printers affected by spray fluid would be willing to submit to examination.

One printer, among those routinely examined from the one firm, at first maintained that he had no symptoms attributable to the spray. He was actually distressed at the time of examination and had severe bronchospasm. He later gave a history that left no doubt that his asthma resulted from exposure to spray fluid.

It was known that many printers with asthma had not responded to the letters to their chapels asking them to attend for examination. For example, none of the 6 printers with asthma found in the one firm had come in response to the original letters sent to their chapels. Many printers with asthma knew colleagues who had left colour-printing because of symptoms similar to their own.

For these reasons the incidence of asthma in the one printing firm gives a better indication of the extent of the industrial hazard. The firm chosen for the investigation used the spray fluid extensively. The management had installed exhaust ventilation and fitted an automatic device to stop the ejectors from spraying fluid when the printing-machine stopped. This useful device had not been fitted at other colour-printing works visited.

Of 31 workers in this firm, 19% had printers' asthma. Probably the incidence would be as high in other firms doing colour-printing.

The number who had already left the firm to avoid the spray fluid was not known. One printer, who came for examination in response to a letter to his chapel, had developed asthma in this firm but had left before the investigation there was made.

An ominous indication of this hazard to printers is the high proportion of men who had early symptoms of asthma. Of the 12 men in one printing firm who had early symptoms, 8 complained of some wheezing and a feeling of tightness in the chest. Although not yet incapacitating, these early symptoms were by no means trivial.

The efficiency of the industry has not yet been affected, because many printers take a long time to become sensitised and the spray fluid has only been used in heavy concentrations since the late war. The disease, however, has already caused much suffering to individual printers.

Although it is well recognised that, once a person develops asthma, multiple sensitivity tends to develop, this has not yet happened in any of these 32 cases; they all remain well when not exposed to spray fluid.

Efficient ventilation can only mitigate the hazard. It can be eradicated by the substitution of dextrose for gum-acacia, as Bohner et al. (1941) suggested.

SUMMARY

Asthma is reported in 32 printers exposed to a spray fluid containing gum-acacia. A further 14 printers had symptoms of sensitisation to the spray fluid.

The average duration of exposure before asthma developed was 4·8 years, but the period of exposure was half as long for the 6 printers who had a past or family history of allergy.

In one firm 19% of the printers had asthma and a further 30% had early symptoms of asthma due to sensitisation to the spray.

This industrial hazard can be eradicated by the substitution of dextrose for gum-acacia in the spray fluid.

I am grateful to Dr. N. S. Plummer for the encouragement and help he has given me in preparing this paper. I am also indebted to Mr. P. Astins, C.B.E., secretary, and Mr. F. R. Norman, assistant and organising secretary, of the Printing Machine Managers' Trade Society, who gave me every facility to make this investigation on members of the society.

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EFFECT OF INTERRUPTED COURSES OF CHLORAMPHENICOL ON RELAPSE-RATE IN TYPHOID FEVER

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THE effect of chloramphenicol on the course of typhoid fever is uniformly good, but the rate of relapse is high (see table I).

In attempts to prevent relapses, administration of the drug has been prolonged for some days after fever and other symptoms have subsided. The lowest relapse-rate so obtained was 16% in the 25 cases reported by Woodward et al. (1948). Therefore a search for a more efficient method of preventing relapses was indicated; and administration of chloramphenicol in interrupted courses (Smadel 1950) seemed to us to be the one most likely to succeed.

TABLE I—RELAPSE-RATES IN TYPHOID FEVER TREATED WITH CHLORAMPHENICOL

Reference	No. of cases	No. of relapses
Smadel et al. (1948)	10	2 (*20%*)
Hill et al. (1950)	25	12 (*57%*)
Woodward et al. (1948)	25	4 (*16%*)
Chatterjee (1950)	24	4 (*17%*)
Lantin et al. (1951)	23	7 (*30%*)
Cook and Marmion (1949) ..	14	3 (*21%*)
Total	121	32 (*26%*)

We report here the response of 20 cases of typhoid fever to interrupted courses of chloramphenicol, compared with those of 17 cases to single continuous courses.

We observed that, in almost all our cases of typhoid fever treated with single continuous courses of chloramphenicol, relapses occurred, if at all, between the ninth and the twenty-second days after the patient had become apyrexial (table II). Therefore, to prevent relapses, instead of continuing the administration of chloramphenicol uninterruptedly for so many days after clinical cure, we withdrew it soon after the pyrexia had subsided, and started a second course just before the earliest time at which a relapse might be expected.

METHOD

As soon as typhoid fever was diagnosed, the patient was given chloramphenicol 0·25 g. two-hourly till his

TABLE II—CASES OF TYPHOID FEVER TREATED WITH SINGLE CONTINUOUS COURSES OF CHLORAMPHENICOL

Case no.	Sex and age (yr.)	Days' fever before treatment	Days' fever during treatment	Total dosage of chloramphenicol (g.)	Severity of fever	Toxæmia	Day of start of relapse*	Chloramphenicol used for relapse (g.)
1	M 15	12	5	18	+ + +	+ + + +	..	..
2	M 20	15	5	12	+ + +	+ +	..	..
3	M 5	7	3	24	+ + +	+ + + +	..	..
4	M 6	14	2	12	+ + +	+	..	..
5	M 31	18	3	18	+ +	+	..	..
6	M 12	10	3	9	+ + +	+ + +	..	..
7	M 16	8	4	15	+ + + +	+ + + +	..	..
8	F 23	10	5	22	+ + + +	+ + +	21	12
9	M 30	10	5	24	+ +	+ + +	..	..
10	M 13	9	2	24	+ +	+	..	..
11	M 18	9	4	20	+ + +	+ + + +	9	Nil
12	F 8	8	6	24	+ + +	+ + + +	10	12
13	M 27	9	3	18	+ +	+	21	12
14	F 9	12	4	12	+ + +	+	..	..
15	M 30	?	5	18	+ + +	+ + + +	16	9
16	M 39	8	13	27	+ + + +	+ + + +	22	12
17	M 26	12	5	14	+ + +	+ + + +	14	8

* Calculated from the day the patient became apyrexial. Relapses were confirmed by positive culture.

Case 1.—Patient developed a parotid abscess from which streptococci and staphylococci were isolated.

Case 15.—A second course was started but not completed, because no more chloramphenicol was available.

temperature touched normal. Thereafter chloramphenicol 0·25 g. was given four-hourly till the patient had been apyrexial for forty-eight hours. No chloramphenicol was given in the next five days. On the sixth day (the eighth day after pyrexia had subsided) a further course was started, consisting of chloramphenicol 0·25 g. six-hourly *for six days. All the cases treated in this way* are included in table III. We should mention, however, that, because of the high cost of the drug, it was not possible to give chloramphenicol to all patients with typhoid fever admitted during the investigation. Only two categories of patients received it: (1) all those who could afford to pay for it; and (2) those who could not afford to do so, in whom pyrexia, toxæmia, and other symptoms were severe.

Table II gives details of 17 cases of typhoid fever treated with single continuous courses of chloramphenicol. Most of them received chloramphenicol for some days after pyrexia and other symptoms had subsided. Of these 17 cases, 10 were treated before the new dosage scheme was introduced. The remaining 7 are from the early stages of the investigation when alternate cases were given continuous as opposed to interrupted courses of chloramphenicol. During the later stages of the investigation all the cases were given interrupted courses, because this method had proved superior to continuous courses in preventing relapses. Further, the administration of chloramphenicol in interrupted courses proved more economical of the drug, which was costly and scarce.

All the patients received general treatment along accepted lines—i.e., rest in bed, a restricted high-calorie low-residue diet, careful nursing, and vitamin supplements. (Vitamin supplements are very important in cases derived from a population constantly on the brink of nutritional deficiency.) These measures were all continued for twenty days after pyrexia had subsided. This was considered necessary in view of the fact that, in cases treated with chloramphenicol, complications—e.g., perforation and hæmorrhage—have developed even after pyrexia and other symptoms had subsided, thereby indicating that the pathological processes in the intestines take time to heal (as long as the usual clinical course in cases not given chloramphenicol), though clinical cure has apparently taken place.

RESULTS

Three patients with typhoid fever died during treatment with chloramphenicol. All of them had severe toxæmia, and death took place early in the course of the treatment. They are excluded from the tables.

Of 20 cases of typhoid fever treated with interrupted courses of chloramphenicol 1 relapsed, the relapse-rate thus being 5%. Of 17 cases of typhoid fever treated with single continuous courses of chloramphenicol 7 (41%) relapsed. Of these 17 cases 12 had *chloramphenicol* for six days or more after they had become apyrexial; and 4 (33%) of these relapsed. The two groups of cases in tables II and III are comparable as regards age, sex, general immunity, and nutritional status. The source of infection in all the cases in both the groups was the city of Madras, where typhoid fever is endemic. As already stated, the lowest relapse-rate hitherto published is 16%.

In the present series the average quantity of chloramphenicol given to each of the 20 patients treated with interrupted courses was about 19 g. (table III), whereas the average quantity given to each of the 17 patients treated with single continuous courses (including the quantity used for treating relapses) was about 22 g. (table II).

CONCLUSIONS

Interrupted courses of chloramphenicol seem to give better results than do continuous courses in preventing relapses in typhoid fever. The relapse-rate is highest when chloramphenicol is withdrawn soon after the pyrexia has subsided; it is lower when chloramphenicol therapy is continued for some days after clinical cure; but it is lowest when chloramphenicol is given in interrupted courses, being withdrawn soon after clinical cure and given again just before a relapse can be expected.

The average quantity of chloramphenicol used in interrupted courses is less than that used in continuous courses—an important consideration in the case of so expensive a drug.

We wish to thank Dr. K. C. Paul, on whose suggestion and under whose guidance this work was done; Dr. C.

TABLE III—CASES OF TYPHOID FEVER TREATED WITH INTERRUPTED COURSES OF CHLORAMPHENICOL

Case no.	Sex and age (yr.)	Days' fever before treatment*	Days' fever during treatment	Chloramphenicol used in 1st course (g.)	Chloramphenicol used in 2nd course (g.)	Total dosage (g.)	Severity of fever	Toxæmia and other symptoms	Day of start of relapse
1	M 24	8	7	15	6	21	+ + +	+ + + +	Nil
2	F 19	10	6	18	6	24	+ + +	+ + +	Nil
3	M 27	12	3	9	6	15	+ +	+ +	Nil
4	F 9	14	4	9	6	15	+ + + +	+ + + +	Nil
5	M 7	9	5	14	6	20	+ + + +	+ + +	Nil
6	M 17	10	9	25	6	31	+ + + +	+ + + +	Nil
7	M 25	10	4	15	6	21	+ + + +	+ + + + +	Nil
8	M 36	9	5	12	6	18	+ + +	+	Nil
9	M 17	16	6	17	7	24	+ + + +	+ + + +	Nil
10	M 25	16	5	12	6	18	+ + +	+ +	Nil
11	F 40	18	5	16	6	22	+ + +	+ +	Nil
12	M 9	10	6	9	6	15	+ + +	+ +	Nil
13	F 8	11	4	9	6	15	+ + +	+ +	Nil
14	M 12	14	4	12	6	18	+ + +	+ +	Nil
15	M 15	?	4	12	3	15	+ + +	+ + + +	Nil
16	M 29	11	4	9	6	15	+ + +	+ +	24
17	M 30	11	4	12	6	18	+ + +	+ +	Nil
18	M 10	6	4	12	6	18	+ +	+ + +	Nil
19	M 7	6	4	12	6	18	+ + + +	+ + + +	Nil
20	F 21	9	3	11	6	17	+ + +	+ + + +	Nil

* In some cases the history of duration of fever was vague, conflicting, or otherwise unreliable.

Case 11.—This case was diagnosed and partly treated before admission to hospital.

Case 13.—Developed parotitis, with pyrexia, on 8th day of normal temperature, but cultures of blood, urine, and fæces were negative.

Case 15.—Second course curtailed owing to lack of drug.

Case 16.—The period of 24 days before the start of the relapse is longer than in any case given a single course. This delay is probably due to the second course. The relapse was very mild.

Raghavachari for supplying chloramphenicol for many of the cases and for permission to publish; Dr. P. K. K. Raja for allowing us to include some of his cases; and the house-staff and nurses for their willing coöperation.

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THE TRENDELENBURG POSITION

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THE surgeon who operates in the pelvis, whether it be on the bowel or on the urinary or genital tract, needs a clear field. To obtain this he will use some degree of Trendelenburg's tilt. With a well-trained team this presents little difficulty, but there are certain problems inherent in the position which may be a source of danger to the patient and embarrassment to the surgeon:

(1) The safe suspension of the patient in the tilted position.
(2) The disposal of the arms so that, while they are available for intravenous injection and infusion and the recording of the blood-pressure, they do not hinder the surgeon.
(3) The care of the legs.
(4) Some method of providing a small instrument table so that the surgeon's tools do not slip down the patient into the wound or on to the floor.

SUSPENSION OF PATIENT

There are three methods of suspending the patient.

(1) *Support by Shoulder Rests.*—The whole weight of the patient is taken on the shoulders; and if, in addition, the arm is abducted for intravenous and other manipulations, there is a real risk of brachial palsy. Several cases have been recorded and many more have occurred which have not been recorded.

Another criticism is that the thorax is compressed by the weight of the abdominal viscera above and the shoulder supports below, leading to a decrease in the vital capacity. Any surgeon who doubts this statement should have a flight in an old-fashioned aircraft, like an open Moth or Magister, in the inverted position, after being carefully strapped in: he will then appreciate the weight of his own viscera on the diaphragm and the difficulty in respiration which the unconscious patient must suffer.

(2) *Suspension by the Legs.*—This is effected by bending the table at the knee-joints so that the knees are flexed to almost a right angle. This is efficient but open to the criticism that it injures the veins of the gastrocnemius and soleus muscles and impedes the venous return from the leg by kinking the popliteal veins. I suggest that those surgeons who use this method of suspension should try it on themselves, with the table tilted: they will then appreciate the very great weight put upon the legs. It is theoretically possible that the common incidence of phlebothrombosis after pelvic operations is partly caused by the trauma to the calf veins inherent in this method of suspension, which may also cause palsies from too tight and improperly padded strapping of the legs.

(3) *Ogier Ward's Iliac-crest Supports.*—These supports, which have now been made for me by Allen & Hanburys in two sizes—one for fat and one for thin patients—fix the patient firmly and efficiently somewhere near her centre of gravity, leave the thorax and legs unembarrassed, and have been used by me for nearly five years in four hospitals. Their proper adjustment needs special drill on the part of the operating-theatre personnel: it takes a little longer than other methods but is absolutely efficient. Since using these supports I have had no fatal cases of pulmonary embolism after abdominal operation.

A modified form of the supports was described by Mr. Stanley Hans in THE LANCET of Oct. 4, 1952, p. 664.

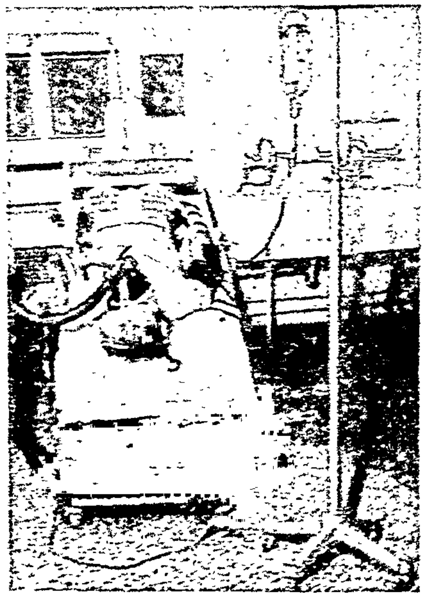

Fig. 1—Trendelenburg position, showing the two positions of the arms, leaded arm rests, pelvic-crest supports, operating-table, and extended legs.

DISPOSAL OF ARMS

The arms may be folded on the chest, and the dorsum of the hand secured with strapping to the chest wall (fig. 1); in this position intravenous injections and infusions can be given by the anæsthetist using the veins on the back of the wrist and hand. An alternative method is to place the arm alongside the patient (fig. 1) and to secure it there with lead arm-rests which can be bent to suit any size and shape of limb. It is important to pad all metallic protuberances which could injure the arm. The use of a wooden abduction splint, either on one or both sides of the patient, is dangerous because gravity and the movements of assistants during the operation tend to abduct the arm more and more, thereby causing brachial palsy—a serious and actionable disaster. Special attention should be paid, by a responsible person, to the firm fixation of the arms, because nothing is more annoying than having to stop an operation to secure an arm which has slipped out of position. Fig. 1 also shows how intravenous and blood-pressure apparatus may be applied.

CARE OF THE LEGS

The legs should be quite free and unencumbered by any retaining straps. They should also be straight, since angulation at the knee can only interfere with venous return and lead to stagnation, increasing the danger of phlebothrombosis. The calves should be well padded, because the average operating-table 'Sorbo' mattress is far too thin. Some surgeons use small sorbo rings on the balls of the heels to take some pressure off the calf muscles. The most important thing, however, is a really thick mattress.

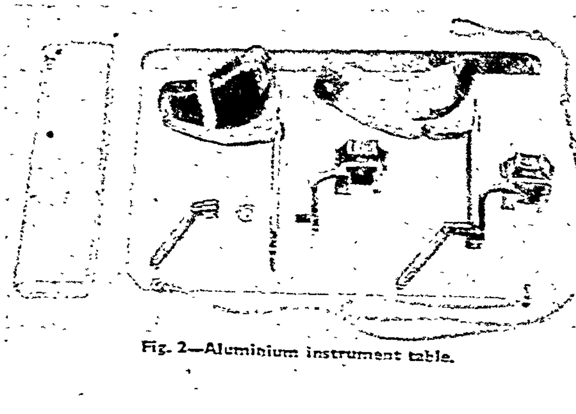

Fig. 2—Aluminium instrument table.

INSTRUMENTS

After experimenting with tables independent of and attached to the operating-table, I have come to the conclusion that the best, cheapest, and most efficient method of providing an instrument table for the surgeon is to take a piece of aluminium 18 in. wide by 12 in. long, bend up one end for $1^{1}/_{2}$ in., drill a hole $1^{1}/_{2}$ in. from the side and $^{1}/_{2}$ in. from the top at each end, and tie a piece of string through the holes. The surgeon then has an instrument stand which he can put as high or as low on the patient as he pleases and cut to a size acceptable to his own fancy (fig. 2).

SUMMARY

The Trendelenburg position, when properly employed, should be safe for the patient and comfortable for the surgeon and his assistants.

Three methods of suspending the patient are described, of which suspension by Ogier Ward's iliac-crest supports is considered the best.

The disposal of the arms and legs is described, and special emphasis is placed on the risks of brachial palsy when shoulder rests are used with the arms abducted. Suspension of the patient with the knees flexed may well favour phlebothrombosis in the veins of the calves.

A simple, cheap, and efficient instrument tray is described.

I should like to thank the photographic department at St. Bartholomew's Hospital for assistance with the illustrations.

Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

THIS association met in London on Oct. 2–4. During the course of the meeting Prof. R. J. V. PULVERTAFT delivered a presidential address, on the Individual and the Group in Modern Medicine; and Dr. S. C. DYKE gave the first Foundation lecture, on the Development of the Concept of Pernicious Anæmia.[1]

Benign Polypoid Gastric Tumours

Dr. H. G. H. RICHARDS (Winchester) classified benign tumours of the stomach as adenomas, pancreatic rests, fibromas, leiomyomas, neurogenic tumours, lipomas, angiomas, and miscellaneous rarities. At his own hospital such tumours formed about 10% of all gastric tumours (6 benign and 53 malignant). Epithelial polyps varied from what amounted to simple hypertrophy of the gastric mucosa to frankly adenomatous tumours with early malignant change. Dr. Richards described a case of polypoid gastric tumour due to a pancreatic rest, and commented on the absence of islet tissue. He also described three cases of leiomyoma, pointing out the importance to the radiologist of the central crater in these tumours.

Pathology of Gastric Arteries

Dr. G. R. OSBORN (Derby) said that although it had been taught for over a hundred years that peptic ulcer was related to arteriosclerosis the gastric arteries were practically free from the usual forms of sclerosis. In 1951 there were 327 partial gastrectomies at the Derbyshire Royal Infirmary; arteriosclerosis was not seen in any of these. The gastric vessels were examined in 32 sudden deaths from coronary thrombosis. There were 25 males aged 41–85 (average 61) and 7 females aged 55–82 (average 74). The gastric vessels were all normal with 4 minor exceptions: 3 had localised lesions of inflammatory origin; only 1 (a woman of 74) had an atheromatous plaque, and this was too small to affect lumen size. The splenic and superior mesenteric arteries did not share this immunity from sclerosis. Possibly the five series of anastomoses protected the gastric arteries from stresses which produced sclerosis elsewhere. Arterial lesions related to peptic ulcers should be termed chronic, subacute, or acute erosion. In chronic erosion mucinous infiltration of the intima greatly reduced lumen size; this was the main reason why every peptic ulcer did not cause fatal bleeding. In subacute erosion there was an organising thrombus at the distal (eroded) end; elsewhere the artery was normal. The typical lesion of fatal hæmorrhage was acute erosion; this would lead to death if gastrectomy was not performed in the pre-uræmic stage.

Difficulties with Antibiotics

Dr. J. D. A. GRAY said that antibiotics had conferred such benefits on mankind that their dangers had tended to be overlooked. The toxic effects, such as damage to the 8th nerve by streptomycin and the blood dyscrasias after chloramphenicol, were now well known and could usually be avoided. Modern penicillin was non-toxic but large doses intrathecally were dangerous. Sensitisation of patients to antibiotics had occasionally produced alarming effects. To prevent sensitisation penicillin should not be used for minor skin ailments. Sensitivity to one antibiotic might imply sensitivity to others. It was difficult to determine whether the mucous membrane lesions were due to avitaminosis or to a change in the flora. When penicillin was used as a prophylactic in surgery of the urinary tract or meninges, infections with *Pseudomonas pyocyanea* were common and might be prevented by giving a sulphonamide at the same time. After antibiotic therapy moniliasis might occur in the alimentary, respiratory, and urinary systems, and might be fatal in a lung abscess or bronchiectatic cavity. When an organism became resistant during treatment, further administration of the antibiotic might harm the patient and expose his contacts to infection with resistant organisms. The incidence of resistance was increasing. Antagonism between bactericidal and bacteriostatic antibiotics fortunately seemed to be limited to cases where the organism was sensitive to the bactericidal drug.

Origin of Visceral Melanomata

Dr. O. C. LLOYD (Bristol) described a case of primary melanoma of the adrenal gland with multiple metastases. Sixteen other instances had been described; in four of these there were no metastases, so there could be no doubt that primary melanomata did occur in the adrenal. Specific silver stains for melanin showed granules to be present in 57% of 44 human adrenals examined, irrespective of age or sex. They were found in the cytoplasm of the adrenal medullary cells (phæochromocytes). The cells affected were often scanty. Fontana's silver solution applied for eight hours or less was not quite specific for melanin, as claimed by Masson, since it also blackened the pigment of ganglion cells. Baker's[2] method was to use 5% silver nitrate at 37°C for one to two hours. Used for only one hour, it would blacken nearly all true melanin, including that found in the phæochromocytes. All adrenal pigments, including melanin, were bleached by nascent chlorine. Dr. Lloyd concluded that adrenal melanomata were derived from medullary phæochromocytes, and that the fact that they could be melanogenic was scarcely surprising in view of their common origin from the neural crest with the melanoblasts of the skin and meninges.

Lingula Biopsy in Mitral Stenosis

Dr. J. B. ENTICKNAP said that specimens had been taken from the lingula segment of the upper lobe of the left lung during operations for mitral stenosis, in the hope that examination of them would be useful in assessing prognosis. They had not been found of much value in individual cases, but some useful information has been derived from the series as a whole. While the parenchymal changes in the lingula were not typical of the entire lung, the vascular changes did appear to be so. Arteriolar sclerosis and hypertrophy were common, and both reduced the vascular lumina; as these occurred in similar morbid physiological conditions they had been assessed together by measurement of lumen/wall ratios. Considerable reduction of the lumina was seen, the mean ratio being about 4 : 1. All the patients had pulmonary hypertension and the lower ratios occurred with the higher pressures. A significant correlation was discovered which could be expressed by the formula:

$$\text{Arteriolar lumen/wall ratio} = 21{\cdot}3 - \frac{\text{mean pulmonary artery pressure}}{3{\cdot}03}.$$

Arteriolar hyalinisation was not seen in these sections; a possible explanation of this was to be found in the fact that he highest pulmonary systolic pressure in these patients 120 mm. Hg) was much less than that found in the brachial rtery in cases showing renal arteriolar hyalinisation. In two ases with necrotising arteriolitis the pressures were about 20 mm. lower than the highest in this series, and both showed ither histological or clinical signs of active rheumatism. It seemed probable therefore that arteriolar necrosis in mitral stenosis was related to circumstances other than simple excessive strain. Capillary dilation was seen in about a third of the cases; in these the pressures did not differ from those of the remainder, and they showed no arteriolar changes.

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[1] See *Lancet*, Oct. 11, 1952, p. 721.

[2] Baker, M. R. *Arch. Path.* 1938, 26, 845.

Differentiation of Primitive Leukæmic Cells

Dr. D. ROBERTSON SMITH (Cambridge) described a method of differentiating myeloblasts, lymphoblasts, and monoblasts by a simple in-vitro culture method. The bone-marrow or peripheral blood is placed in heparinised Tyrode solution, and the nucleated cells are separated by centrifugation or sedimentation. Cultures are set up in a medium consisting of equal parts of serum from the patient and Tyrode solution, the final cell concentration being about 2000 per c.mm., and 3 ml. amounts are placed in each of three McCartney bottles. A total and differential count is made, and bacteria (either staphylococcus or *Bacterium coli*) are added to one tube. The bottles are incubated at 37°C and examined after 4 hours and 24 hours. Dr. Robertson Smith said that myeloblasts showed evidence of maturation into promyelocytes and myelocytes after 24 hours, but showed no phagocytic activity. Lymphoblasts did not mature or show phagocytic activity in vitro, but degenerated rapidly into smear-cells. Monoblasts were highly phagocytic in culture and developed into more mature forms. In the Naegeli type of monocytic leukæmia some of the blast cells were phagocytic (monoblasts) and others non-phagocytic (myeloblasts), whereas in the Schilling type all were phagocytic. This simple in-vitro culture method was valuable where routine methods of distinguishing primitive leukæmic cells failed.

Antihæmophilic Potency of Plasma

Dr. W. R. PITNEY (Melbourne) and Dr. J. V. DACIE described a method of studying the generation of thrombin in recalcified citrated plasma by means of subsampling into fibrinogen solution. Normal thrombin generation curves were contrasted with the far slower evolution of thrombin in hæmophilia.

Cytochemical Methods in Hæmatology

Dr. F. G. J. HAYHOE (Cambridge) discussed cytochemical staining methods used in hæmatological research from the viewpoint of their applicability to routine diagnostic work. The *Feulgen reaction* specifically demonstrated desoxyribonucleic acid which was confined to the cell nucleus. The pattern of nuclear staining resembled that seen in a good Leishman preparation. The intensity of the reaction increased with maturity of the cell. Nucleoli were invariably negative and surrounded by a strongly positive ring of nucleolus-associated chromatin which made them readily recognisable. The reaction had practical value in routine hæmatology in assessing cell maturity, enumerating nucleoli, and defining nuclear chromatin patterns. The demonstration of glycogen by the *periodic acid-Schiff reaction* gave consistent results, and the method was satisfactory and valuable in academic studies. Glycogen was confined to the cell cytoplasm. The erythropoietic series was negative at all stages. The myeloid series showed increasing numbers of positive granules with increasing maturity; eosinophil granules were negative against a positive cytoplasmic background. Lymphocytes and monocytes contained small amounts of glycogen. No significant variations in cell-glycogen content seemed to occur in blood dyscrasias, however, and the method had no great practical application in diagnostic work. *Sudan black B* stained lipids excellently. The myeloid series showed increasing numbers of positive granules with increasing cell maturity. Eosinophil granules showed a positive periphery with unstained centre. Basophil granules were negative. Lymphocytes were negative; but monocytes contained scattered granules. Although cells from blood disorders did not greatly differ in reaction from comparable normal cells, the reaction was of diagnostic value in demonstrating positive granules in early cells of the myeloid and monocytic series. For this purpose Sudan black seemed superior to the commonly used peroxidase reaction. The *techniques of Gomori* for demonstrating acid and alkaline phosphatase were too unreliable for routine work.

Coagulation Defect in Tromexan Therapy

Dr. A. S. DOUGLAS (Oxford) described an investigation designed to elucidate the prolonged one-stage clotting-time following the administration of 'Tromexan.' Factor v was found to be normal. The addition to tromexan plasma of small proportions of normal serum, which contained no prothrombin, was found to shorten the one-stage clotting-time often to normal, while tromexan serum was deficient in this property. This action of serum was its factor VII property. Therefore the one-stage test in tromexan therapy reflected a deficiency other than that of prothrombin. From study of the plasma in a case of idiopathic prothrombin deficiency (a very rare condition) a new two-stage method for measuring prothrombin had been devised. This patient's plasma, with 10% prothrombin by this method, had a one-stage clotting-time only slightly prolonged, and his plasma corrected the defect in tromexan plasma as well as did normal plasma. By the two-stage technique the prothrombin content of tromexan plasma was only occasionally found to be lower than 40% of normal, and usually it lay between 40% and 100%. In tromexan therapy the one-stage clotting-time measured factor VII rather than prothrombin. By these methods the effect of therapy on prothrombin and factor VII was followed. The factor VII dropped at the start of therapy to a very low level, the prothrombin some days later and to a much smaller extent.

Iron in Sternal Marrow Biopsies

Dr. H. E. HUTCHISON (Glasgow) had estimated the amount of stainable iron in sternal aspirates by the prussian-blue reaction. In disorders of the blood this procedure provided a simple means for the control of iron therapy. In an anæmic subject the absence of stainable iron meant that the patient was iron-deficient, and in Dr. Hutchison's opinion this technical method gave the most decisive hæmatological indication yet devised of iron deficiency and of the necessity for iron therapy. The converse had also proved true—if stainable iron was present in the marrow the anæmia would not be improved by the administration of iron whether by mouth or intravenously. Over the past two years, used in this way for the control of iron therapy, the method had not failed, and it had proved possible to predict when an anæmia would be likely to respond to iron. The method also indicated when enough iron had been given and so could obviate the danger of overdosage when iron was being administered intravenously. The method might possibly help to distinguish the hypochromic anæmias of chronic intoxication from those due to iron deficiency.

Tubeless Test-meal

Dr. JOHN HARKNESS and Dr. J. A. DURANT (Portsmouth) reported their results with Segal's tubeless gastric analysis. This depended on the power of the hydrogen ion of free hydrochloric acid in the gastric juice at a pH below 3 to displace the quininium ion of a quininium-resin compound; the liberated quinine was absorbed from the intestine and excreted in the urine where it could be estimated readily. Segal's quininium-resin indicator was not available commercially in Britain, but an equivalent product had been made from material available here. 124 duplicate gastric analyses were made in 104 subjects by the ordinary alcohol method and the quinine-resin method. Histamine had to be given in some cases to ensure the secretion of hydrochloric acid for both methods. The patients with free hydrochloric acid excreted considerably more quinine than did the achlorhydrics—the results of the two groups did not overlap. Four patients had discrepancies; two patients with free HCl could not excrete quinine because of poor renal function, one achlorhydric patient excreted quinine because of interference by aluminium silicate therapy, and one apparent discrepancy was still being investigated to decide which method was actually yielding the correct results. The achlorhydrics with pernicious anæmia excreted less quinine than achlorhydrics following partial gastrectomy. Wider trials of the new technique were recommended.

Values for Blood Constituents

Dr. I. D. P. WOOTTON and Prof. E. J. KING said that normal values for most of the commonly determined blood constituents had now been determined. Only some of the constituents were distributed among the population as "normal curves"; almost all the remainder showed frequency distributions which were skew and fitted by lognormal curves. Tables had been calculated showing the limits within which 80% and 98% of the population of healthy people fell. To determine the possibility of using these tables in other hospitals, agreement between hospitals had been examined. One blood sample and one synthetic solution had been analysed and reported by 25 and 36 laboratories respectively. For most constituents there were very wide variations in the results, the highest figures reported being 2–5 times the lowest figures, although results for the solution were better than for the blood. This gave a very bad impression of the reliability of the work of clinical laboratories. In the case of hæmoglobin measurements an attempt had been made to improve the situation by the Medical Research Council hæmoblogin standard scheme, operated from the Postgraduate Medical School of London.

Action of Calciferol in Lupus Vulgaris

Dr. G. WETHERLEY-MEIN described the results of a study in which standard virulent tubercle bacilli (H37RV) were cultured and subcultured on a variety of media containing calciferol in concentrations of 50–100,000 units per ml. of medium. Certain strains were subcultured at intervals of about thirty days for over two years. Calciferol had no effect on the rate of growth, the colonial or bacillary morphology, or the virulence. Similar studies using lupus strains of attenuated virulence showed that these also were unaffected by culture and subculture in the presence of calciferol. The sera of various tuberculous and non-tuberculous patients receiving high doses of calciferol (150,000 units daily) had no effect on the growth or morphology of tubercle bacilli. The rate of healing and histological changes occurring in experimental wounds in guineapigs were in no way modified in animals receiving high doses of calciferol. These findings coupled with other observations[3] suggested that calciferol itself acted by enhancing the specific cellular reaction of the body to the chemical fractions of the tubercle bacillus following local accumulation of the vitamin in the skin.

Detection of Potassium Deficiency

Dr. L. NAFTALIN (Lincoln) said that in the postoperative state the amount of potassium excreted in the urine was correlated with the clinical condition. The relation was not a directly causative one in every case, but it had been found that patients with good nutritional status excreted a larger amount of potassium and had an easier clinical course than the more poorly nourished patients who were unable to excrete potassium. At present this was usually recognised only after the event; and Dr. Naftalin proposed an approach to the earlier detection of potassium deficiency based on the finding of a high serum-bicarbonate, low serum-chloride, normal or near normal serum-sodium, and reduced food intake.

Paper-strip Electrophoresis

Prof. N. H. MARTIN said that analysis of serum-proteins by paper-strip electrophoresis had become a routine technique in many laboratories. In his own laboratories, exercised by the atypical separations that he believed one was liable to get when the serum-proteins were dried on the filter-paper, he had been elaborating "wet boundary" techniques; this involved some loss of clarity of outline. A rigid comparison with the classical electrophoresis showed that differentiations achieved by the old technique were not constantly mirrored in the new. The variation in mobilities obtained with purified fractions, whether using dextran or albumin markers, indicated that these could only form the crudest means of identification. Quantitative studies showed that the binding capacities of the various proteins differed so much that correlation between the classical and the paper method by dye-elution techniques was impossible without some form of correction factor. It was impossible, with present knowledge, to forecast how far empirical correction factors for normal sera were valid for pathological sera. It was difficult to understand the good agreement obtained by some workers between the classical and the paper technique using the Folin reagent, if the known difference in tyrosine content of the purest isolated protein fraction was borne in mind. While the Kjeldahl analysis on sectioned strips would be satisfactory, the labour involved seemed to rule this out as a routine procedure. With widening experience the hope that the classical and paper-strip methods might be equated was diminishing. Clearly the technique of paper electrophoresis should, in future, stand alone.

Sensitivity and Resistance to Izoniazid

Prof. ROBERT KNOX said that strains of tubercle bacilli freshly isolated from the sputum of forty patients with pulmonary tuberculosis were found to be initially sensitive to isoniazid in a concentration of around 0·01 µg. per ml. by a tube-titration method in Dubos liquid medium. Standard conditions must be used because the end-point changed with prolonged incubation—partly because of deterioration of the drug, partly because of the development of resistance. In the course of treatment of a small series of patients with isoniazid resistant cultures developed very rapidly. The numbers of tubercle bacilli in the sputum showed a rapid decrease at first, followed by a reappearance associated with the development of resistance. The relation, however, between resistance in the test-tube and in the patient was not always clear. Compared with resistance to streptomycin, resistance to isoniazid seemed to be produced even more easily, at least in the laboratory; but it did not seem to reach the very high levels sometimes found with streptomycin-resistant organisms. Isoniazid-resistant organisms retained their sensitivity to streptomycin, and vice versa. On the other hand streptomycin appeared to delay the development of isoniazid resistance both in the laboratory and clinically.

Risk in Routine Tuberculosis Investigations

Dr. W. HOWARD HUGHES said that, in an attempt to assess the risk to the laboratory workers from the spilling of tubercle bacilli during the routine investigation of infected material, cultures were made regularly from the working site after the batch of work had been completed. The method used was to work in large enamel developing dishes lined with 'Cellophane.' and then to wash this and culture the centrifuged deposit. Results showed that the spluttering seen when wires were sterilised was of little importance, whereas pouring homogenised material from the original containers to 15 ml. centrifuge tubes was accompanied by heavy contamination. This spilling could be reduced, or eliminated entirely, by special care at this stage and by substituting 25 ml. wide-mouth bottles or 25 ml. centrifuge tubes for the smaller sizes. Change of staff or alteration of method always caused temporary increase of risk.

Renal Localisation of Ps. Pyocyanea

Dr. R. H. GORRILL had tested the pathogenicity of *Ps. pyocyanea* by injecting organisms intravenously into groups of white mice. It was found that with large numbers of organisms the mice died of septicæmia in one to two days. When the dose was lowered the mice survived the first two days and then died within the next fortnight of renal carbuncles. In all, twelve strains were tested; these were derived in equal numbers from wound and urinary tract infections, and the same results were obtained with them all. The earliest renal lesions, at twenty to twenty-six hours after injection of a suitable dose of *Ps. pyocyanea*, consisted of a focal embolic nephritis. After intravenous injection the blood became sterile in twelve to eighteen hours, and the lungs in twenty-four to forty-eight hours. The liver showed progressively fewer organisms throughout the experiment, but rarely became sterile. In the spleen the number remained about constant or fell; but the kidneys showed a progressive rise in bacterial count. It was suggested that, owing to its special anatomical and physiological properties, the kidney tended to filter out all types of particulate matter passing through it. When pathogenic bacteria like *Ps. pyocyanea* were filtered out they multiplied and rapidly attacked the kidney tissue, producing renal abscesses.

Physiological Variations in the Blood-count

Dr. JOHN MARKS (Cambridge) said that the value of a laboratory test depended on the accuracy of the method balanced against the range of physiological variation. In blood-counts venous blood gave lower results than capillary. Venous blood was used throughout. The factors mentioned were as follows:

Age.—Variations in age had no effect on the blood-count.

Sex.—The red-cell counts were well known to be lower, and the erythrocyte-sedimentation rate higher, in the female. The leucocyte-count was also significantly higher in females.

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[3] Jensen, T. *Ann. Derm. Syph.* 1948, 8, 36. Stringer, H. W. C. Ph.D. Thesis, Edinburgh University, 1948. van der Lugt Personal communication, 1952.

Time of day.—The blood-count of both red and white cells was lowest in the early morning and rose to a maximum in the afternoon.

Exercise.—Even moderate exercise produced a rise in the leucocyte-count.

Environmental temperature.—During acclimatisation to heat there was a fall in the red-cell count. Exposure to cold caused a rise.

Menstruation.—No significant differences occurred during the various stages of the menstrual cycle.

Dr. Marks suggested that serial counts should be performed under "basal" conditions—i.e., in the early morning, with activity and temperature change restricted. He gave a set of basal normals.[3] This range was smaller than the "random" range for routine diagnostic counts on capillary or venous blood with the causes of variation not controlled. The values quoted differed from the accepted range.

Detection of Rhesus Antibody

Dr. K. L. G. Goldsmith said that papain is a proteolytic enzyme extracted from a plant called *Carica papaya*, or pawpaw. Like trypsin, it may be used to render a saline suspension of rhesus-positive cells agglutinable by incomplete rhesus antibody. The method he used was modified from a technique described by Kuhns and Bailey.[4] 650 maternal sera were examined and only two false-positive results were obtained, these both being due to cold agglutinins. Twenty-one sera containing rhesus antibody were examined, and in no case was agglutination absent when papain-treated cells were used. The antibody titre was noted, using saline, albumin, antiglobulin, trypsin, and papain techniques. In all cases the titre with the papain method was as high as, if not higher than, with the others. During tests with papain-treated red cells in other blood-grouping systems enhancement of agglutination was noted with anti-A, anti-B, anti-P, anti-M, anti-N, anti-Le^a, and anti-Le^b. No agglutination occurred with anti-Fy^a. Papain was readily obtainable, and cheaper than commercial bovine albumin or crystalline trypsin. Rouleaux formation was largely obviated, and the technique seemed to be as sensitive for routine use as any other yet available.

Hæmolytic Disease of the Newborn

Dr. J. F. Horley (Brighton) analysed a series of cases of hæmolytic disease of the newborn. Cases of artificially produced prematurity were not included. 83 cases of maternal rhesus sensitisation resulted in 11 stillbirths, 11 deaths (7 from kernicterus, 1 moribund at birth, 1 from alimentary hæmorrhage, 1 from heart-failure, 1 from pneumonia), and 61 living, including 9 rhesus-negative babies. The living babies were followed up and only 1—a case of neonatal kernicterus with permanent nervous sequelæ—was abnormal. The treatment used was conservative, the babies receiving transfusions only when their anæmia demanded it. By this method the cases were divided into two syndromes: one (82% in this series) a hæmolytic anæmia proportional in severity to the maternal antibody titre, adequately and simply treated along the lines indicated; the other, kernicterus. It was suggested that it was unsound to treat by exchange transfusion a series of cases in order to avoid kernicterus, and that as an alternative the babies should be allowed to declare themselves as belonging to one of the two groups and then be treated accordingly—the hæmolytic-anæmia group by simple transfusion, and the kernicteric group by exchange transfusion in the pre-kernicteric stage. In the absence of more specific tests, jaundice out of proportion to the hæmolytic process, as shown by the rate of fall of hæmoglobin, could be used as an indication for exchange transfusion. By this means babies with an excellent prognosis would not be endangered in trying to save those with a more uncertain outlook.

Reviews of Books

Housing and Family Life

J. M. Mackintosh, M.D., F.R.C.P., professor of public health, University of London. London: Cassell. 1952. Pp. 224. 16s.

For many years Professor Mackintosh has been keenly interested in housing, and in the relation between housing and health. His *Rural Housing* was based largely on conditions in Northamptonshire, where he was medical officer of health, and since that was published in 1935 he has seen at first hand the housing problems of Scotland, surely among the worst in Britain, and particularly the housing problems of Glasgow, undoubtedly the most grievous in Scotland. He has listened to the deliberations of those concerned with planning our new homes, and he has studied housing problems overseas, especially in Sweden and in America. He believes that the house—which has so much to do with the home—largely sets the standard of family life, and in this book he discusses the makings of the slum environment and the approach to rehousing. He pleads, as before, for more research and investigation: "So far we have not done nearly enough, and the houses are being built with all their sins upon them." Among non-material considerations, he thinks the first essential is to relieve overcrowding—one family, one dwelling—and the second to make the best use of the house as a whole by distributing family life intelligently within it. The chapter dealing with rehoused families adds something to our knowledge of the effects of housing on health, which—though we all feel it to be above question—still lacks overwhelming proof. This book will be widely read, with enjoyment and with profit.

Diary of a Psychiatrist

James T. Fisher, M.D., and Lowell S. Hawley. New York & London: Medical Publications Ltd. 1952. Pp. 256. 16s.

Dr. Fisher is a psychiatrist who has had a varied and interesting life, and this book is written by his collaborator, Mr. Hawley, as a series of loosely connected chapters of autobiography mingled with thinking aloud on divers medical topics in which the doctor, so to speak, lay on the analytic couch while his lay colleague took over the rôle of recording the flow of free associations. Unfortunately, we hear all too little of the doctor's life, which was interesting, enterprising, and original, and there are far too many of his reflections and opinions, which are none of these.

Dr. Fisher, who dictated this book in his 87th year, was raised on a ranch in Illinois at the whim of his wealthy father and received no formal education until he returned to the family home in Boston at the age of 13. He gained a lot by his early experience of life among animals and simple working people, and on his return to "civilisation" went through school and college and became first a veterinary surgeon and then a doctor. He decided to specialise in psychiatry, and made the first of numerous trips to Europe to meet and study under such authorities as Freud—without, it seems, being unduly impressed by the results of his travels. He then settled in Los Angeles and has practised there, apart from travels and service in both wars, as one of the leading psychiatrists and physicians of that region, at one time being assistant dean to the University of South California Medical School. The glimpses we get of the doctor's life and personality are tantalising, suggesting what a really interesting autobiography Mr. Hawley had on his line.

Tubercle Bacillus and Laboratory Methods in Tuberculosis

M. A. Soltys, PH.D., lecturer in bacteriology, school of veterinary science, University of Liverpool; C. A. St. Hill, M.B., consultant pathologist, Royal Southern Hospital, Liverpool; I. Ansell, M.D., M.R.C.P., consultant physician, Liverpool Chest Hospital. Edinburgh: E. & S. Livingstone. 1952. Pp. 212. 20s.

Research on tuberculosis flourishes so profusely that a periodic pruning of the side-shoots is necessary if the casual observer is to inspect the main stem and its important branches. This book gives a useful account of modern work. Part I deals with the morphology and chemical and antigenic structure of *Mycobacterium tuberculosis*, as well as the cultural characters, metabolism, and virulence of the organism. The second, and much longer, part describes laboratory methods of diagnosis, together with chapters on tuberculin and chemotherapy. The unwary reader might infer that great progress had recently been made in the means of demonstrating the organism or isolating it from patients, but this is not so; and though the various methods of concentrating tubercle bacilli are described in detail, a fully satisfactory work on this subject has yet to be written. Greater prominence might have been given both to the non-pathogenic acid-fast organisms which can readily be confused with *Myco. tuberculosis*, and to pseudotuberculosis of the guineapig.

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[4] Kuhns, W. J., Bailey, A. *Amer. J. clin. Path.* 1950, 20, 1067.

Architecture of Normal and Malformed Hearts

ALEXANDER SPITZER, late professor of anatomy, University of Vienna. With a summary and analysis of the theory by MAURICE LEV, M.D., associate professor of pathology, University of Illinois College of Medicine, and ALOYSIUS VASS, M.D. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 145. *36s.*

IN 1923 Alexander Spitzer, professor of anatomy in Vienna, put forward a phylogenetic theory of the development of the heart, and on this basis endeavoured to explain most of the malformations commonly encountered. This theory has not received wide notice, nor has it been extensively accepted, but the authors have tried to clarify an extremely complicated German article and to elaborate it with criticisms and comments of their own.

The basis of Spitzer's theory is that the mammalian heart possesses certain atavistic structures which are only present as rudiments. He postulates that hydrodynamic factors, such as blood-volume and blood-pressure, play an important part in alteration of structure, and shows how in mammals the development of the pulmonary circuit leads to a change from the single circulation, as found in a fish, to a double one. A two-sided heart must evolve from a one-sided or single one; and the sides should be, to use electrical terms, in parallel though functioning in series. Division of the heart by a straight septum would produce the parallel system but not one which works in series where the blood from one side is returned to the other side. The complicated torsions of the heart-tube and developing septums are in part influenced by the pulmonary circulation. The development of this torsion and extension of rudimentary structures has been used to explain such abnormalities as transposition of the great vessels.

Though this short monograph aims at simplification it is not written in an easy style.

Guide to Filter Paper and Cellulose Powder Chromatography

J. N. BALSTON, B.A., and B. E. TALBOT. London: H. Reeve Angel. 1952. Pp. 148. *8s.*

MANY analytical operations on the micro scale can nowadays be performed by chromatographic methods, accurate and simple, which have displaced many older and much more cumbersome techniques. As our knowledge of cellulose chromatography widens every day, it is no fault of the authors that their work is not "up to the minute." Nevertheless, this is a valuable work containing over 550 references, nearly all dated between 1949 and 1951. Methods and materials are considered in one section and applications to various types of analyses in another. Workers in both routine and research laboratories will find this well-indexed book of great assistance.

Health and Agriculture in China

A Fundamental Approach to Some of the Problems of World Hunger. JAMES CAMERON SCOTT, M.A., B.SC., formerly professor of soil science, Cheeloo University, North China. London: Faber & Faber. 1952. Pp. 279. *25s.*

THE author of this work was formerly a member of a research team at Cheeloo University engaged in a study of agricultural sanitation from 1935 to 1941. Chinese farming depends on the use of human fæces as a fertiliser on a vast scale (an estimate in 1924 put the annual value of the manurial output of the Chinese people between £50 million and £80 million). How this fertiliser can be most efficiently collected, prepared, stored, and utilised, and how, at the same time, fæcal-borne diseases can be controlled, is the theme of the book. The problem is never simple, and Professor Scott makes it clear that the investigations which he describes have raised more questions than have been answered. But the questions he raises are practical and demand a scientific solution, if the people of China are ever to enjoy reasonable health. He was sent to China by the Baptist Missionary Society, and much of the expense of the investigation was borne by the Rockefeller Foundation. It is one of the tragedies of our time that humane scientific work can no longer be carried out in China by great organisations such as these.

The book is written simply for the general reader, but the expert sanitarian will find plenty to consider, and each chapter has a full list of references.

Essentials of Neurosurgery

LESLIE C. OLIVER, F.R.C.S., neurosurgeon, West End Hospital for Nervous Diseases, London. London: H. K. Lewis. 1952. Pp. 256. *25s.*

IN just under 200 pages Mr. Oliver has provided a short account of neurosurgery which should prove useful to students reading for higher degrees. The section on cerebral tumours particularly will repay study. It is disappointing, however, to find that the book is not well balanced; a disproportionate amount of space has been given to some neurosurgical topics which could have been better devoted to commoner conditions, and this will limit its appeal as a general introduction to the subject. There are 50 illustrations, but some of the radiographs are poorly defined.

British Dental Annual 1952

Editor: EVELYN SPRAWSON, M.C., D.SC., F.D.S., M.R.C.S. London: Butterworth. 1952. Pp. 262. *35s.*

THE original articles which make up two-thirds of this book are all of high quality. A useful article describes the public dental service, its history, development and present position, and discusses its future. But more space might well have been given to advances with which the dentist must keep abreast to maintain his professional efficiency, and illustrations of operative techniques would be a welcome addition to the next issue.

Current Therapy (Philadelphia and London: W. B. Saunders. 1952. Pp. 849. *55s.*).—The editor-in-chief, Dr. Howard F. Conn, has again cast his net widely; there are over 350 contributors to this massive American annual, of whom 189 are making their debut in this year's edition. Moreover, the book goes far beyond the purely medical conditions, and tackles, for instance, acute appendicitis and ectopic pregnancy. Spectacularly complete and helpfully concise, it maintains its place as a reference work of the first class.

Tuberculosis of Bone and Joint (2nd ed. London: Oxford University Press. 1952. Pp. 314. *45s.*).—In the first edition of this book the late Prof. G. R. Girdlestone did not set out to write a compendium of treatments of tuberculous disease of bones and joints as practised in the British Isles, but rather to describe well-tried methods based on the teachings of Robert Jones with the addition of his own long personal experience and the methods developed at the Wingfield-Morris Orthopædic Hospital. In addition to treatment, there were chapters on general diagnosis of bone and joint tuberculosis, and in regional chapters differential diagnosis was discussed. In this second edition, in which he had the assistance of Mr. E. W. Somerville, F.R.C.S.E., the general scheme has remained unchanged but there have been additions and minor alterations. These include an outline of chemotherapy in tuberculous disease, and references to compression arthrodesis of the knee and to anterolateral and lateral spinal decompression in Pott's paraplegia. There is now a very useful appendix on splints and appliances commonly used in the treatment of this disease. Throughout the book stress on the importance of general treatment and the established methods of local treatment balances the emphasis nowadays laid on chemotherapy. More space and detail might have been given to some of the advances which have proved valuable since the publication of the first edition. Nevertheless this remains a good straightforward textbook on the diagnosis and treatment of bone and joint tuberculosis as practised in the British Isles.

THE LANCET

LONDON: SATURDAY, OCT. 18, 1952

Frozen Storage for Red Cells

Freezing in glycerol has been used for many years as a method of preserving viruses; and three years ago Polge et al.[1] found that spermatozoa could be similarly preserved and retain functional activity. Red blood-cells stored by the usual methods at about 4°C can be kept for only four weeks at the most; and for this reason a team of workers at the National Institute for Medical Research have been examining the possibilities of preserving red cells by freezing techniques.

In 1950 Dr. Audrey Smith[2] showed that red blood-cells could be preserved in the frozen state if suspended in a mixture containing 10–15% glycerol. She carried out experiments with heparinised rabbit blood diluted with an equal part of a glycerol-Ringer solution. In low concentrations glycerol is hæmolytic, but at higher concentrations there was no trouble from this effect. The blood-glycerol mixture was quickly frozen to −79°C (the temperature of a solid carbon dioxide and alcohol mixture) and stored at this temperature. On subsequent thawing at 40°C most of the red cells were found to have survived and to be of normal shape after various periods of storage up to three months. Similar treatment given to red cells diluted only with Ringer solution without glycerol resulted in almost complete hæmolysis. Sloviter,[3] continuing this work with human red cells, found that these could also be recovered after freezing and storage in a 15% glycerol-saline mixture; but when the cells were resuspended in plasma, hæmolysis occurred rapidly because the glycerol in the cells attracted water into the cells so that they quickly swelled until they burst. To get over this difficulty the thawed mixture was dialysed in a sausage-skin tube against saline containing diminishing proportions of glycerol, and finally against isotonic saline alone. Even this did not give really good survival, and it proved necessary to begin the procedure by allowing the mixture of blood and glycerol-saline to stand at 5°C for one to two hours before freezing. With these methods Sloviter recovered 79–94% of the red cells, and these recovered cells were shown to have a normal resistance to hypotonic saline. The next step[4] was to take rabbit red cells that had been kept at −79°C for up to forty-two days and then, after thawing and recovery, to mark them with radioactive phosphorus (P^{32}). These marked cells were transfused into rabbits, and it was shown that frozen and thawed cells were as viable as marked red cells that had not been so treated. These experiments only covered a few days, because of the short half-life of P^{32}.

Mollison and Sloviter[5] carried out the same sort of experiment with human red blood-cells. They devised a suitable technique for freezing to −79°C a volume of 500 ml. of red cells mixed with 15% glycerol-saline and for recovering the red cells freed from glycerol after thawing. Their method gave on the average about 70% recovery of red cells. As sterility had to be maintained throughout, the technique was somewhat elaborate. The red cells were kept frozen for only two to three hours before thawing; but before the recovered cells were transfused sterility had to be ensured by cultures, and this involved a delay of seven days during which the blood was kept at the usual 4°C. Blood of group A N Rh-positive was used for freezing, and blood of group O M Rh-positive drawn at the same time and stored throughout at 4°C was used for control. These bloods were transfused into group A M Rh-positive recipients, and the survival of the transfused red cells was followed by the Ashby technique of differential agglutination. The results of two such survival experiments suggested that there was little difference in viability between the frozen and thawed cells and the cells that had been kept at 4°C. For instance, in one experiment after twenty-four hours 86% of the control red cells were present and 76% of the frozen cells; sixty-seven days after the transfusion 37% of the control cells and 33% of the previously frozen cells were still there. A few months ago Sloviter[6] reported that human red cells had been frozen, stored at −79°C for up to nine months, and then satisfactorily recovered after thawing. The percentage of recoverable cells dropped during storage. For example, after one day of storage 90% of the cells were recovered, after one month 80%, and after six months 70%; but at nine months the recovery-rate was still about 70%. Last month Mollison et al.[7] described results obtained when red cells that had been kept in the frozen state for nine months were thawed, freed from glycerol, and transfused into suitable recipients. The same technique was used as that for cells frozen for a few hours. The survival of the long-frozen red cells was compared with the survival of red cells stored at 4°C for eleven days, because the preliminary stages before freezing, and delays while sterility was confirmed after thawing, meant that the red cells were kept at 4°C for about eleven days. Results with five transfusions showed that the cells stored for nine months in the frozen state had the same order of viability as the cells that had not been frozen at all. They also showed that storage at only −15°C also preserves red cells in a viable state, but a large proportion of cells stored at this relatively high temperature are lost by hæmolysis during the recovery process; consequently −79°C remains at present the recommended temperature for storage.

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1. Polge, C., Smith, A. U., Parkes, A. S. *Nature, Lond.* 1949, 164, 666.
2. Smith, A. U. *Lancet*, 1950, ii, 910.
3. Sloviter, H. A. *Ibid*, 1951, i, 823.
4. Sloviter, H. A. *Ibid*, p. 1350.
5. Mollison, P. L., Sloviter, H. A. *Ibid*, 1951, ii, 862.
6. Sloviter, H. A. *Nature, Lond.* 1952, 169, 1013.
7. Mollison, P. L., Sloviter, H. A., Clapham, H. *Lancet*, Sept. 13, 1952, p. 501.

It has thus been established that human red cells can be suspended in a 15% glycerol-saline solution, frozen to −79°C, recovered after up to nine months, and still be suitable for transfusion purposes. There are, however, still two practical difficulties about applying this knowledge on a large scale: it takes quite a lot of effort to deal with 500 ml. of mixture (equivalent to only 250 ml. of red cells); and the technique of freeing the thawed mixture from glycerol by dialysis in a sausage-skin, maintaining sterility at all times, is particularly limiting. Lovelock[8] has described an alternative technique that may help because it does not use dialysis. He adds to the newly thawed mixture of red cells, glycerol, and saline a substance that will raise the osmotic pressure of the suspending medium, but to which red cells are relatively impermeable; sodium citrate in a concentration of 0·33 *M* or glucose 1·0 *M* are suitable. After the addition of citrate or glucose the temperature of the mixture is raised to 20°C and the glycerol escapes from the red cells in about five minutes. The cells can then be separated by centrifuging and resuspended directly in isotonic saline or plasma. The other practical difficulty is that the recovery-rate of red cells after being frozen and kept for nine months is on the average only 70% and may, in individual samples, be as low as 50%. This is too large a loss for the method to be of practical use. Further research is going on and this obstacle is likely to be overcome.

If the technical difficulties, particularly those of reconstitution, can be solved, it will be very useful to be able to store red cells more or less indefinitely, and much waste could thus be avoided. If the antigenic properties of red cells also survive this treatment, red cells of rare groups could be stored for reference. Another practical problem that has to be faced is whether red cells suspended in saline are an adequate substitute for the concentrated red cells so much used nowadays in the treatment of anæmia. For the treatment of shock whole blood is important, and preserved red cells would have to be suspended in plasma or possibly in a transfusion substitute like dextran. These points are all likely to have the attention of the Medical Research Council team.

Polypoid Growths of the Intestine

Polypoid growths of the intestine are not very common, yet they have great interest and importance in surgical practice. Whenever such a growth is found the possibility of multiple growths and of malignancy has to be considered. The problem may present itself in several ways. Almost one might say that polyp formation in the intestine causes three types of disease. In one the surgeon removes a single rectal polyp, and he has to decide, with the guidance of the pathologist, whether this is benign or shows a low or high degree of malignancy, and thus whether he has probably cured his patient by a limited operation. In quite a different category is the patient whose repeated attacks of intestinal colic draw attention to multiple polypi of the small and large intestine which are causing recurrent intussusceptions. This is the familial disease associated with facial pigmentation described recently in our columns by Dr. Wolff[1] and Professor Basu.[2] Finally, there is the rare familial intestinal polyposis in which cancer of the rectum arises with great frequency and at an exceptionally early age. The hereditary factor in this disease has been very convincingly demonstrated by Cuthbert Dukes,[3] who has shown that polyposis is inherited as if it were a mendelian dominant.

On another page of this issue, Mr. Lockhart-Mummery and Dr. Dukes discuss the surgical treatment of the single malignant rectal polyp. Such polyps are often removed locally without a preoperative diagnosis of malignancy. A report from the pathologist of malignant change limited to the mucosa means that the grade of malignancy is unlikely to be high; anaplastic carcinoma of the rectum tends to grow rapidly, soon invading the deeper tissues. Patients with such limited growths have done well with local excision, and Lockhart-Mummery and Dukes conclude that this suffices. The after-history of patients who had local excision of polyps in which carcinoma cells had already invaded the stroma or submucosa varied with two factors: (1) the grade of malignancy, as determined histologically; and (2) the extent, if any, of the free margin of tissue removed beyond the growth. Cases of "invasive" carcinoma in which the grade of malignancy was low also did well with complete local excision. Lockhart-Mummery and Dukes say that lymphatic spread in these cases is improbable, and a local recurrence is within easy reach of further operation. With high malignancy or removal of insufficient margin, the growth tends to recur; and a histological report suggesting either of these states should be followed by radical surgery. With these views American workers are in substantial agreement. Sandusky and Parsons[4] voice the general perplexity about the correct treatment of the rectal polyp first excised and then found to be malignant. Dr. Frank Lahey, in discussing their paper, mentioned another very pertinent point when he described the dilemma of the surgeon who at laparotomy fails to find a polyp he knows to be present in the colon. American surgeons seem to agree that where the diagnosis of cancer rests solely on microscopic evidence, there is no invasion of the deep tissues, and the whole polyp has been removed, one may safely forgo radical surgery.[5][6] American surgeons, while acknowledging the importance of close coöperation between the surgeon and the pathologist in decisions on treatment, do not seem to pay much attention to the grading of tumours. Here we feel that Dukes's experience that grading provides a valuable guide deserves careful consideration.

Familial polyposis of the large gut presents a much more complicated problem. The patient most often comes with a history of diarrhœa and bleeding—possibly with a provisional diagnosis of "colitis." Sigmoidoscopy reveals the extensive disease of the rectum and colon. The family history may include accounts of other patients with a similar history.

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8. Lovelock, J. E. *Ibid*, 1952, i, 1238.

1. Wolff, H. H. *Lancet*, 1952, i, 446.
2. Basu, A. K. *Ibid*, Sept. 20, 1952, p. 586.
3. Dukes, C. E. *Ann. Eugen.* 1952, 17, 1.
4. Sandusky, W. R., Parsons, J. R. jun. *Ann. Surg.* 1952, 135, 818.
5. Fisher, E. R., Turnbull, R. B., jun. *Surg. Gynec. Obstet.* 1952, 94, 619.
6. Binkley, G. E., Sunderland, D. A., Miller, C. J., Stearns, M., Deddish, M. R. *J. Amer. med. Ass.* 1952, 148, 1465.

Since J. P. LOCKHART-MUMMERY,[7] then senior surgeon to St. Mark's Hospital described in these columns in 1925 the history of three polyposis families, the hospital has made a special study of the hereditary aspect of intestinal polyposis and now has records of 22 families with more than one member affected. In these 22 families, there are 407 members the state of whose health is known. 133 are known to have developed polyposis, and in 99 of these polyposis has eventually been followed by cancer of the rectum or colon. This gives an incidence of 32·6% for polyposis, and of 24·3% for cancer. The incidence is really higher, for the onset of polyposis is unusual before the age of 10 years, and the average age at onset is 20 years; carcinoma develops about 15 years after the start of polyposis. Some members of the families under observation are too young to have developed the disease. DUKES[8] concludes that in most polyposis families half the children are likely to inherit the abnormality. As a rule, only those who inherit the disease transmit it to the next generation; but it can be transmitted by either males or females, and either sex can be affected.

Polyposis is not a disease in which several isolated tumours appear in otherwise healthy mucosa. The mucosa is almost carpeted with tiny adenomata formed by excessive proliferation of the glandular epithelium of the rectum and colon; in places these adenomata are large enough to be described as tumours. As months or years go by, one or more of the tumours becomes malignant. Symptoms vary in severity, and may remain insignificant for many years after the known onset of polyposis. Treatment is a matter of grave concern and of great difficulty. The polyposis patient is safe only without his colon. In the presence of carcinoma the operation should be very radical—even to the extent of complete colectomy, leaving the patient with an ileostomy. Non-malignant cases may be treated by a combination of endoscopic diathermy and subtotal colectomy, with anastomosis of the ileum to the rectum. Local recurrence of polyposis in the rectal mucosa can be treated by repetition of diathermy. DUKES[8] considers that milder cases can be kept under control by periodic endoscopic diathermy without radical treatment.

Two cases of the rare familial disease in which multiple polypi of the small, and possibly of the large, intestine are associated with congenital pigmentation of the skin and mucous membrane of the face, have been reported in our columns. WOLFF,[1] who recorded one of these cases, referred to 26 previous records. Attention is drawn to the syndrome by repeated attacks of small-intestine obstruction, caused either by a large polyp or by intussusception. The incidence of carcinoma is very low. In affected families pigmentation may occur in some members without abdominal symptoms. At operation, which may be an emergency procedure, the surgeon has to decide which polyps to remove and which to leave. Recurrence of symptoms is all too likely. This is a rare disease, but attacks of abdominal pain in a patient with dark pigmentation of the lips and mouth who does not have Addison's disease should, in WOLFF's opinion, arouse strong suspicion of polyposis of the small intestine.

Age and Earning

LIKE guests afraid of outstaying their welcome, those over and approaching 65 are developing an alert look. What is the proper move, how shall they avoid a gaffe? Only a few years ago it would have been right to retire, to make way for the young ones, to relieve unemployment by accepting their old-age pensions, and to die early, if need be, of boredom. Now, it seems, it is their duty to keep going, to stave off senescence with work, and to postpone drawing their pensions as long as possible; but to make way for the young ones, all the same, by stepping down from the top jobs. At any moment, they feel their hosts, in the productive years, may say brightly: "It's *lovely* to have you with us, of course, but there *are* rather a lot of you, aren't there, ha ha ha? And not too many of us to hand round the cake." There is even some danger, as three Conservative Members of Parliament hint in a recent pamphlet,[1] of a political conflict between the young and the old. Indeed, they seem to be doing a little towards promoting the conflict themselves, by presenting one aspect of the case incompletely. "Today," they say on their first page, "there are more than $5^{1}/_{4}$ million old people in the country, representing 11% of the population: for every old person there are now only six of working age. In twenty-five years' time the number will have soared to $8^{1}/_{4}$ million men and women over the age of 65—no less than 16% of the population. For every old person there will be only four people of working age." The fact is, of course, that those in the productive years have to maintain *all* the non-producers—the young as well as the old; and while the old have been increasing, the ranks of those under 15 have thinned. In 1901 37% of the population were in the non-productive age-groups, so there were less than two producers to work for each of them. By 1944 the non-producers (despite the increase of old people) had fallen to 30%. Careful forecasts suggest that even in fifty years' time the aged will not have increased beyond 18% of the population, while the young will account for only about 16%—a total of 34% in the non-productive age-groups. The producers will still be less burdened than their forerunners of 1901, and indeed will not be much worse off than their counterparts of today. Since the numbers of the old cannot exceed a fixed upper limit, the only thing which could change the picture for the worse (as far as producers are concerned) would be a phenomenal rise in the birth-rate.

But of course the whole theory of "non-productive age-groups" is a convenient fiction. In COBBETT's time, as we all know, children over the age of four could usually be classed as producers. In our own day the 15-year-olds have recently joined the non-producers, and another large group will be added when the school-leaving age goes up to 16. There is not the least reason for assuming that every man over 65 and every woman over 60 would be the better for not working any more. In the case of women the assumption is particularly odd, since more of them live longer, and most of them are more active and enterprising in old age, than men. But, as the writers of the pamphlet point out, the idea of retirement at 65 or 60 is now ingrained in the nation, among both employers and employees. Some employers impose early retirement in their superannuation schemes, and are reluctant to engage anyone in the middle or later years. Of the present unemployed most are over 40, and unemployment is twice as common among those over 50 as among the population as a a whole. Certainly people in every walk of life are well aware of a prejudice against the employment of older men and women. The reasons most employers give for this reluctance, the pamphlet says, are a wish to promote younger people, unwillingness to adapt employment policies to an era of full employment, unwillingness to find suitable tasks for the old, and difficulties with superannuation schemes. Moreover, many employees regard retirement at a given age as a right. All the same, 46% of men aged 65–70, and 10% of women aged 60–65 stay on at work, and more might do so with encouragement.

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[7] Lockhart-Mummery, P. *Lancet*, 1925, i, 427.

[8] Dukes, C. E. *Ann. R. Coll. Surg. Engl.* 1952, 10, 293.

[1] The Care of Old People. By KENNETH THOMPSON, JOHN VAUGHAN-MORGAN, and ANGUS MAUDE. Conservative Political Centre Discussion Series. Pp. 30. 6*d*.

At present the "earnings rule," which limits the pensioner's additional earnings to £2 a week, is a serious deterrent. The scale of increments to pensions, for remaining at work longer, is perhaps not sufficiently attractive; and there are some who wish to go on working but cannot find the work. Again, some could go on with their jobs after retiring age if they worked fewer hours; but they cannot live on the reduced pay they would then earn. Some, having tried retirement, do not like it, and might come back to work if the new spell of employment increased the final pension. The writers of the pamphlet believe we might attract a great many seasonal workers if every 25 stamps, however long it took to collect them, counted towards an increment. Again, a large source of labour might be tapped by making a sliding-scale reduction in pensions for those undertaking half-time or part-time work. Employers, too, might well spend more thought on providing appropriate jobs and sheltered workshops for those who need a gentler pace. The skills of the aged are by no means negligible. Apart from the elderly of the professional, technical, and administrative classes, who can put a great fund of knowledge and experience at the disposal of the nation, there are all the skilled craftsmen, many of whom are already kept on by their employers. But even the rank and file of the elderly, it seems, have an accuracy and reliability not so common in the young; and they are often capable of being trained in new work, especially if it uses old skills.[2]

These writers recognise that the proper care of the elderly includes more than the adequate treatment of their disorders when these arise: the resources of social medicine can do much to preserve their health, improve their nutrition, and enable them to keep their independence. Nowadays, as Mr. JOHN A. OLIVER, PH.D., has recently pointed out,[3] it is generally agreed that the proper place for old people is in their own homes, and this pamphlet, too, advocates the humane and economic policy of helping them to stay there. Many local authorities now build special cottages for old people on their housing estates, but few build enough of them. The writers quote the experience of Hornsey Borough Council, who built 34 cottages for old people, and found when the tenants moved in that they had released 6 houses with six rooms, 22 houses with four or five rooms, and 4 houses with three rooms—277 rooms in all. Even some old people living with married children would be glad of a small home of their own. The burden of the old on the young has often been aired: this pamphlet refreshingly mentions the burden of the young on the old. The patter of little and not-so-little feet is not everybody's idea of a delightful accompaniment to a swan song.

On the question of medical care for the old the writers are cautious—as they may well be in dealing with so confused a topic. They note the lack of beds for the elderly, but recognise that the demand for beds could be much reduced by more preventive care for the old, more residential homes, and more "half-way" convalescent homes. It is difficult, they say, to develop this last type of institution while the responsibility for maintenance cannot be exactly fixed between the local authorities, the National Health Service, and the National Assistance Board. All the same, one institution of the kind has been started—Springbok House at Stanmore, set up by the National Corporation for the Care of Old People. The experience gained there is bound to be valuable. The prognosis of the pamphleteers, that perhaps "such problems cannot be finally settled while local government areas and hospital areas differ," seems hardly justified; though things would certainly be simpler if these territories were conterminous.

Annotations

PULMONARY COMPLICATIONS OF INFLUENZA

BY all the rules, there should be no large epidemic of influenza A in the coming winter; but the rules are often broken, as the sharp Liverpool outbreak in 1951 showed. The general practitioners, who have to deal with both the sheer mass of sickness and the pulmonary complications that call for special treatment, face the hard task of distinguishing those patients who are likely to need admission to hospital and urgent chemotherapy from the many who can be safely left in their homes. This task involves the recognition of severe influenzal pneumonia at an early stage, before the onset of the rapid deterioration that sometimes occurs. Unfortunately, the clinical picture of influenzal pneumonia is not as clear-cut as some descriptions suggest, and the doctor is in fact confronted by a whole range of patients with various forms of chest complication, many of which will respond well to the up-to-date treatment for bronchopneumonia or lobar pneumonia. Indeed, some people doubt whether influenzal pneumonia is a distinct entity, differing clinically from other forms of pneumonia, though Scadding[1] thought that it was.

Tyrrell[2] has now reopened the question by making a detailed analysis of the chest complications of influenza. His results justify the continued use of the name "influenzal pneumonia," but they underline the difficulty of recognising such cases clinically. Before the epidemic of influenza A in Sheffield in March, 1949,[3] Tyrrell examined a number of patients with bronchitis, and others with bronchopneumonia or lobar pneumonia, who were admitted to hospital for treatment and were found to show no serological evidence of infection with influenza virus. His work began at the time described by Bradley[4] as the influenzal nadir of 1948, and in many cases the illness had a sudden onset, with definite signs of lobar pneumonia. Some patients had had chronic chest disease in the past, but the response to chemotherapy was good, and only 2 patients died.

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[2] *Lancet*, 1949, ii, 469, 753.

[3] *Ibid*, Oct. 4, 1952, p. 669.

[1] Scadding, J. G. *Quart. J. Med.* 1937, 6, 425.

[2] Tyrrell, D. A. J. *Ibid*, 1952, 21, 291.

[3] Stuart-Harris, C. H., Laird, J., Tyrrell, D. A., Kelsall, M. H. Franks, Z. C. *J. Hyg., Camb.* 1949, 47, 434.

His second group included patients who were admitted during or after the epidemic of influenza A and who were found to have infections of the lower respiratory tract, including bronchitis or pneumonia. Some were proved to have influenza-virus infections, either by serological tests or by isolation of the virus, and others gave serological evidence of influenzal infection before the onset of the pneumonia. Tyrrell noted two groups of influenzal cases that could be recognised clinically—those with severe tracheobronchitis, and those with fulminating staphylococcal pneumonia. The other forms of pneumonia seemed more severe than those seen before the epidemic, and more patients died. Moreover, in the pneumonias associated with influenza-virus infection, mental changes, cyanosis, and widespread râles and rhonchi outside the area of consolidation were commoner than in the non-influenzal cases. Chemotherapy was less effective in the influenzal cases, as judged both by mortality and by the time taken for the fever to subside.

This work emphasises how necessary it is to give particular care, during an influenza epidemic, to patients with chronic bronchitis or pre-existing heart-failure, and also to old people. The rapid deterioration, intense dyspnœa and cyanosis, and bloody sputum of staphylococcal pneumonia distinguish this most dangerous form of chest complication, which must be continually borne in mind if it is to be recognised quickly.

The way in which the influenza virus alters the clinical picture of bacterial infection of the lungs was not dealt with in this investigation. Harford and Hara[5] found evidence in mice to suggest that the œdema caused by the influenza virus facilitates invasion of the lung by pneumococci. Moreover, the tracheobronchitis of virus infection can cause mucus plugs to form in the bronchi and areas of collapse to develop in the lungs. Yet, as others have shown,[6] many less extensive lung changes may take place in influenza, some resembling atypical pneumonia; but these are fortunately benign and hardly enter into the clinical diagnosis. Now that more outbreaks of influenza are being investigated by clinical and laboratory methods, two facts are beginning to stand out: the staphylococcus is the bacterium to fear in the sputum; and the virus itself is certainly closely concerned with the increased severity and mortality of pneumonia during an epidemic.

MORE HERESY

Dr. Adrianus Pijper of Pretoria is a heretic, and it is fortunate for him that he studies microbiology in the 20th century and not theology in the 4th. We have on several occasions mentioned his view that the bacterial flagellum is the consequence, and not the organ, of progression; and if this unorthodoxy has had no other merit it has been the stimulus to many elegant and interesting experiments designed for its refutation. His latest communication[7] concerns a less outrageous denial of established belief but will, we hope, have the same result.

Many of us have seen the iridescent sheen on a confluent culture of bacteria held obliquely to the light, and most have accepted it without much thought of its cause. Many years ago Pijper[8] guessed that such a thin film of bacteria might act as a diffraction grating, so that the diameter of the spectral halo thrown on a screen by a beam of light passing through the bacterial film would bear an inverse ratio to the size of the bacteria making up the film. The principle is not new; it was first devised by Thomas Young, physician to St. George's Hospital (in the intervals of describing his modulus and deciphering the Rosetta stone) as an aid to classifying wool fibres. Pijper's attention was diverted to the use of this device, the "halometer," for measuring the diameter of red blood-cells; and older hæmatologists will bear witness to its value before the more informative hæmatocrit came into use. That happened thirty years ago, and now he has given some further observations on this method. It measures the diameter of cocci and the breadth of bacilli, and such measurements are better expressed in relative than absolute values. If the breadth of *Salmonella typhi* be given a value 1·0, *S. paratyphi B* is found to give a figure of 0·94 and members of the coli-aerogenes group figures ranging from 1·08 to 1·38. These are constant for each species, provided it is measured at the same stage in the growth cycle.

Since species differ in their least dimension, might they not be separated by differential filtration? If a barrier of sterile sand be placed in the loop of a U-tube filled with nutrient broth and if a mixture of organisms including *S. typhi* be added to one limb, this species is usually the first that can be recovered from the other side of the sand. But sand is awkward stuff to handle, and a "fairly tight" plug of cotton-wool in a Craigie tube gave more consistent results. All organisms will of course find their way through the obstruction in time, and the medium on the "arrival side" must be subcultured at short intervals if *S. typhi* is to be found in pure culture. Anomalous results revealed some interesting antagonisms between species. *Brucella abortus* penetrated the barrier quicker than staphylococci, but when cultures of the two were mixed the brucella never came through the barrier at all. Suspended in saline, however, it won every time. Similarly *S. typhi* died in the presence of *Bact. cloacæ*; but when the experiment was performed in Wilson and Blair's liquid medium it was possible to plant these species in a ratio of 1 : 100,000, and yet *S. typhi* came through the barrier first. Thin bacteria not only get through the fence quicker than the fat, but they ascend higher on a strip of filter-paper dipped in a bacterial mixture. *S. typhi* reached an altitude of 4.1 cm., while *Bacillus anthracis* could get no higher than 1·1 cm. and the obese sarcina stopped even lower. Others have noticed this phenomenon and have given diverse explanations. Motility, electrical charges, and "wettability" have all been suggested; but Pijper contents himself with the idea that to climb through the hairy pores of filter-paper may entail the same troubles as pushing through a barrier of cotton-wool.

Some of these observations are not entirely novel. Attempts to put them to a useful purpose have been made in the past; and as a result of this paper they will no doubt be made again. But we are better pleased to see how far uninhibited curiosity has led an inquiring mind in thirty years. Once again Pijper will set many of his colleagues observing and experimenting—and probably contradicting—and for this alone he will deserve well of them. We hope he will be careful. He may read of the penalties of heresy in Gibbon; and we have heard rumours that there are places even today where scientific unorthodoxy is curbed with almost byzantine ferocity.

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[4] Bradley, W. H. *Proc. R. Soc. Med.* 1951, 44, 789.

[5] Harford, C. G., Hara, M. *J. exp. Med.* 1950, 91, 245.

[6] Scher, J. M., Jaruszewski, E. *Arch. intern. Med.* 1952, 90, 201.

[7] *J. Path. Bact.* 1952, 64, 529.

[8] *Med. J. S. Afr.* 1918, 14, 211.

THE INEXPANSIBLE LUNG

THE recent decline in the death-rate from tuberculosis has not been matched by a corresponding decline in its morbidity. As Daniels[1] points out, the advent of streptomycin and the advances of chest surgery have prolonged the lives of many patients who would otherwise have died in a year or two. The increasing number of these long-standing cases throws into relief the problems of the late results of treatment in pulmonary tuberculosis. One of these difficulties is the inexpansible lung, to which attention has lately been directed by Jackson.[2] Ten years ago Farber[3] estimated that in 5% of patients who have had an artificial pneumothorax there is a persistent pleural dead space. Jackson noted that in two wards at Clare Hall Hospital there were 11 out of 70 patients in whom the inexpansible lung had become an important factor in determining the course of the disease and its treatment.

It is difficult to define the term inexpansible lung. Jackson uses it to include any condition in which a pleural dead space persists, whether the space is filled by air, fluid, fibrin, pus, blood-clot, or a combination of these. Nature tends eventually to obliterate this space by mediastinal shift, falling in of the chest wall, elevation of the diaphragm, and compensatory emphysema with occasional herniation of the contralateral lung. The sum of these compensatory mechanisms he calls "false expansion."

The functional results of a persistent pleural dead space and of false expansion are the same, and in such cases Pinner et al.[4] found that the patient is lucky if he keeps 50% of normal function in the affected lung. Very often the functional capacity of the inexpansible lung is negligible. If the process is bilateral it is easy for the patient to become a respiratory cripple, and he may die from pulmonary heart-failure rather than tuberculosis. Dragging chest pain, dyspnœa, and palpitations are common symptoms in the milder cases. In addition, where fluid persists there is the constant danger of empyema. The encasing of the lung in a rigid thick fibrotic pleura may, paradoxically, prevent selective collapse, and, particularly if there is much associated bronchial tuberculosis, it may do nothing to prevent the continued activity of the disease.

An inexpansible lung is almost always the aftermath of an effusion, which may be quite small at first. Collapse or bronchopleural fistula often determines the onset of the effusion. Once established the condition is difficult to treat. When a pneumothorax has been induced, attempts to refill it may be continued indefinitely, but this is seldom profitable. False re-expansion may be allowed to occur at the risk of producing a respiratory cripple, or of lighting up quiescent disease in the over-distended contralateral lung. Oleothorax was invented to deal with this problem, but its use has been generally abandoned. Phrenic crush provides another method of obliterating the dead space, but it is apt to prove a two-edged weapon. Thoracoplasty, if undertaken for these cases, must be very extensive, and pockets of fluid are liable to give trouble. Pneumonectomy is needed when infection smoulders in a shrunken fibrotic lung, and especially when there is associated endobronchial disease. Decortication has its advocates, but it can only restore function if performed before pleural thickening has become too extensive. Plombage, in which the dead space is filled by packing some neutral substance outside the pleura, is another alternative. But the best treatment is prophylactic. Stricter selection of cases for artificial pneumothorax is desirable, and chest physicians are becoming increasingly aware of this. Jackson goes so far as to advocate routine bronchoscopy before the induction of any artificial pneumothorax in order to avoid the atelectasis and its sequelæ that may result from tuberculous bronchitis. In the patient who shows a tendency to thickening of the pleura, it is wise to keep the pneumothorax as shallow as possible, and there is a danger in maintaining even a good artificial pneumothorax for too long. Perhaps three years is long enough in the majority of cases. In patients with a primary tuberculous pleural effusion, the tragic complication of a "frozen chest" might become less common if aspiration was performed more often. In any case the dangers of the inexpansible lung must be weighed against the dangers of too early re-expansion of a well-collapsed lung, and the decision will continue to tax the skill and judgment of the chest physician as it has done in the past.

EFFECTS OF LEUCOTOMY

PSYCHOLOGISTS have so far been of little help in unravelling the changes observed by the clinician after the operation of prefrontal leucotomy in mental illness or in cases of intractable pain. One of the reasons for their lack of success was the obvious difficulty in testing psychotic patients before operation, for comparison with later tests. Mrs. Petrie[1] reports test results in 50 cases of neurosis treated in the psychiatric department of St. George's Hospital, London. As their mental function was comparatively little impaired, and as the patients coöperated well from the start, a clearer and less equivocal picture was to be expected than in any psychotic group. Moreover, two different operations were used, besides the standard coronal cut which was carried out in the majority of patients.

The tests used were those of H. J. Eysenck; and Mrs. Petrie's psychological views, as well as her painstaking treatment of figures, are what one would expect from a worker trained in the Maudsley department of psychology. While the care and industry of the work is impressive, and the presentation is lucid, the results are disappointing because almost nothing was found that has not been described before by numerous observers: for example, reduced "neuroticism" (which here can only mean some clinical improvement); lack of self-criticism; increased speed and reduced exactness in motor performance; more extraversion and carelessness; and less regard or interest for other people. The variation of operative procedure had little and only quantitative influence on the test results. The only new and interesting observation was a disturbance of speech discovered by chance during intelligence testing: the abstracting ability and that of generalisation by means of language were found to be impaired, vocabulary was poorer, while the use of words was indiscriminate and lacking in finer differentiation. This seems important because the site of the standard leucotomy is close to Broca's speech centre in the left 3rd frontal convolution. Nobody seems to have noticed this before; the observation was made fortuitously and would have deserved more detailed analysis and fuller description. Altogether, Cattell's statement, quoted by Mrs. Petrie, that in psychology "statistical analysis is a device to bring out relationships and patterns which unaided observation and memory could not perceive" is hardly supported by the work she describes.

It is inevitable that this book should be compared with Partridge's study,[2] published two years ago, of 300 leucotomies done by the same surgeon. He provided a mass of interesting clinical data, but, in rejecting a statistical approach, did not even add up the number of patients in each [illegible] Mrs. Petrie's work is unsatisfying fo: [illegible] that her experiments strike one as too far detached from clinical reality. She gives no account of the condition of the patient at the time of testing, and in only 4 cases offers a short survey of the illness. In their several ways, these two studies thus reflect the continuing lack of an established tradition of clinical research in psychiatry. In this kind of work it is exceptionally difficult, but none the less desirable, to combine a disciplined approach, supported by clear concepts, with a thoroughgoing observation of clinical facts, including test results.

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[1] Daniels, M. *Proc. R. Soc. Med.* 1952, 45, 11.

[2] Jackson, S. L. O. *Tubercle, Lond.* 1952, 33, 216.

[3] Farber, J. E. *J. thorac. Surg.* 1942, 11, 424.

[4] Pinner, M., Leiner, G., Zavod, W. A. *Ibid*, p. 241.

[1] Personality and the Frontal Lobes. By ASENATH PETRIE. London: Routledge & Kegan Paul. 1952. Pp. 188. 21s.

[2] Prefrontal Leucotomy. By MAURICE PARTRIDGE. Oxford 1950. See *Lancet*, 1950, ii, 694.

THE HERXHEIMER REACTION

DERMATOLOGISTS know of many drugs only as mischief-makers. It fell to Herxheimer to describe the untoward effects of the drugs invented by his fellow-countryman, Ehrlich. Ironically, the more specifically treponemacidal the preparation, the more likely it is to cause a Herxheimer reaction. There are several objections to the simple explanation that the drug, in killing the parasites, causes the sudden release of breakdown products which then intoxicate the host. Severe reactions sometimes take place where diligent histological search brings to light the presence of no more than a few spirochætes. Furthermore, reactions may follow the administration of therapeutically ineffective quantities of a drug. If, however, a patient is hypersensitive to products of *Treponema pallidum* such reactions are more easily explained.

Anti-histamine drugs given to patients under treatment for syphilis have failed to prevent Herxheimer reactions.[1] This might be due to the release of histamine in the "shock tissues" themselves; certainly, histamine-like substances do not appear in the blood during Herxheimer reactions.[2] Experimentally, infected rabbits treated for three days with 5 mg. A.C.T.H. per kg. body-weight and then given penicillin continue to show the histological changes of the Herxheimer reaction in skin lesions.[3] These changes consist of increased œdema, vascular congestion, and invasion with polymorphs which are later replaced by mononuclear cells. Heyman and his colleagues[3] found it impossible to produce Herxheimer reactions in syphilitic rabbits by injecting spirochætes alive or dead, or after freezing, heating, or mixing the organisms with antisyphilitic drugs. They succeeded, however, in producing a reaction by injecting the animals with pooled immune serum from rabbits with untreated syphilis. Animals infected with *Spirillum minus* and subsequently injected with a serum containing lysing and immobilising antibodies against the organism also had Herxheimer reactions. The solution of this and other immunological problems in syphilis would be greatly helped by culture of the organism and isolation of its antigenic elements.

The histological changes described by Heyman et al. parallel those found by Rich[4] in tuberculous foci after the injection of tuberculoprotein. Specific treatment may aggravate the disease even in the absence of a skin reaction of the delayed type. As Heyman points out, this may be due to lack of adequately antigenic test-solutions rather than to basic differences in the type of disease. He lists reports of Herxheimer reactions in brucellosis, glanders, tularæmia, leprosy, and spirillar and leptospiral infections. To these might be added blastomycosis and paracoccidioidal granuloma, both of which may be made worse by iodides if desensitisation with vaccines is not undertaken. It is curious that such reactions have not proved common in tuberculosis treated by specific chemotherapy, particularly since patients can be sensitive to tuberculin in almost infinitesimal amounts; Goldsmith's[5] patient, for example, showed a severe necrotic reaction to an intracutaneous injection of tuberculin diluted 1 in 20,000,000.

A VITAL EXPERIMENT

THOUGH on a disappointingly small scale, the experiment of general practice from health centres is at last beginning to take shape: the opening of the centre at Knowle West, Bristol,[6] has been closely followed by the ceremony which Mr. Somerville Hastings performed this week on the London County Council housing estate at Woodberry Down. The new centre at Woodberry Down, which is described in a special article on p. 772, is the first realisation in bricks, mortar, and medical care of an ambitious plan; the council has divided its county into 162 health-service areas, each with a population of about 20,000, and it proposes that a health centre be built in each of them. The fulfilment, modification, or abandonment of this plan must depend very largely on the success or failure of Woodberry Down; for the Council's declared policy is to make its health centres "comprehensive"—in other words, to collect, as far as possible, all the health services required by an area into one building—and this policy is now going into practice for the first time.

It is not only the physical properties of a building and the soundness of its functional design that will be put to the test: we can look for new evidence on the equally important questions of how best to organise the health-centre team to bring out the full efficiency and coöperative effort of which it is clearly theoretically capable; and how to rear a new centre in an environment of old-established general practices in such a way as to win over those doctors who are doubtful of its value and disarm the frankly antagonistic. The outcome of Woodberry Down will be important enough to the future of the London medical services, but it will have an even greater national significance, especially if it gives useful answers to these questions; for the comprehensive health centre is probably the kind most likely to give the best service to an urban community and to enable the general practitioner to include a satisfying share of true preventive medicine in his work.

At all events, few have disputed that the experiment is worth trying; and whatever the final judgment on health centres, as a whole or individually, may be those who have been able to inspect the splendid building at Woodberry Down will agree that here are the major ingredients of success. Whether they have been blended in the right proportions, whether there are incompatibilities that have been overlooked, and what further trimmings are desirable, we should know in two or three years' time. When the evidence has accumulated here and elsewhere, it will be possible to assess the experimental centres, not as the wonderful showpieces they now seem, but as the potential working units of the health service.

Sir CHARLES SYMONDS, neurologist to Guy's Hospital, and Mr. H. R. DEW, professor of surgery in the University of Sydney, have been appointed Sir Arthur Sims travelling professors for 1953.

Prof. E. D. ADRIAN, F.R.C.P., P.R.S., and Mr. DENIS BROWNE, F.R.C.S., have been appointed to the reconstituted general advisory council of the British Broadcastng Corporation.

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1. Stewart, J. J. *Arch. Derm. Syph., Chicago*, 1949, 60, 427.
2. Morrison, J. L., Heyman, A., Sheldon, W. H. Cited by Heyman et al. (footnote 3).
3. Heyman, A., Sheldon, W. H., Evans, L. D. *Brit. J. vener. Dis.* 1952, 28, 50.
4. Rich, A. R. Pathogenesis of Tuberculosis. Springfield, Ill., 1944.
5. Goldsmith, W. N. Recent Advances in Dermatology. London, 1936.
6. See *Lancet*, Sept. 27, 1952, p. 645.

Special Articles

WOODBERRY DOWN

A Comprehensive Health Centre

THE London County Council health centre on the Woodberry Down housing estate at Stoke Newington in North London was opened on Oct. 14 by Mr. Somerville Hastings, F.R.C.S., M.P. Mr. Iain Macleod, Minister of Health, was among those at the ceremony. Next day parts of the school-health, child-welfare, and antenatal units in the centre, and the day nursery next door, came into use. The general medical and dental practitioners' unit will start working later.

As a matter of health-centre policy, the L.C.C. decided that London centres should house as many as possible of the health services needed in a district; and Woodberry Down is the first of the council's "comprehensive" health centres. As Mr. I. J. Hayward, leader of the council, pointed out at a press conference on Oct. 10, the centre represents an experiment, the results of which "will be invaluable in providing the necessary experience to be used in due course in the planning of other health centres."

Built at a cost of about £151,000, the centre contains:

A general medical and dental practitioners' unit.
A school-health unit.
A child-welfare unit.
An antenatal unit.
A remedial-exercise and child-guidance unit.

The day nursery which has been built next to the centre has cost about £21,000.

The centre is a two-storey building on a site of about $1^1/_2$ acres (see fig. 1), with a view over the New River, a reservoir, and an open space. The plans (a part of which are shown in fig. 2) were prepared by Mr. W. J. Durnford, F.R.I.B.A., and Mr. A. E. Miller, F.R.I.B.A., under the direction of the council's architect, Mr. R. H. Matthew, A.R.I.B.A. The former medical officer of health

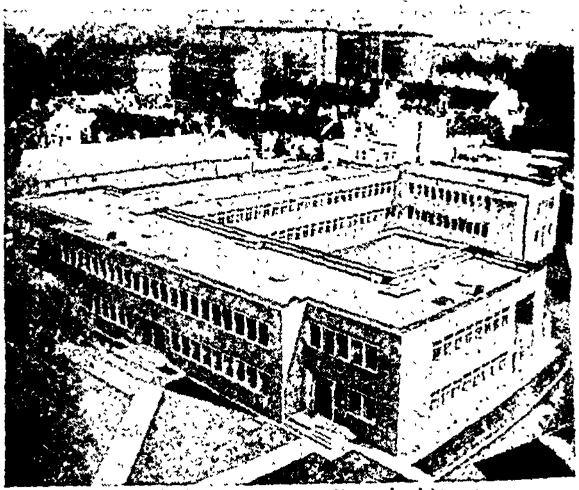

Fig. 1—The Woodberry Down health centre.

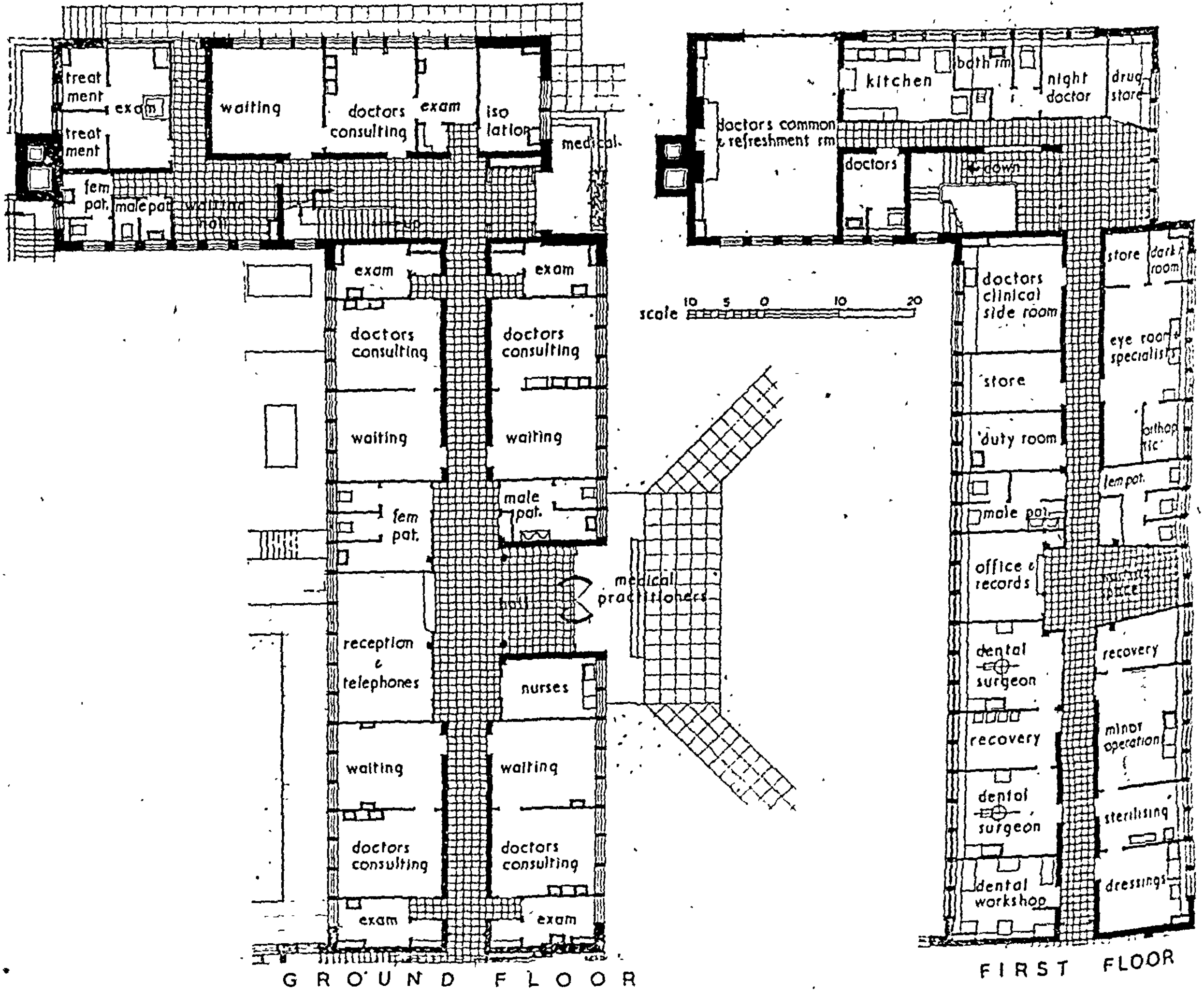

Fig. 2—Part of the plans, including general practitioners' suites on the ground floor.

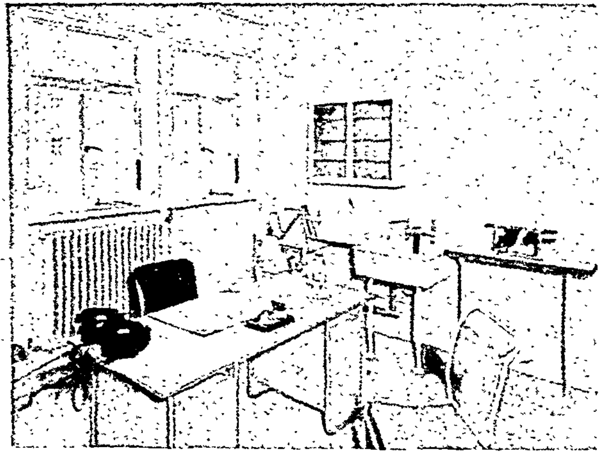

Fig. 3—A general practitioner's consulting-room.

for the county, Sir Allen Daley, F.R.C.P., the present M.O.H., Dr. J. A. Scott, and their colleagues have given detailed advice at every stage.

The design has carefully avoided a single entrance leading to a large waiting-space, common to all the units; instead each unit has its own entrance, and the G.P.s' unit has an entrance and two exits. Though the site was large enough to enable everything to be included on only two floors, it was still hard to decide which of the various units had the strongest claims to ground-floor accommodation. In the end, the ground floor was given to the G.P.s' suites and the adjoining foot clinic, and to the antenatal, child-welfare, and school-health units. This left the upper floor to take the dentists' suites, the minor-operations theatre, the eye-rooms, the doctors' clinical side room, the ultraviolet-light and remedial-exercises rooms, the child-guidance unit, and staff refreshment-rooms and common-rooms. Work on the building began in March, 1949, and it was finished last month.

For planning purposes the L.C.C. has divided the county into 162 health-service areas, each with a population of about 20,000; the ultimate aim is to provide a health centre in each area. But the use of the new centre will not be restricted to those in the Woodberry Down area, and the centre may well serve as many as 24,000 until other centres are built in adjoining areas.

PROVISIONS FOR GENERAL PRACTICE

Six doctors will run their practices from the centre. For some time the L.C.C., the London Executive Council, and the Local Medical Committee for London have been discussing the arrangements under which G.P.s should work in the centre. There are at present about sixty doctors in practice within a mile of the centre, and it is expected that the executive council will nominate the six from among them. Clearly the terms of the contracts that will be made have required very careful consideration, and the legal advisers of the Ministry of Health and the British Medical Association have been consulted. The precise terms have not yet been announced, but it is known that each practitioner will be asked to pay a certain sum in return for the facilities which he will use in the centre. This sum will be based on an estimate of what it costs to provide an adequate surgery, waiting-room, and so on in private premises in the district; the figure of £350 a year has been mentioned as a possibility. It is hoped that the doctors will be chosen in time to allow them to start practice from the centre early next year.

The layout of five of the doctors' suites is shown in fig. 2.

The central entrance opens into a small waiting-hall with a record office and inquiry desk, and corridors lead from the hall to the doctors' rooms. Each suite consists of a waiting-room (14 ft. by 12 ft.), a consulting-room (the same size) (see fig. 3), and an examination-room (9 ft. by 8 ft.). There are washbasins in the consulting and examination rooms. A door leads directly from the consulting-room into the main corridor, so that patients need not return to the waiting-room.

The unit includes an isolation-room near one exit where infectious cases can be dealt with and, if necessary, await removal by ambulance. The foot clinic is also in this part of the building (at the end of the wing shown in fig. 2), but it has its own entrance.

The other rooms which will be used regularly by the G.P.s are on the first floor, immediately above the consulting-rooms, and are reached by two wide staircases. There is a minor-operations theatre, with a sterilisation room, a room for doing wound dressings, and a recovery room.

Another set of rooms has been designed for ophthalmic work; they include a darkroom and an orthoptic room. The main eye-room is intended for the use of other consultants who may visit the centre.

An important feature is the clinical side room where doctors can themselves carry out the simpler investigations. A small medical store has been provided in which materials to be used on the premises will be kept; drugs will not be dispensed from the centre, and patients will take their prescriptions to the chemist in the usual way. A part-time pharmacist will be employed in the medical store.

This part of the building also includes a bedroom and bathroom for the doctor who is on duty for night calls; and there is a common-room for the medical and dental staff, with a small service kitchen attached.

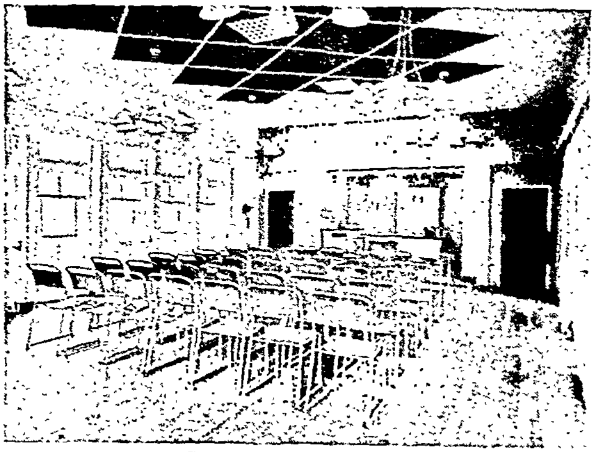

Fig. 4—The lecture hall.

THE DENTAL SURGERIES

The two dental surgeries shown in fig. 2 will deal with dental patients generally; two other surgeries nearby will be used exclusively by the priority classes (expectant and nursing mothers and children). Recovery-rooms and dental workshops are attached. A dental X-ray unit has been installed in a room large enough to take equipment of higher power, should it be decided later to do more radiological work in the centre.

Two dental practitioners, to be selected and engaged by the London Executive Council, and two dental officers of the maternity, child-welfare, and school-health services will work in the centre. Two surgeries may seem inadequate for a population of 20,000, but the unit is not intended to replace all dental surgeries in the area.

THE COUNTY-COUNCIL SERVICES

School-health Unit

A separate entrance from a quiet side road leads to a waiting-hall, a room for dealing with minor ailments, a doctors' consulting-room, a nurses' room, and a record office. On the floor above are the two dental surgeries for priority patients, and another eye-room, with darkroom and orthoptic room attached.

Antenatal Unit

Here there are interviewing rooms for the use of health visitors and midwives, a room with undressing-cubicles and urine-testing facilities, where patients will be seen by the midwives, and a doctors' consulting-room.

Child-welfare Unit

This unit also opens off the quiet side road. There is a large room for toddlers near the door (which looks out on to a playground) a pram store, and a room where welfare foods will be on sale. A test-feed room and a weighing-room are included in the unit.

Child-guidance Unit

There are consulting-rooms for the psychiatrist, the educational psychologist, and the psychiatric social worker; and a playroom for the children.

Other Facilities

Ultraviolet-light treatment will be provided on the first floor, mainly for patients from the antenatal and child-welfare units; and the remedial-exercises room, primarily intended for schoolchildren, will also be shared by the various units. A lecture hall (36 ft. by 22 ft.) on the ground floor is equipped for showing films, and also contains a demonstration kitchen (see fig. 4).

STAFF AND MAINTENANCE COSTS

Apart from the six general and two dental practitioners, and certain specialists to be provided by the North-East Metropolitan Regional Hospital Board, the L.C.C. will staff the centre. A provisional indication of the staff required is as follows:

G.P. Unit	
General medical practitioners	6
Dental practitioners	2
Pharmacist (part-time)	1
Clinic nurses	2
M[illegible] Child-welfare and School-health Services	
[illegible]	1
[illegible]	1
[illegible]	2
Centre superintendent	1
Health visitors	4
Midwife	1
Psychiatrist (part-time)	1
Educational psychologist	1
Psychiatric social workers	2
Physiotherapist (part-time)	1
Chiropodist	1
All Services	
Senior dental technician	1
Dental technicians	2
Dental attendants	4
Centre administrative officer	1
General clerical officers	6
Telephone operators	2
Caretaker	1
Cleaners	7
Stoker-porters	3

It is estimated that the cost of running the centre in its first full year of work will be about £21,000 for the local-health-authority services and about £12,700 for the general medical and dental services. But some of the expenditure on the council's services will be offset by the transfer to the centre of staff and clinics from premises that are being closed.

OPENINGS FOR GENERAL PRACTITIONERS

THE Medical Practices Committee has now classified the practice areas in England and Wales into three categories instead of four, in accordance with the recommendations of the Working Party on the Distribution of Remuneration among General Practitioners. The new classification comes into force at once for the purpose of admission to the medical lists of executive councils. The list will be revised from time to time, and a doctor who is proposing to enter practice should apply for up-to-date information from the local executive council before taking steps to secure surgery and waiting-room accommodation. The three categories are as follows.

Designated Areas

Admission to the medical list in any of these areas will be automatic. In urban areas the designation does not necessarily apply to any part where the population density is lower than in the area generally—e.g., the rural fringe of many urban areas. In rural areas the designation applies to the centres of population only. The position in designated areas is fluid and may change rapidly with the introduction of new doctors. The names of areas where the position is finely balanced and the admission of one or two doctors only may result in reclassification are marked with an asterisk on the committee's list. Under the Working Party's report an initial practice allowance may be claimed only for new practices in a designated area. Details of the scheme for the payment of these allowances are to be published later.

Doubtful or Intermediate Areas

Admission to the list to practise in these areas will be decided in the light of circumstances at the time of application. Automatic acceptance cannot be assumed. In the areas where the position may be changing at the time an application is made—perhaps because of housing development—the classification may, after the comments of the executive council and local medical committee have been considered, be amended to designated. The designation will apply only to the practice district for which application has been made. Other considerations may lead the committee to decide that the number of doctors already practising in the area is adequate and that the application be refused.

Restricted Areas

These are areas in which the committee has decided that the number of doctors practising is adequate. Normally applications to start new practices will not be granted, but in an existing practice regard will be had to all the circumstances of the case.

Further particulars may be had from the Medical Practices Committee, 3, Deans Yard, Westminster, London, S.W.1, but details of individual areas should be obtained from the local executive council.

Occasional Survey

FIBRILLOGENESIS

THE effects of adrenal corticosteroids on the collagen diseases have not only stimulated conjecture about the causes and relationships of these conditions, but have also led to a renewed interest in the structure and physiology of normal connective tissue. Much of the recent work on this complex, labile, and largely extracellular tissue centres around the nature and origin of its fibrillar elements, and the relation they bear to the mucopolysaccharides of the ground substance.

The electron microscope has been a great help in these investigations. Electron micrographs show that collagen fibres, as identified histologically, are composed of bundles of smaller fibrils embedded in cementing substance. As Gross [1] points out, histological alterations in collagen fibres cannot therefore be ascribed to collagen itself, unless the abnormality can be localised in its component fibrils. The interfibrillary ground substance has an organised molecular structure,[2] but it does not seem to be closely adherent to the fibrils, for it can be washed away from teased tissue with water. Electron micrographs also show that the washed collagen fibrils vary considerably in width (700–1400 A°), but they are regularly cross-banded,[3] [4] the average distance between bands being 640 A°.[5] There is also a characteristic

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1. Gross, J. *Ann. N.Y. Acad. Sci.* 1950, 52, 961.
2. See *Lancet*, July 19, 1952, p. 123.
3. Hall, C. E., Jakus, M. A., Schmitt, F. O. *J. Amer. chem. Soc.* 1942, 64, 1234.
4. Schmitt, F. O., Hall, C. E., Jakus, M. A. *J. cell. comp. Physiol.* 1942, 20, 11.
5. Gross, J., Schmitt, F. O. *J. exp. Med.* 1948, 88, 555.

complex of intraperiodic sub-banding, which serves as a "finger-print" for the identification of normal collagen, independent of age and (probably) of vertebrate species.[5]

This precise and complicated picture of the collagen fibril at once poses the question of fibrillogenesis. Is this highly organised structure condensed from the intercellular substance, or does it originate in the connective-tissue cells themselves? Earlier workers favoured the extracellular concept, and some later experiments have supported this view.[6] It was shown in 1927 by Nageotte [7] that rat-tail tendon was partially soluble in dilute acid, and that when salt was added to the solution fibrous collagen was precipitated. This reconstitution phenomenon has been closely investigated in attempts to test the extracellular theory of fibrillogenesis. The X-ray diffraction pattern [8] and the appearances under the electron micrograph [4] of such reconstituted collagen confirm that it retains its characteristic striations. In-vitro studies by Vanamee and Porter,[9] who used the electron microscope to follow the stages of reconstitution of fibrils from acid solutions of collagen, showed that salt solutions and an increased pH (5·3) were equally effective in precipitating collagen-type fibrils. When a film of dissolved collagen was exposed to these conditions for short controlled periods, they found that, at an early stage in fibril formation, needle-like crystals of collagen were produced, which showed periodic banding at intervals of about 210 A°. Fibrils were found in which regular stressing of two out of three such bands resulted in the typical 640 A° macro-period of normal collagen. They concluded, as others had done, that what they were observing was the aggregation of the smallest units that can be resolved by the electron microscope; and they inferred that in acetic-acid solutions, at any rate, these units were still fibrous, and that they were probably basic collagen units, or molecules, 640 A° long.

The experiments of Gross et al.[10] with acid extracts of carp swim-bladder showed that collagen fibrils may be effectively reconstituted by a low concentration (0·001%) of serum-acid-glycoprotein; but this effect was nonspecific for it was also produced by a variety of other substances, such as thrombin, papain, *Clostridium histolyticum* proteinase, and adrenocorticotropic hormone. They showed, too, that mucopolysaccharides (chondroitin-sulphate hyaluronate and heparin) precipitated salt-free collagen solutions, but that the fibres formed showed periodic banding with much longer spacing (2100 A°) than normal collagen. This and other work on reconstituted collagen, although of great interest in clarifying its structure and nature, does not give conclusive evidence of its source in connective tissue. Porter [11] has lately studied the formation of fibrils in tissue cultures of chick-embryo skin, fixed in osmium tetroxide, after different periods of growth. His observations with the electron microscope are convincing proof that collagen fibrils are actually formed at the surface of fibroblasts, and suggest that they originate in the ectoplasmic zone beneath the cell-membrane.

Meyer's theory of fibrillogenesis [12] proposes that collagen is precipitated on to polysaccharide fibrils, whose regularly spaced acidic groups form a template on which the fibril is built. Morrione [13] points out that although most observers believe that fibroblasts elaborate the ground-substance polysaccharides, definite proof of this is lacking. His experiments show that very low concentrations of heparin (1 in 80,000) can precipitate typically striated fibrils from collagen solutions, and he suggests that, in vivo, the heparin produced by mast cells plays a part in the formation of collagen. Although mast cells may be present in increased numbers in chronically inflamed connective tissue, there seems little reason at present to conclude that heparin is of major importance in fibrillogenesis. It has been shown [10] that collagen fibrils themselves possess a carbohydrate-containing fraction which is still detectable in reconstituted collagen; and an interesting report from Leeds University [14] says that polysaccharide and sulphuric acid are intimately associated with the protein of elastic tissue, another fibrillar element of connective tissue.

The functional relationships of the fibroblast with both the fibres and the ground substance of connective tissue may be of great importance in the pathogenesis of the collagen diseases. Modern research techniques are quickly expanding our knowledge of the processes involved.

Medical Congresses

NUTRITION RESEARCH

THE Second International Congress of Nutrition was held in Basle on Oct. 1–4. The First International Congress, held in London in 1946, owed its inception to the British Nutrition Society, and was made financially possible by the generous aid given by the British Council. The London congress afforded to nutritional scientists from many lands—13 different countries were represented—the first opportunity of getting together again after the war, and discussing their wartime experiences and problems: most of them had been under enemy occupation or had suffered from food shortages. It was at that Congress, too, that an International Union of Nutritional Sciences took shape, the aim of which was to bring together the nutrition societies and scientists of different lands. A committee was formed with representatives from 14 countries, Prof. E. J. Bigwood, of Brussels, being elected the chairman and Dr. L. J. Harris, of Cambridge, the secretary-general. Subsequently, various business meetings and small-scale conferences were held in London, Copenhagen, and New York; and the Union became officially affiliated to the appropriate United Nations organisations.

This second full-scale congress at Basle, which was held in the buildings of the new university there, owed its success largely to the efforts of the local organising committee, under the enthusiastic directorship of Prof. F. Verzár. Some 150 registered members from 18 countries heard about twenty-five papers or formal contributions to the discussions. The social occasions, which always form so important a feature of such international meetings, did everything possible to confirm the high reputation which Switzerland holds for hospitality and generosity.

National Nutrition Policies and Problems

The topics discussed at the scientific sessions covered a wide range. Adequate nutrition depends ultimately on an effective agricultural system; and at the first session Prof. A. I. VIRTANEN, of the Biochemical Institute, Helsinki, stressed how pressing is the need for agricultural production to be stepped up by the application of modern scientific principles. It was essential, however, that full consideration should always be given to important regional differences and requirements.

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6. Stearns, M. L. *Amer. J. Anat.* 1940, 66, 133; *Ibid*, 67, 55.
7. Nageotte, J. *C.R. Soc. Biol. Paris*, 1927, 96, 172, 464, 828.
8. Wyckoff, R. W. G., Corey, R. B. *Proc. Soc. exp. Biol., N.Y.* 1936, 34, 285.
9. Vanamee, P., Porter, K. R. *J. exp. Med.* 1951, 94, 255.
10. Gross, J., Highberger, J. H., Schmitt, F. O. *Proc. Soc. exp. Biol., N.Y.* 1952, 80, 462.
11. Porter, K. R. 2nd Conference on Connective Tissues. New York, 1951; p. 126.
12. Meyer, K. 1st Conference on Connective Tissues. New York, 1950; p. 32.
13. Morrione, T. G. *J. exp. Med.* 1952, 96, 107.
14. Hall, D. A., Reed, R., Tunbridge, R. E. *Nature, Lond.* 1952, 170, 264.

He declared himself an optimist in the race between increasing populations and a developing agriculture. J. Trémolières, chief of the nutrition section of the Institute of Hygiene, Paris, emphasised how much the dietary patterns, and the expenditure on food, varied from country to country and from one part of a country to another, and also how these patterns might change with the passage of years. The increased consumption of milk, and the growing desire for pasteurised milk in France is beginning to follow the trend with which we have already become familiar in the United Kingdom.

Later, D. P. Cuthbertson, director of the Rowett Research Institute, Aberdeen, brought the congress back to underlying scientific theory by recalling that it is the physiology of ruminant digestion—detailed knowledge of which is still in a relatively rudimentary stage—upon which depend all our meat and milk production. Prof. H. Kraut, of the Institut für Arbeitsphysiologie, Dortmund, raised the question of the influence of diet on muscular stamina. He maintained that he had found stamina to be subnormal in groups of German workers or students when their daily dietary intake of protein had fallen below 1 g. per kg. of body-weight.

The practical significance of vitamins in relation to national health policy was the theme of a paper by Leslie Harris, director of the Dunn Nutritional Laboratory, Cambridge. He compared the official measures taken in Britain and elsewhere to ensure an adequate vitamin intake, such as the vitaminisation of margarine, the longer extraction-rate of wheat flour, and the provision of vitamin concentrates for mothers and babies. He also reviewed critically the various claims advanced for vitamin therapy, some of which he regarded as legitimate, and others to be attributed to "sales pressure" or to the overenthusiasm of experts.

Interrelations of Vitamins, Minerals, and Hormones

The remarkable variety of abnormalities which can result in animals from a deficiency of vitamin E were enumerated by Prof. H. Dam, of the Polytechnic Institute, Copenhagen. Cod-liver oil, as he mentioned, can oppose the action of vitamin E; and, on the other side, administration of the dyestuff, methylene-blue, can replace the vitamin. After a full discussion, in which T. Moore, of the Dunn Nutritional Laboratory, Cambridge, S. Markees, of Messrs. Hoffmann-La Roche, Basle, and I. Leitch, of the Imperial Bureau of Animal Nutrition, Aberdeen, participated, the eventual conclusion seemed to emerge that the cod-liver oil probably exerted its anti-vitamin-E effect by promoting the oxidation (and hence the destruction) of the vitamin, whereas the methylene-blue, in the contrary direction, acted as an antoxidant.

Further reviews of the interactions between vitamins and vitamin antagonists, or anti-vitamins, were contributed by Prof. J. Kühnau, of theBioch emical Institute, Hamburg, and by J. C. Somogyi of Berne.

In Switzerland, as in many other countries, dental caries is prevalent; but speakers from different regions—for example V. Demole, of Lausanne, Prof. T. Gordonoff, of Berne, and Prof. A. J. Held, of Geneva—expressed rather divergent views about the desirability of adding traces of fluoride to drinking-water or to table salt. One speaker held that added fluoride might adversely affect the iodine balance—and this might be of practical consequence in localities where endemic goitre had been prevalent. A paper by Prof. H. D. Cremer, of the biochemical institute of Mainz University, went further to stress how much still remained unknown *about human requirements for the various* ineral elements.

S. J. Folley, of the National Institute for Research in Dairying, Shinfield, revealed new horizons in describing how the artificial application of hormones to farm animals might be used, for example, to increase the production of cow's milk or even of poultry meat. A hope was expressed by some that, for the present, these new developments might be regarded as no more than a valuable tool in research—and not as a practical proposition in current veterinary or clinical practice.

The effect of cortisone in influencing the utilisation of food was discussed by S. G. Greenberg, of the University of California, Los Angeles.

Fat and Protein in Nutrition

Contributions to our knowledge of fat and protein in nutrition were made by several speakers. Prof. E. J. Bigwood, of the laboratory of physiological chemistry and nutrition of the University of Brussels, described *developments in chromatographic technique*, by which he could identify the constituent amino-acids in intact *protein-containing foodstuffs.*

Prof. K. Bernhard, of the biochemical institute at the University of Basle, found that phytol, a component of chlorophyll, had a physiological rôle similar to that of choline, in preventing an undue accumulation of fat in the liver.

The surprising claim was made by A. B. L. Bezsák, of the department of physiology, Birmingham, that rats receiving diets low in fat and in vitamin B_1, and therefore failing to thrive, had done better when they were forced to undergo strenuous physical exercise.

Food Manipulation

Prof. Karl Thomas, now working at the Max-Planck Institute, Göttingen, referred to the investigations which have been proceeding in Germany to explore the possibility of converting paraffin oils or waxes, and various waste materials, into fats, which could then be used for foods. He discussed the metabolism of abnormal fats, as influenced by the presence in the molecule of branched chains, and of methyl groups. A. Schürch, of MacDonald College, Montreal, and Zürich, warned the meeting that linseed oil, which had been used in America for culinary purposes, might when heated give rise to undesirable toxic products. Prof. K. Lang, of the biochemical institute of the University of Mainz, in turn described the changes which might be undergone by protein as a result of heat, or of conservation processes.

Such contributions as the foregoing set the background for Prof. O. Högl, of the Public Health Office, Berne, and Prof. E. Abramson, of the National Institute of Public Health, Sweden, both of whom spoke of the need for more effective control in checking *the practice* of adding chemicals or "improvers" or other artificial colouring, flavouring, or preserving agents to foodstuffs. Professor Abramson argued persuasively for the setting up of a central laboratory for examining these problems, and for exchanging information, on an international level.

Finally, W. R. Aykroyd, director of the Nutrition Division of F.A.O., spoke of the current activities, and problems besetting that organisation. He did not hide some of its past disappointments and failures, but neither was he without hope for the future.

* * *

Before leaving Basle, the committee gratefully accepted an invitation to hold the next congress in 1954 in Amsterdam—a very happy choice in view of the pioneer work in nutritional research of many Dutch investigators, including Eijkman, Pekelharing, and Jansen.

L. J. H.

In England Now

A Running Commentary by Peripatetic Correspondents

WHAT a convenient thing for authors and scenario writers hysterical conversion has turned out to be. Other aspects of character which go with this disorder can be ignored in favour of a nice paralysis at once romantic and emotionally loaded, developed as an isolated symptom and capable of perfect cure. In *Limelight* Mr. Chaplin endows the prettiest of ballerinas with this convenient disability, and capably restores her by a combination of Freudian catharsis—as early as 1914, too!—and a severity out-Gordoning Holmes. Both methods are successful on their appropriate occasions and the lady dances devoted attendance on him till he pegs out, more or less in the big drum. But he has been clever about releasing her from the transference, and clearly she is going to grow up and be as happy as most. There is nothing new in this particular plot, but Mr. Chaplin cheers it up enormously. What's more, he gives us a first-class psychological study of an ageing comedian, with his sense of failure, his outstanding gifts, his moodiness, generosity, vanity, and courage. We all know well enough that the ability to be funny must depend on self-confidence—everything falls flat when the comedian doubts himself—and that the flimsiest material can explode into wit when it is backed by craftsmanship and belief. But he shows us the mechanism of this common theatrical experience most beautifully in the final uproarious scene with Buster Keaton, a piano, and a violin, and there is some glorious nonsense when one of Charlie's legs is attacked with bouts of shrinkage. It takes all his contemporaries back to the laughter of their youth just as it is meant to do.

* * *

The ambitious student has always begrudged the hours he must spend in idle sleep. But the results of a recent American experiment—highly reminiscent of Aldous Huxley's *Brave New World*—suggest that he may be able to increase his store of knowledge even while taking the necessary amount of recuperative slumber. A class of American students, who were learning Chinese, was divided into four groups. The first, while sound asleep between the hours of 2 A.M. and 3.30 A.M., had a record played to them of a list of unfamiliar Chinese words followed by the English equivalents. It was found next morning that they took considerably less time to learn this list than a second control group who had been allowed to slumber unserenaded in this polyglot fashion. To the third group Strauss waltzes were played in the small hours, and this had no effect one way or the other on their learning-rate. But the fourth batch, to whom the same list of Chinese words was played, but with inaccurate English equivalents, found it took them a good deal longer next day to learn the correct meanings. This investigation may comfort lecturers who are apt to feel disheartened by the postprandial somnolence of their audience. Some, at any rate, of their precious flow of information may be soaking into the stony ground before the rostrum.

* * *

"There you are Mr. Thurkington. Now go home, take things easy, and come in again tonight for another injection. If it isn't beginning to clear up by tomorrow, we'll have to take sterner measures, but I hope this'll do the trick."

"Darling, I think I must have something coming up on my arm, a boil or something. No, it isn't very much, just an area of redness and tenderness, but it might develop. Probably bruised myself going through Casualty doors this morning. No, I shan't be home late—I'll just have a game of squash with *Bill*—I promised I would—so, it'll probably be about eight o'clock. See you later, darling."

"Yes, dear, it does seem to be a bit worse this morning. Perhaps I'll pop down to Casualty and get Sister to give me a shot of penicillin later on. No, not really painful, thanks. I'll see how it goes. Yes, I remember Mrs. Thingummy and the time you had an abscess *on* your cheek. No, nothing much today, I'll be home early—just a swim before I come down."

"No, I haven't been to Casualty yet—I'm such a coward about these injection things—always think the Sister has a grudge against me or something. Yes, I promise I'll go if it gets any worse."

"Sorry, old man, I don't think I'd better play tonight—I seem to have a carbuncle developing on my arm. No, I haven't taken medical advice yet—I'm scared stiff of doctors really. Yes, I know what advice I'd give a patient but it doesn't seem to be very bad, it may clear itself. Still, perhaps I'd better not play squash tonight. Sorry."

"No, darling, I haven't had time to go to Casualty yet. Don't nag, my sweet."

"Sister, do you think I could have a brief course of penicillin and so on? I seem to have a boil of sorts on my arm. Had it a couple of days now, as a matter of fact. Yes, Sister. All right, Sister—ouch!"

"Yes, darling, I have been to Casualty, and I'm going again tonight. It's a bit more painful, but I'm too busy to do much about it."

"Yes, dear, I'm having a course of penicillin—of course, we don't know that it's a penicillin-sensitive bug I've got, but still. Yes, they generally take cultures, but I didn't bother with that. Yes, there do seem to be some red lines up my arm, and it's a bit tender in the armpit."

"Fortescue, do you think you could possibly have a look at my arm? It seems to be a trifle worse today. What, have it incised? Is it absolutely necessary, old man? I mean, I'm such a coward over these things. Oh well, if you promise to put me to sleep nicely."

"It was very sweet of you to turn up so promptly, my love—awful coming round from an anæsthetic—can't think how patients stand up to it."

"Yes, thank you, healing nicely—can't think why I made such a fuss really. Well, say in about a week—bet you five bob I beat you hollow."

"Well, Mr. Thurkington, that seems to have done very well. These things generally heal beautifully if you only take them in time."

* * *

On the road to the south, and but a few miles from Stonehenge, is a large military establishment in a country estate which, without disguise, proclaims itself a Joint Concealment Centre. The most unkind guess from our party was that it contained a depot of the Ministry of Food.

* * *

Perhaps it was as well that I was in the manic phase when the examiners in Anatomy failed me. Instead of troubling the river police, I spent quite a useful long weekend. Not content with distempering one room, I redecorated the flat and was only just restrained from doing the neighbour's. In case there should be any physical energy left to vent on the examiners, and thus add trial by jury to my misfortunes, I then resurrected the car from a trans-Sahara state to the most indecent showroom condition. (I now spend sleepless nights listening for sounds of someone attempting to restore her to the showroom, but at last my friends believe me when I try to convince them that I own an A 40.) My literary energy I diverted from the President of the College to the Editor of THE LANCET. A spate of contributions will be loosed on the unsuspecting man at seemly intervals (his non-committal acknowledgments jar the Ego so much less than the rejection slips which are said to paper the way to literary adequacy). I then took out a dignified sheet of paper and wrote a letter to the Editor of a rival weekly, gently chiding a great one who had had the temerity to allow his article to be published the day the results were out. At this rate I should be able to master Anatomy in the weekend before the next exam.

On second thoughts, I will have my chest X-rayed. One of my other diseases would be preferable to a depression centred over the next ten guineas' worth.

* * *

News from School.—Yesterday we had a lesson in Biology on Harvey's experiment. We had to tie a cloth round our arms and then watch the veins appearing. When they did we drew them in with blue chalk. Then we found the arteries and did them in red. That with a lot more went to prove that blood circulated, which was pretty obvious anyway.

Letters to the Editor

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS

SIR,—The paper by Mr. Bolton Carter and his colleagues (Oct. 4) on this topic has been of particular interest to us as we have been conducting an investigation along rather similar lines.

During 1951, thrombophlebitis after intravenous infusions was very common in this hospital and was often a cause for more complaint than the operation which occasioned the infusion. Despite the severity of some of the reactions suppuration never ensued, and this suggested that bacterial infection was not the cause. Good splintage and use of 'Polythene' cannulæ did not reduce the incidence of thrombophlebitis in a short series: it therefore seemed unlikely that damage to the intima by cannula or needle was the cause of the reaction. We were left with the possibility of a chemical irritant introduced in the infusion fluid, and believed that we had discovered this when we found that the 4% dextrose with 0·18% saline solution in use had a pH of 3·6 to 4·0. A solution of this degree of acidity seemed likely to irritate a vein with which it was in contact over a period of some hours. In view of the results obtained by Bryan and Grainger[1] it was decided to add a buffer to the infusion fluid immediately before administration. After trials it was found that the addition of 2·5 ml. of a 5% solution of disodium hydrogen phosphate in distilled water consistently raised the pH of the dextrose-saline to 7·0. For convenience the dose of buffer was sterilised in 5 ml. insulin bottles, one of which was strapped to each bottle of dextrose-saline. The buffer was tipped into the dextrose-saline immediately before use.

From January to June, 1952, trials were conducted using this buffer solution, and a control solution which was simply sterile water for injection. The latter was also packed in insulin bottles strapped to the dextrose-saline bottles, and both buffer and control were labelled with key letters so that neither the nursing staff nor the investigator who recorded the state of the patient's arm knew whether plain or buffered dextrose-saline had been given. Precautions were taken, however, to ensure that each infusion once started was continued with the same buffered or control solution, and buffers and controls were used concurrently throughout the period of investigation. The dose of buffer was easily added, and as it was secured around the neck of the bottle it could not be forgotten. All drips in this investigation ran for more than 12 hours, most for more than 24 hours, and all patients received more than 1500 ml. of dextrose-saline. Results were as follows:

	Buffer series	*Control series*
Thrombophlebitis	5	19
Thrombosis..	6	5
No reaction..	13	5
	24	29

These results appeared to be significant, and it was decided to make a trial of buffered solutions only. In view of the report of Handfield-Jones and Lewis,[2] it was felt desirable to control the tubing used in the giving sets. New sets were therefore obtained fitted with one particular brand of rubber tubing only. The tubing used in previous sets had been of various makes. Since the end of June, patients receiving dextrose-saline infusions have been given only buffered solutions and only the new sets used. It soon became apparent that the incidence of thrombophlebitis was again very high. In a series of 28 consecutive patients, 18 had thrombophlebitis and most of these suffered very considerable discomfort. Many other cases were seen, including some patients who had blood or Hartmann's solution only. It now appears that the tubing used in these new sets was of the same make as that found by Handfield-Jones and Lewis to produce a high incidence of thrombophlebitis. Clearly, any possible benefit from using buffered solutions was being masked by the effects of a more vigorous irritant, probably derived from the tubing.

We record these experiences because they seem to have an important bearing on the results obtained by Mr. Bolton Carter and his associates. Glucose solutions are generally recognised as liable to produce thrombosis. There must be a reason for this, and an acceptable explanation would be their unusual degree of acidity, correction of which might be expected to reduce the incidence of thrombotic complications. Our first series lent support to this theory; though admittedly small it was carefully controlled, and it seems unlikely that irritant types of tubing were used almost exclusively in giving non-buffered solutions. Further, most of the drips in this series had the more stringent test of running for 24 hours: we feel it should be our aim to secure conditions in which intravenous drips will run for days, if need be, and not only for 8 hours.

With these results in mind, we suggest that the negative results in the trial of buffered solutions by Bolton Carter and his colleagues may be explained in two ways. First, the rubber tubing. The type used in their trial is not mentioned, and possibly if it was not controlled there may have been a change of make during the time of the trial and more irritant brands may have been used during the tests of the buffered solutions. Your annotation (Oct. 4, p. 672) is a startling disclosure of the many toxic substances which rubber may contain. Secondly, the buffering. The "deep brown" solution had a pH of 5·6; although this reaction is less acid than some glucose solutions, it is still distinctly acid.

It is our conclusion that the effects of buffering solutions of glucose can easily be masked by other factors producing thrombophlebitis. In a complete trial of buffered solutions these other factors must be controlled, and only then can we be reasonably certain whether the correction of the acidity of glucose solutions affects the incidence of thrombophlebitis.

B. H. PAGE
G. RAINE
P. F. JONES.

North Middlesex Hospital,
London, N.18.

BUTAZOLIDINE

SIR,—During the past three months I have treated 15 cases of rheumatoid arthritis which had been present for at least three years, and in some cases for as long as fifteen years.

All 15 patients were admitted to hospital and a diagnosis of rheumatoid arthritis established as accurately as possible by evaluation of the history, clinical signs, X-ray examination of the affected joints, and the erythrocyte-sedimentation rate. All had been treated previously with one or more courses of gold during the past two and a half years, the majority under my own supervision, without any marked influence on the course of the disease.

After about a week in hospital I gave 800 g. of butazolidine by mouth daily. Without exception, after the first dose the patients noticed improvement in their joint conditions. The joint pain and swelling began to disappear after the first dose; the joints which had been affected the longest responded the earliest. Within a day the pain had subsided, and within three days the maximum improvement in the swelling of the joints was achieved.

I have particularly noticed that the small joints of the hands and feet responded better than the larger joints when these were also affected. After a day's dosage, 3 of the patients, hitherto in severe pain and with much reduced activity, had so improved that they demanded to go home. I have continued treatment with this drug for fourteen days. In all cases within a week of stopping the drug the condition

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1. Bryan, G., Grainger, H. S. *J. Pharm., Lond.* 1950, 2, 471.
2. Handfield-Jones, R. P. C., Lewis, H. B. M. *Lancet*, 1952, i, 585.

deteriorated and became as it was before giving the butazolidine.

I have not experienced any of the serious side-effects, such as the generalised œdema or severe maculopapular eruptions described by Dr. Loxton and his colleagues (Oct. 4). Only 1 of my patients suffered from a mild maculopapular type of skin rash, which affected the face and upper part of the body and disappeared within three days of stopping the treatment. My experience, therefore, is more in keeping with that of Dr. Peebles Brown and Dr. Currie (Oct. 4) who reported that of 280 patients only 3 had developed skin rashes.

I asked each patient the same question: "Have you ever had any tablets or other treatment for your rheumatoid arthritis which has been as effective as these tablets?" and in each case the answer was "No."

I am convinced that here we have an effective new weapon in our fight against the disabling symptoms of rheumatoid arthritis.

Dudley Road Hospital,
Birmingham.
R. O. GILLHESPY.

SIR,—I have been following the correspondence about this drug with considerable interest. A recent three months' trip to the United States, where, of course, it is being used extensively, convinced me that it was valuable though it had disadvantages. As far as I can see, most of the complications mentioned by your correspondents have also been noted in America, and evidence was accumulating there that gastric and duodenal ulceration was commoner in cases treated with butazolidine than in untreated cases. I heard of no fatalities.

Personally, since I came home I have not felt inclined to give butazolidine to outpatients, and so far I have confined its use to patients in my wards. Its greatest value—and this, I think, has not been mentioned by any of your correspondents—is that, given in conjunction with cortisone, it allows the dosage of the latter to be reduced to such an extent that side-effects are practically eliminated.

Butazolidine is, without doubt, useful in the treatment of certain of the "rheumatic" diseases but should be given only under close supervision. Because of certain undesirable side-effects, we should not condemn it entirely but treat it with the respect given to other useful drugs with equally unpleasant side-effects.

Southern Hospital,
Dartford, Kent.
J. C. HOGARTH.

SKIN BANKS

SIR,—The strict conclusion to be drawn from the investigation by Dr. I. J. Good (Aug. 9) is that if there are n independent skin antigens then the probability P that the skin of a donor chosen at random will survive permanently when grafted to a recipient also chosen at random is such that $1 \geqslant P \geqslant (3/4)^n$.

This is an interesting result which might be used to estimate a lower limit for n if we had enough reliable observations of the behaviour of skin homografts in man to make a reasonable guess at the value of P. Unfortunately, at present, this is not so.

Good attempts to reverse this procedure and suggests that it is possible "from what is known of skin grafting in rabbits and the transplantation of tumours in mice" to make a "fair guess" at n and so estimate P. This claim is, however, open to grave objection, as the following considerations will show:

1. As far as I am aware, no instance of permanent survival of a skin homograft in the rabbit has ever been reported (excluding the special case where members of a highly inbred strain are used). The most one can do, therefore, is to estimate a lower limit for the value of n in this species.

2. Even if we knew the value of n for the rabbit it would be dangerous to assume the same value for man.

3. Homotransplants of tumours are much more successful than homotransplants of normal tissues, one likely reason being, as Gorer has shown, that tumours are in general antigenically simpler than normal tissues. How then can one deduce the behaviour of transplants of skin from observations on tumours?

In this connection it is worth mentioning that it seems likely that the number of antigens differs even for different normal tissues. In my own experiments, for example, there have been several instances of very long survival of subfascial homotransplants of thyroid in guineapigs from a mixed population without special treatment. Transplants of skin in the same species have, on the other hand, been uniformly unsuccessful.

In conclusion it must be emphasised that a small change in the value assigned to n makes a vast difference to the lower limit we obtain for P. Thus it will be clear from the following figures:

n	$(3/4)^{-n}$
20	316
21	422
25	1334
30	5623
50	1,778,000
100	$3{\cdot}16 \times 10^{12}$

The optimist will be happy to choose n = 20 corresponding to $P \geqslant \frac{1}{316}$; if, however n = 30 all we can say is $P \geqslant \frac{1}{5600}$. If n = 100 our only consolation is the knowledge that $P \geqslant \frac{1}{3 \text{ million million}}$. It would be unreasonable to put $P = \frac{1}{3 \text{ million million}}$ (corresponding to the "unduly pessimistic" assumption that all the πs in Good's terminology are zero) but even so the outlook would seem to be pretty bleak.

Speculation of this kind is, however, fruitless, and the important thing is to get on with the job of making accurate observations of the behaviour of homotransplants *in man*.

Department of Surgery,
The University, Aberdeen.
MICHAEL F. A. WOODRUFF.

PHLEBOTHROMBOSIS AND NERVOUS STRESS

SIR,—Mr. Stoker (Oct. 11) has done a considerable service in pointing out that recumbency in the home is less likely to produce phlebothrombosis than recumbency in hospital. His hypothesis that the difference can be explained by the mental stresses inseparable from hospital treatment may be correct, and (if he will forgive the pleasantry) has long been accepted by thriller-writers, whose characters frequently suffer from curdling of the blood when startled by some menacing sound or sight.

However, one cannot help feeling a little sceptical at the ever-increasing number of gross bodily diseases that are being attributed to mental stress. I should like, if I may, to offer the simpler explanation that patients in bed at home are generally less ill than their fellow sufferers in hospital. It is the illness, and not the associated but purely coincidental recumbency, that is the precursor of phlebothrombosis.

When a *person* becomes a *patient* many things happen—one of which must be the cause of phlebothrombosis. Most workers agree that it is the venous stasis in his legs; Mr. Stoker thinks it is the mental stress; I have suggested[1] that it might be the filling of his veins with irritating products of tissue breakdown. Time will show which, if any, of these hypotheses is correct, but it is interesting to see that the solitary patient described by Mr. Stoker (*a*) was gravely ill, (*b*) was fully ambulant, and (*c*) had lost a lot of weight.

A tremendous amount of painstaking work has gone into proving the very reasonable assumption that the axial stream in the leg veins is slowed down by recumbency. No work at all has gone into proving that this stasis causes clotting of the blood, although many workers, including Lister himself, have carried out experiments purporting to show that it does not. It may be opportune to draw attention once again to that forgotten but uncurdled moiety of our life blood which remains relatively stagnant whether we are in hospital or at home, sick or well, asleep or running for a bus.

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[1] *Lancet*, 1951, ii, 1180.

Barnet General Hospital,
Hertfordshire. V. J. DOWNIE.

INFECTIOUSNESS OF COMMUNICABLE DISEASES

SIR,—May I reply to the valuable critical letter from Dr. Bradshaw (Oct. 4).

The effect of some of the variables he mentions has in fact been investigated, but there is a limit both to the patience of non-specialist readers and to the forbearance of editors. A full account would have necessitated a paper of formidable dimensions. The material chosen for publication (Sept. 20) was limited to what was considered necessary to make the principles and methods clear enough for others to be able to corroborate, correct, and extend these studies. I am accordingly grateful for the opportunity to deal with some of the difficulties, although the discussion of them in the space of a letter may prove inadequate.

The Effect of Age

When our figures are broken down into single years of age they show approximately the same relative infectiousness for the three diseases at each age. The most serious disturbing influence is the immunity conferred on newborn infants by their mothers. This cuts down by more than a half the susceptibility to infection with measles or chickenpox in the child of less than one year of age, and the group is sufficiently big to have a perceptible effect on the final figure for infectiousness. There is, therefore, a good case for leaving out this group though we have in fact included it.

Composition of the Families

The majority of the mumps families feature in the chickenpox studies, and most of the chickenpox families occur again in the measles studies. In this respect we were very fortunate in that it ensures that the home conditions in the studies of the three diseases were similar. It also ensures, however, that the composition of the families as regards both age and numbers of susceptibles will differ especially for mumps owing to the effect of the different degree of infectiousness. In table I, for example, one finds relatively fewer families with only one susceptible at risk in the mumps study.

TABLE I—NUMBER OF FAMILIES ACCORDING TO THEIR CONTENT OF SUSCEPTIBLES AT RISK

Susceptibles at risk	No. of households		
	Measles	Varicella	Mumps
1	140	104	78
2	34	40	40
3	9	16	27
4	4	1	8
More than 4	..	2	4

It is well known that the incidence and age-distribution of these diseases tends to be different in rural and urban areas. It is therefore of particular interest that the homes in urban areas show almost the same attack-rate for all of the diseases as the homes in rural areas (see table II).

TABLE II—INFECTIOUSNESS IN URBAN AND RURAL HOUSEHOLDS

Infectiousness	Measles	Varicella	Mumps
Rural :			
Exposures	136	171	152
Transmissions	104	69	42
Rate	76·5 %	59·6 %	27·6 %
Urban :			
Exposures	130	112	39
Transmissions	97	71	10
Rate	74·6 %	63·4 %	25·6 %

On the whole there seem to be good grounds for hoping that the method described in the paper gives a fairly stable figure for infectiousness. When the larger groupings are broken down for analysis into small groups—as, for example, in the seasonal studies and in studying the attack-rate at different ages and in urban and rural homes—the same relative infectiousness is found in the three diseases. It is probably justifiable, therefore, to continue to use the method to study the epidemiological importance of the many influences that affect the spread and distribution of these and similar diseases in different sorts of community.

Epidemiological Research Unit,
Cirencester. R. E. HOPE SIMPSON.

THE SAFE HEARTH

SIR,—The coal fire-guard illustrated in the Birmingham leaflet, *Advice on Fireguards*, mentioned in your issue of Oct. 4 (p. 689), was designed by one of our members, Mrs. Darcy Braddell, and is being shown by us all over the country. Our constituent women's organisations, with a membership of over 2 million, are greatly concerned at the high rate and serious consequences of burning accidents due to unguarded fires. Anyone interested can see the guard in our offices at 18, South Molton Street, London, W.1. We particularly welcome all those associated with children's and old people's welfare.

Women's Advisory Council
on Solid Fuel. ELSPET FRASER-STEPHEN
General Secretary.

A CHEAP SURGEONS' CAP

SIR,—Mr. John Howkins (Sept. 27) described a cheap and comfortable surgeons' cap, and he included a photograph in which the surgeon was shown with hair and ears exposed. Mr. John Whittingdale (Oct. 4) evidently objects to the photograph, and recounts that Sir Holburt Waring insisted on hair being completely covered—an insistence which is in line with present-day knowledge. Unless Mr. Howkins's stockinette cap is also comfortable when covering the ears and all the hair, it cannot be regarded as an effective head-dress for an aseptic operation. I have yet to find a cap to equal that made by Robinsons of Chesterfield for wearing with their 'Cestra' mask.

These letters raise the larger question of aseptic technique with which every surgeon is inevitably concerned—a question which can be answered better by bacteriology than by the vague generalisations of Mr. I. A. McGregor (Oct. 11). Some of my colleagues and I, while visiting hospitals in England and abroad, have noticed a widespread slackness in aseptic technique in operating-theatres. It is by applying our knowledge of bacteriology to the subject that this deplorable tendency can be arrested and remedied.

We know that the bacteria which may infect surgical wounds have no power of movement themselves; but they can be projected into a wound on droplets from the noses and throats of people present, and they can be carried on particles of dust. Dust may enter operating-theatres on the clothes and footwear of attendants, on blankets, and in other ways; it may also fall from the hair and ears of those leaning over the operation area. It would be of great interest to operating surgeons to learn, through your columns, whether there is any operating-theatre in this country in which everybody wears an impervious mask over nose and mouth, in which the scrubbed-up staff have hair and ears completely enclosed, and in which all staff and patients completely change or cover their dust-laden clothing and footwear in an anteroom, so that as little dust as possible is brought into the operating-theatre. If there is an operating-theatre which is run on these lines every day of the week, it would be of great value if we could know the incidence of infection in the wounds of its clean cases.

London, W.1. ALISTAIR GUNN.

CURE OF TOBACCO-SMOKING

SIR,—Dr. Lennox Johnston's article (Sept. 6) and the subsequent correspondence are of great interest and considerable importance. The disease, as stated, is pandemic and the cure is not easy for many reasons. As one who was addicted to 35 cigarettes a day for 30 years I write with feeling!

However, I am convinced that the majority of people can get rid of this addiction if they realise it is harmful and that they will be able to face both the major and minor problems of life at least as well without a cigarette. A quiet determination to abstain, associated with having a cigarette available in the pocket, to avoid a panic search throughout the whole house, were my two best aids in the early days of complete abstention.

The main difficulty is that the risks of smoking are being purposely kept from the public today. The chief risk is cancer of the lung. In this country in 1951 more people died of this condition than from tuberculosis. A close association has been proved beyond any doubt. If such a close association had been shown between rapidly increasing cancer and any other social phenomenon publicity would have been nation-wide.

Many powerful bodies have a vested interest in playing down such publicity. The Treasury is foremost in this respect because it receives £610 million yearly from the tobacco tax. The national press is interested in revenue from advertisements, and the cinemas are also recipients of advertising revenue from the tobacco companies. One of the pleasures of being in the Services is that tobacco is less expensive. I understand the American Forces are supplied with large numbers of cigarettes free each week; thus we have the big battalions on the side of the pandemic condition.

A reasoned statement about the ill effects of tobacco is rarely given to the public. I doubt if my own experiences have been exceptional—my father developed cancer of the lung after 55 years of fairly heavy smoking; my father-in-law developed cancer of the lung after 50 years of heavy smoking; while my chief, a senior medical administrator, developed this condition after 40 years of smoking. These three deaths occurred within 18 months. In my own medical wards I have never less than three or four cases of this condition at any one time. Careful investigation constantly shows that they have been heavy smokers, while the work of Bradford Hill and Doll gives statistical confirmation of these clinical impressions.

The reports of the medical officers of health for Wembley and Willesden, areas served by this hospital, show that in 1951 more than twice as many people died from cancer of the lung as from pulmonary tuberculosis. This situation is becoming so serious that we cannot allow it to continue without emphatic protest.

Central Middlesex Hospital,
London, N.W.10. HORACE JOULES.

SIR,—I think we have a lot to learn from a group of addicts who have found a cure that works in many cases after the complete failure of medical treatment, exhortation, spiritual counsel, and so on: I mean Alcoholics Anonymous. By their anonymity, members of this group are protected from the pressure often applied by the uncured and from many other difficulties. They do not say that they will stop drinking next week, or that they will never drink again, or that they will try it again after a while. All they need think of is "not today," and they have found that this works best.

I suggest, therefore, that smokers who feel that it might be a good thing to stop should announce their intentions to nobody until the craving has really gone. It is difficult to say "not today" when one wants to smoke, but surprisingly easy to say "not now." It can be tried as an experiment, to see how long it keeps the craving from becoming intense. If curious friends inquire, one can put them off with a vague remark such as "been smoking too much lately."

I suggest that those who are smoking too much, and know it, try this method. I see no point in putting one's honour or self-respect to the test, and suffering needlessly, until this way has been tried. Many who try it out of pure curiosity will be surprised.

TOBACCO-ADDICT ANONYMOUS.

OTITIS EXTERNA

SIR,—For the past fifteen years in my own experience otitis externa due to a fungus infection has been a rarity in this country, and I am sure it is generally believed that the condition is a bacterial one. In many cases there is an underlying seborrhœic tendency, and any form of treatment in this type of case, whether successful or not, still leaves behind the constitutional condition, and therefore a tendency to recurrent attacks. Local applications should be of as benign a character as possible, as the skin rapidly becomes sensitive to chemicals of any kind. Some of the worst cases of external otitis one sees are almost certainly the result of ill-advised and too active treatment. In this category must be placed watery and oily preparations of the more recent antibiotic drugs. Penicillin drops are undoubtedly a common cause of persisting unhealed external otitis, and it is to be feared that chloramphenicol and terramycin will accompany penicillin in this unhappy position.

Knowledge of the character of the organisms present is by no means the only factor, and treatment in the sense of killing off these organisms is not necessarily the best means of achieving a successful result. Careful and clean removal of debris and unhealthy skin is at least as important, and attention to the scalp is perhaps even more so.

I cannot help regarding with considerable fear the "plugging" to which the profession is now being subjected of preparations containing the newer antibiotics for use on eczematous surfaces. It is true that your annotation last week also indicates some such attitude, but I personally could have wished it put more prominently and with a stronger emphasis. The indiscriminate use of these antibiotic preparations will almost certainly create as many problems as they solve—at a fantastic financial cost.

London, W.1. MAXWELL ELLIS.

SIR,—I feel that your annotation calls for some comment.

You cite Singer et al. as stating that this irritating disorder is usually caused by bacterial infection with *Pseudomonas pyocyanea*. The following points are against this supposition:

1. *Ps. pyocyanea* can usually be grown from any moist skin lesion, being especially common in cultures taken from chronic leg ulcers in patients attending the leg clinic of a skin department.

2. The treatment of external otitis by local antibiotics and especially chloramphenicol is usually quite unsuccessful, even when the organism has been shown to be sensitive to the antibiotic. Not infrequently the condition is worsened by such treatment.

3. The cause of external otitis is in nearly all cases an interference phenomenon. Thus a mild original itch receives undue interference, and *stimulation* of the wax glands by such interference produces an unduly sticky waxy secretion which fails to dry and drop out as do the normal ear secretions. This sticky substance forms an excellent culture medium for *Ps. pyocyanea* and other organisms.

4. I have never seen a case of external otitis which cannot be cured by proper firm packing of the ear daily with gauze

tape moistened with glycerin and ichthyol performed by an efficient outpatient sister. Alcohol, however, must be avoided absolutely. This method acts as a splint to reduce the œdema of the meatal wall and prevents access of the patient's fingers to a large extent. This method should always be combined with adequate wrist splinting at night, as the patient commonly attacks the ears during sleep. Fractional X-ray therapy, though of value in relieving the itching, is a small and inessential part of the treatment. The only cases in which this method is not successful are those of such chronicity that secondary stenosis of the orifice and chronic lymphangitis have supervened.

5. A further point indicating the interference nature of this disease *is the frequent association of Bact. coli* with *Ps. pyocyanea* and other organisms in cultures from the ear.

Sunderland. P. INMAN.

NEW OUTLOOK ON MENTAL DISEASES

SIR,—In your review (Oct. 4) of this book by Dr. Pickworth you praise him for his morphological study of the smaller blood-vessels of the brain and for pursuing original and unaccepted ideas about the cause of mental disease.

I think that a more sympathetic view of these ideas is justified than you express. You state that Dr. Pickworth has left the highroad of contemporary thought about the pathology of mental diseases; but, surely, the only thing that is agreed about the understanding of mental diseases and their pathology is that there is no highway known that leads to it. This is the only conclusion that can be drawn from the bewilderment expressed at a conference held by the Mental Health Research Fund this year and from the many methods of investigation which were suggested there.

In my opinion, Dr. Pickworth's hypothesis that reaction to infection has a much larger part than we realise in mental disease has much to support it. For instance, we believe that serious mental disease of almost any form may be caused by almost any infectious disease; it is common personal knowledge to all that the minor sinusitis associated with a cold in the head often produces distinct impairment of mental functions; the cure of severe mental disease after cure of long-standing infection, as recorded by Dr. Pickworth and Dr. T. C. Graves and others, is very impressive; and Dr. Pickworth's suggestion that alterations in local blood-supply of the brain may cause abnormalities in cerebral function is supported by our knowledge of the confusion of senses and thoughts during recovery from fainting. What is needed is a fuller understanding than we possess of the action of infection in chronic forms.

London, W.1. J. M. ALSTON.

THE NOTIFICATION OF DISEASE

SIR,—In his article in your issue of Oct. 11, Dr. E. D. Irvine rightly stresses that to be effective for control purposes notification must be statutory, since informal notification is almost necessarily incomplete. He then poses the question "Who can doubt that more accurate information will be obtainable in Manchester, where german measles is notifiable, on the effect of this disease in pregnancy than will be obtained by the voluntary inquiry now being made in regard to this and other diseases by the Medical Research Council?" Personally, being in charge of the inquiries made under the Medical Research Council, I can see no reason whatever to suppose that they will lack accuracy for the reason put forward by Dr. Irvine. They are not, in fact, dependent upon "voluntary inquiry."

Valuable information, though on a small scale, can clearly be obtained in Manchester from the notifications made to the medical officer of health *if* each reported attack in an adult woman is followed up to see whether she was pregnant at the time and, if so, whether she had a normal baby.

My own inquiries are also limited geographically—broadly to London and the Midlands—but they are based upon neither statutory nor informal notifications of the kind Dr. Irvine is discussing. Within these regions I am informed by the chief medical officer to the Ministry of National Insurance of the occurrence of each "double event" in an employed woman. The "double event" comprises: (1) the medically certified occurrence of german measles (or other specified disease) in such a woman; and (2) the subsequent birth of a baby within 12 months of the illness, as known by the claim to maternity benefit. Such mothers are then visited by one of my medical colleagues who examines the baby. (I have deliberately excluded the study of abortions.) With the coöperation of the general practitioners concerned, freely and invariably given, my colleagues in this work have experienced no difficulties in visiting all these babies.

We may well fail to collect enough data by these means, for the "double" is a relatively rare event. I do not believe we shall fail for the reason Dr. Irvi has in mind because it is not relevant. Possibly he merely confusing these inquiries under the Medic Research Council with the concurrent inquiries bei made by the General Register Office through medic officers of health.

London School of Hygiene
and Tropical Medicine,
London, W.C.1.

A. BRADFORD HILL.

Public Health

THE SANITARY INSPECTOR

AT their annual conference at Brighton last mont members of the Sanitary Inspectors' Association aga made clear their conviction that they have now grow to full stature, and their impatience to occupy, manag and improve their estate—even to change its name and define its boundaries more acceptably. Their wish f independence and betterment is a sign of profession restlessness, proper and understandable in a vigoro body of men who have been on the go for the past eigh years, and present-day changes in the pattern of publi health administration offer them a fair opportunity to state their case.

PAST ACHIEVEMENTS

The Public Health Act of 1872 was the outcome of the mid-19th-century outcry for cleaner streets, more wholesome houses, purer water, and better disposal of refuse and sewage. This Act authorised the first appointment by local sanitary authorities of "inspectors of nuisances," and this title remained unchanged until 1921, when the Public Health (Officers) Act substituted for it the new name of "sanitary inspector." Although the work of sanitary inspectors has widened to include food inspection and sampling, infectious-diseases control, slum clearance, factory hygiene, and diseases of animals, the public still sometimes associate the designation "sanitary inspector" with drains and their imperfections.

For the first forty years of this century the sanitary inspector was reasonably content to be the trusted right-hand man of the medical officer of health—his expert executive and technical adviser on drainage, domestic sanitation and hygiene, food and drug sampling, meat inspection, and so on. In most public-health departments a modus vivendi developed whereby the inspector discussed his findings with the medical officer of health and they agreed together what action should be taken. Most of the day-to-day work was usually left entirely to the inspector. Today, in some towns the chief inspector makes his reports to the medical officer of health, who in turn reports to the appropriate committee of the local authority. In others, the chief inspector makes some reports directly to the public-health committee and receives their instructions. Direct responsibility depends mainly on the breadth of the inspector's duties. He may, for instance, be in charge of such services as disposal of domestic refuse, inspection of fresh meat, rat-catching, or sampling of fertiliser and feeding-stuffs. It depends even more on the attitude of the medical officer of health, to whose "general direction" the sanitary inspector is by ministerial regulation subject.

The modern inspector has travelled a long way in training and practice since Chadwick first conceived him as the field worker who inspected nuisances for the medical officer of health. It is understandable that he now feels ready to use his skill in a more mature way by assuming full responsibility for planning, proposing, and operating policy in local matters of hygiene. Chief sanitary inspectors chafe at the restrictions or inhibitions implied, and perhaps too often manifest, in the proviso "subject to the general direction of the Medical Officer of Health."

PRESENT DISCONTENTS

The sanitary inspector would, therefore, like to exchange this title for a more euphonious and savoury designation. "Sanitation," he says, is no longer his most absorbing interest, and "inspector" is too suggestive of snooping. But so far he has not been able to suggest a better name for himself. He regards as unjust and inadequate the present practice of fixing sanitary inspectors' salary scales according to those of other local-authority "administrative, technical and clerical officers," and the association calls for more appropriate national scales negotiated on the lines of those for public-health doctors and nurses.

Training and qualification is another bone of contention. At present the statutory essential first qualification is the certificate of the Royal Sanitary Institute and Sanitary Inspectors' Examination Joint Board. The association, with a membership of some 4000, thinks that its representation, and therefore its influence, on this training and examining body is inadequate.

But the crux of the inspector's discontent is his status. The general council of the association has asked [1] for the establishment of a single type of local sanitary authority to deal with all matters of environmental hygiene and to be responsible to a suggested "Sanitary Services Division" at the Ministry of Health. The local authority's chief sanitary inspector—so the association argues—should acquire, with his new name, complete independence of any medical officer of health and should be directly responsible to his employing authority for the efficiency of the new department, of which he would now become chief officer.

FUTURE PITFALLS

While there is undoubted logic shining through the equally undoubted discontent which inspires this proposal, the association perhaps does not appreciate sufficiently the risks of pressing for the withdrawal of the sanitarians from the public-health team. In trying to escape from the domination of the medical officer of health, sanitary inspectors might fall into other, perhaps less sympathetic, hands. Local authorities are loth nowadays to create new chief-officer posts and departments. A demand for change of title, status, and duties on the part of sanitary inspectors might well be used by some local authorities as an opportunity to transfer them from the health department to that of the engineer or surveyor. Indeed in many of the small local sanitary authorities, the engineer and surveyor's duties are already combined with the chief sanitary inspector's. Nor can there be any guarantee that future officers sequestrated from the public-health department will necessarily receive the improved rank and pay accorded to many of the doctors and clerks transferred in 1948 to the newly formed regional hospital boards. Instead further fragmentation of the public-health service might lead to the appointment of a lay administrator to supervise and coördinate the work of medical, sanitary, children's, and welfare officers.

At the request of the Sanitary Inspectors' Association the Ministry of Health last year set up a Working Party to study "the nature of the work at present being undertaken by Sanitary Inspectors; the nature and functioning of the present arrangements for their recruitment, training and qualifications and the adequacy of such arrangements." The evidence submitted by the association has not yet been published, but the Society of Medical Officers of Health in their evidence [2] insisted that, as sanitary inspectors are concerned with environmental health, they belong to the group of health workers who enjoy reasonable individual freedom in their work but are under the general direction of the medical officer of health. Only thus, says the memorandum, is it possible to ensure that the medical officer of health shall—as required by regulation—"inform himself respecting all matters affecting or likely to affect the public health in the district, and be prepared to advise the Local Authority on such matters." As the purpose of all sanitary business is to conserve the public health, the medical officer of health in the rôle of preventive physician would seem to be the specialist best fitted to pronounce whether aims have been achieved or are correctly directed.

Whatever the outcome of the Working Party's deliberations there can be little doubt that to separate the specialist sanitarian (by whatever name) from the public-health department would be a retrograde move. There can be even less doubt that a chief sanitary inspector merits from his medical officer of health the recognition and consideration due to a mature specialist colleague.

The Second Quarter in Scotland

In Scotland during the June quarter of this year [3] the birth-rate was 18·5 per 1000 population, which was 0·6 below the rate for the corresponding quarter of 1951 and 1·9 below the average for the corresponding quarters of the last five years. The stillbirth-rate was 25 per 1000 total births. The death-rate was 11·2 per 1000 population; this was 0·9 less than in the corresponding quarter of 1951. The infant-mortality rate was 34 per 1000 registered live births—1 less than in the corresponding quarter of 1951. The neonatal death-rate was 22 per 1000 live births, which was the same as in the corresponding quarter of 1951. The death-rate from all forms of tuberculosis was 30 per 100,000 population (compared with 39 in the corresponding quarter last year), comprising 25 (33) from respiratory tuberculosis and 5 (6) from other forms.

Books Infected by Scarlet-fever Patients

In his annual report for 1951, Dr. E. K. Macdonald, medical officer of health for Leicester, refers to an investigation in that city to establish the likelihood of patients with scarlet fever transmitting infection to others through library books. The inquiry was undertaken by Dr. A. I. Ross, deputy M.O.H., in conjunction with Dr. E. H. Gillespie, director of the Public Health Laboratory, Leicester.

Arrangements were made that when a patient found to have scarlet fever had a library book this should be examined bacteriologically, and swabs should be taken of the patient's nose and throat. As a control, books from patients with Sonne dysentery were also investigated.

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[1] *Sanitarian*, 1949, 58, 85.

[2] *Publ. Hlth*, 1952, 65, 137.

[3] Quarterly Return of the Registrar-General, Scotland: Births, Deaths and Marriages Registered in the Quarter ended June 30, 1952. H.M. Stationery Office. Pp. 30. 2s. 6d.

With the inquiry almost complete, 141 books had been examined—91 from patients with scarlet fever and 50 from patients with dysentery. In the scarlet-fever group streptococci of the same serological type were found in both patient and book in 18 cases (19·8%). In the control series a streptococcus was recovered from the book in only 3 instances (6%).

"It is thus evident," says Dr. Macdonald, "that there is a significant difference in the number of times streptococci were recovered from books which had been in contact with scarlet fever compared with those in the control series. This shows that it is possible for books from scarlet fever patients to spread infection and that, therefore, appropriate measures such as disinfection or destruction to deal with them should be continued."

A full account of the investigation is to appear elsewhere.

River Pollution

"I love," wrote Izaak Walton, "any discourse of rivers and fish and fishing." Even those who are not, in his familiar phrase, "Brothers of the Angle" can sympathise with a fisherman's desire that our rivers should not be so foul as to spoil his sport. The Anglers' Co-operative Association has just issued a new edition of what it calls its Pollution Handbook,[1] indicating amongst other things the change made by the Act of 1951.

Previously there had been only one legal definition of pollution. It was the same for the purposes of the Public Health Acts and the Rivers Pollution Prevention Act and for the purpose of proceedings in a civil court for damages or an injunction. Henceforth the requirements are different for criminal and civil proceedings. The criminal offence will ordinarily arise from the discharge of an effluent which violates a standard prescribed by the by-laws of a river board "determining when matter is to be treated as poisonous, noxious or polluting for the purposes of the Act." For the purpose of civil proceedings, on the other hand, pollution will still be judged by what the courts recognise as the common-law rights of a riparian owner—i.e., his right to have the water which passes his property in its natural state unaltered in quality, temperature, or volume.

River water, the handbook explains, is not pure H_2O but a very dilute solution of many different chemicals, including dissolved oxygen. Any alteration in the amounts or proportions of those chemicals, or any addition or subtraction, may alter the quality. There may be additive pollution through the introduction of directly deleterious substances like cyanide, chlorine, arsenic, ammonia, acids, lime, or oil. There may be subtractive pollution such as removes or absorbs the oxygen—for example, by the discharge of hot water or of effluents containing putrefying matter from sewage works, sugar-beet factories, or paper or silk mills. There may be changes in appearance and smell. "Innocuous discoloration" was not an offence under the now substantially repealed Act of 1876; it is not necessarily an offence under the new Act, though section 5 enacts that the standards prescribed by river-board by-laws may take into account both temperature and the effect of discoloration. The handbook doubts whether discoloration can ever be quite innocuous from a fisherman's point of view because, by shutting off sunlight, it must affect the algæ on which insect life depends. Discoloured water is not the water in a natural state to which a riparian owner is entitled. Finally, there is bacterial pollution which may render the water unsafe for drinking, bathing, the growing of watercress, and other purposes. Here the A.C.A. concedes that scientific research is still needed if the danger to fish is to be exactly assessed.

It seems reasonable to assume, as Izaak Walton would doubtless have done, that what is harmful to mankind is harmful to fish, and vice versa. At any rate in the campaign for cleaner rivers the interests of public health and of angling coincide.

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[1] Obtainable, price 1s. 3d., from the association, Ivy House, 30, Newgate Street, London, E.C.1.

Obituary

HERBERT ELDON ROAF

M.D. Toronto, D.Sc. Lpool.

Professor Roaf, who died on Sept. 21, was a Canadian by birth and education, but as a welcome immigrant to this country he had held chairs of physiology at the London Hospital and at the University of Liverpool.

He was born in Toronto in 1881, the son of the late James R. Roaf, K.C. From the Upper Canada College in Toronto he went to the university of that city, where he graduated in medicine in 1902. In the same year, with a Johnston Colonial fellowship, he came to this country to work under Benjamin Moore at Liverpool. In 1904 he took the Conjoint qualification and the following year his M.D. degree. In 1906 he became assistant lecturer in the department of physiology under Sherrington, and in 1909 he was appointed lecturer in chemical physiology. In 1909 he graduated M.SC. at the adopted university where he had settled so happily, and in 1910 he proceeded to the D.SC.

In 1911 he came to London to take up the lectureship in physiology at St. Mary's Hospital Medical School. He held this post till 1920 when he was appointed to the chair of physiology at the London Hospital. Shortly afterwards he produced his book on *Biological Chemistry* which many found to be a readable introduction to biochemistry. In 1932 he returned to Liverpool on his appointment to the George Holt chair of physiology which he held until 1944. On his retirement he received the title of professor emeritus.

During the late war, besides bearing a heavy load of departmental work, Roaf carried out research on vision for the Admiralty. He was the right man to undertake this task, for during his working life as a scientist the problems of colour-vision had always been one of his chief interests. But he was not a narrow specialist, and the breadth of his outlook was shown by his methods as a teacher. It was his practice to introduce his students to physiology by lines already made familiar to them by their study of the preliminary sciences. Thus the physics of the body—movement, respiration, and electrical changes of the heart—led on to the chemistry of organs and their processes, till the students had learned something of almost every system of the body and yet been asked to do little more than apply knowledge they already possessed. Roaf also followed this approach in his *Textbook of Physiology*, of which a second edition appeared in 1936.

Of Roaf's personal qualities R. C. writes: "He was a gentle and indeed a shy man, the soul of integrity and endowed with high ideals of thought and conduct. These expressed themselves in quiet ways—a modesty which did not prevent him from standing firm for a principle, a deep sense of personal responsibility to his students which led him and his wife to keep open house for them in their delightful home at Grassendale, a meticulousness of scientific approach, the satisfying enjoyment of doing his own gardening, and a devotion to his unobtrusive work as chairman of the church committee of the historic Ancient Chapel of Toxteth."

Professor Roaf married Beatrice Sophie, daughter of Sir William Herdman, F.R.S., and she survives him with two daughters and two sons, one of whom is an orthopædic surgeon in Liverpool.

JAMES COWAN WOODS

O.B.E., B.A. R.U.I., M.D. Lond.

Dr. Woods, who died on Sept. 24 at the age of 76, had been for many years lecturer in mental diseases at the London Hospital and at St. George's Hospital.

He was educated at the Royal School, Dungannon, Northern Ireland, and from an early age he wished to take up medicine as a career, but for some time this was impossible for financial reasons. He became, therefore, a schoolmaster, and in 1902 he obtained an honours degree in history at the Royal University of Ireland, where he was awarded an exhibition. Soon afterwards he was able to begin his medical studies at the London Hospital, where he qualified in 1907. Four years later he took his M.B., and in 1914 he was awarded the gold medal in psychiatry for his M.D. thesis. In 1917 he received the Gaskell gold medal and prize in psychology and psychological medicine. For his work during the first world war while in charge of the Special Hospital for Officers at Palace Green he was appointed O.B.E.

H. D. writes: "Caring little for sport in general, Woods was yet an enthusiastic follower and most capable exponent of boxing. Though never more than a lightweight, he successfully represented the London on at least one occasion in the middle-weight division of the inter-hospital competitions. A bachelor, of a singularly diffident and retiring nature, he devoted himself almost exclusively to the conduct of a large consulting practice, until the onset of his last illness in 1949 forced him to retire from active work."

JAMES AITKEN

M.B. Edin.

Dr. Aitken died on Oct. 2 at his home at Stanmore, where he had been in practice for over thirty years. He graduated in medicine at the University of Edinburgh in 1917, and he served in the 1914–18 war with the R.A.M.C. and in the late war with the R.A.F., where he rose to the rank of wing-commander.

S. H. writes: "Dr. Aitken was a man who exhibited the highest qualities which can be associated with a general practitioner, and after he settled at Stanmore he soon built up an excellent reputation. He was superintendent of the cottage hospital and one of its trustees, and under his guidance the hospital saw its best years. He felt a sense of personal loss when the exigencies of the National Health Service led to the conversion of the hospital into a home for the chronic sick. His death will be mourned by many, for he was entrenched deeply in the affections of all who knew him."

PHILIPP ELLINGER

M.D., D.Phil., F.R.I.C.

Dr. Ellinger, who died in London on Sept. 12, came from an old Jewish family that gave Germany several well-known scientists and prominent industrialists.

Born in Frankfort in 1887, he took his PH.D. in chemistry at Greifswald University before he began to study medicine at Munich and Heidelberg. At the pharmacological institute at Heidelberg he spent his most formative years as assistant, lecturer, "professor extraordinarius," and deputy director under Gottlieb, Wieland, and Heubner. In 1931 he was called to the professorial chair of pharmacology at the Medical Academy of Düsseldorf. Dismissed by the Nazis in 1933, he came to this country and in 1934 began work at the Lister Institute, where he was enabled to carry on his varied research projects until his retirement last June. To be free of administrative and teaching burdens suited him well, and in 1937 and 1938 he visited Egypt on behalf of the Medical Research Council to study pellagra and make therapeutic trials in pellagrins which seemed to be promising. Unfortunately, he fell ill during his second visit and he never entirely recovered his former robust physical health.

Ellinger's many contributions to physiology and pharmacology cover a wide field. His first papers dealt with carbon monoxide poisoning; but after a number of other studies in toxicology, he turned to physiology and he began to investigate renal function. The formation of urine, the site of acidification of urine, and the urinary excretion of chlorides in acromegaly were some of the problems he attacked successfully, using his own technique of intravitam microscopy. In this country he is best known for his work on the biosynthesis of nicotinic acid and nicotinamide in the human intestine, on deficiency following the administration of penicillin, and on the effect of liver poisons on the elimination of nicotinamide. In 1949 he was able to show that, in the mouse, high nicotinamide elimination was genetically controlled and probably due to a hereditary recessive character.

A colleague writes: "Ellinger's strength as a research-worker and investigator was based on his comprehensive knowledge of biology and its supporting sciences, which he combined with a lively interest in clinical medicine. Moreover, he had a special flair for the critical assessment of research methods. He not only found ways and means and designed apparatus for his own work, but ungrudgingly advised anyone who asked his help, on the possibilities as well as the difficulties and pitfalls of the way. His judgment of men and of affairs was always reliable: it was founded on an unbending belief in the high responsibility of the scientific worker. His opinion, often critical, but never unjust, was highly respected at the meetings of the physiological, biochemical, and pharmacological societies of which he was a member. He loved Britain and the British way of life and he was happy that his children could grow up in these islands. But it gave him great satisfaction when in 1950 the Düsseldorf Academy invited him to return to his professorial chair and, when he declined, made him an honorary member."

Dr. Ellinger is survived by his wife, one daughter, and two sons.

Appointments

Bolsover, G. D., B.M. Oxfd: appointed factory doctor, Eynsham, Oxfordshire.

Frew, J. F. M., M.B. Glasg., F.R.C.S.E.: consultant in orthopædic surgery, Northern Regional Hospital Board, Scotland.

Gerlis, L. M., M.B. Lond.: asst. pathologist, central laboratory, Grimsby General Hospital.

Hollis, P. W. T., M.B. Lond.: asst. director, mass-radiography units, Bristol.

Jermiah, D. E., M.B. Madras: asst. M.O.H. and asst. school M.O., Salford.

Lawy, H. S., M.D. Bagdad, L.M.S.S.A.: asst. pathologist, central laboratory, Grimsby General Hospital.

Mackenzie, R. M., M.B. Lond., D.A.: consultant in anæsthetics, Scarborough, Bridlington, Malton and Whitby H.M.C.

MacLeod, Mary, M.B. N.U.I.: asst. psychiatrist (S.H.M.O.), Naburn and Bootham Park Hospital, York.

Pleydell, M. J., M.D. Lond., D.P.H.: deputy M.O.H. and deputy school M.O., Northamptonshire.

Roberts, T. B. L., M.R.C.S., D.A.: anæsthetist, Maida Vale Hospital for Nervous Diseases, London.

Rosie, J. M., M.D. Glasg., D.P.M.: consultant psychiatrist and deputy medical superintendent, Craig Dunain Hospital, Inverness.

Trapps, N. C. B., M.R.C.S., D.A.: anæsthetist, Maida Vale Hospital for Nervous Diseases, London.

Yeates, W. Keith, M.D., M.S. Durh., F.R.C.S.: consultant surgeon (asst.), urological department, Newcastle General Hospital.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

Barrett.—On Oct. 6, to Phyllis Eileen (née Batchelor), wife of Dr. G. M. Barrett, of Lancaster—a son.

Henderson.—On Oct. 9, at Meadstead House, Royston, near Barnsley, to Winifred (née Hale), wife of Dr. James Henderson—a daughter.

Hirst.—On Oct. 7, at Oldham, to Dr. Stella Armitage (née Speight), wife of Dr. John Hirst—a daughter.

McMillan.—On Oct. 8, at Flore House, Northamptonshire, to Juliette, wife of Dr. James McMillan—a son.

O'Grady.—On Oct. 5, at the Middlesex Hospital, London, to Madeleine (née Becquart), wife of Dr. Francis O'Grady—a daughter.

Robinson.—On Oct. 9, at Warrington General Hospital, to Janet (née Callow), wife of Squadron-Leader K. F. Robinson, M.B.—a daughter.

Sinclair.—On Oct. 6, to Joyce, wife of Mr. S. R. Sinclair, F.R.C.S., 6, Adelaide Park, Belfast—a daughter.

MARRIAGES

Gibson—Galbraith.—On Oct. 11, in Glasgow, Eric Osborne Gibson, M.B., to Cynthia Graeme Dunlop Galbraith.

Yealland—Simpson.—On Oct. 4, Michael Yealland, M.R.C.P., to Susan Simpson, M.B.

DEATHS

Ashby.—On Oct. 9, at 3, Lancaster Road, Didsbury, Manchester, Hugh Tuke Ashby, M.D. Camb., F.R.C.P., aged 72.

Cogswell.—On Oct. 12, at Red Roofs, Sidmouth, Devon, Philip Dare Cogswell, M.R.C.S., late of *Bromley, Kent.*

Coombes.—On Oct. 7, at Croft Cottage, Horsebridge, Sussex, Percival Charles Coombes, M.R.C.S.

Finny.—On Oct. 10, at 41, Liverpool Road, Kingston Hill, Surrey, William Evelyn St. Lawrence Finny, M.D. Belf., M.CH. R.U.I., J.P., barrister-at-law, Inner Temple, high steward and honorary freeman of the royal borough of Kingston-upon-Thames, aged 88.

Hobbs.—On Oct. 8, at Benghazi, Anthony Arthur Hobbs, M.R.C.S., captain, R.A.M.C., aged 26.

Lawson.—On Oct. 8, at 12, Ovington Court, London, Frederick James Lawson, M.B. Lond.

Wade.—On Oct. 5, Richard Ramsden Wade, M.A., D.M. Oxfd, of The Little House, Hindhead.

Notes and News

RESEARCH AT THE R.C.S.

AFTER the monthly dinner of the Royal College of Surgeons of England on Oct. 8 visitors were able to explore the departments of anatomy, physiology, and pathology, and to see some of the demonstrations and exhibits that had been set out; but it was impossible to get round quickly enough to see all the work that is going on at the college and at the Buckston Browne Research Farm.

In the department of anatomy, Prof. Gilbert Causey explained some of his work on nerve-fibres; he had taken a number of medullated fibres, given them a sharp pinch, and then cut sections of them to see what had happened. Immediately after compression, longitudinal sections showed a complete break in the myelin sheath, but within a few hours the myelin began to "flow" back again across the gap. In transverse sections the normally sharp outline of the sheath was destroyed and its contents emulsified, only for the phases to separate out a little later. These observations on the fluid properties of nerve-fibres recall the Cartesian idea of a physical flow along the nerve—an idea which may be by no means out of date and which may yet fit in with what is known about electrical and chemical changes in the nerve-fibre to give a fuller explanation of the working of the neurone as a whole. Professor Causey also demonstrated the results of rat experiments designed to trace what is usually called the intracellular phosphorus. Autoradiographs of nerve and muscle showed that atoms of the radioactive isotope P^{32} were taken up in the sheaths of the fibres and did not actually enter the cell at all. Dr. Frank Stansfield had been thinking how unreliable some textbook statements really are: for instance, it is often said that the paranasal sinuses are of little importance in preserving the correct balance of the head, because if the maxillary antra were replaced by bone the weight of the head would only be increased by 1%. Dr. Stansfield has shrewdly knocked the bottom out of this argument by a delightfully simple experiment which would convince the most unmechanically minded. He fixed a dried skull on a stand and connected a spring balance between the occiput and a point on the table beneath; the spring represented the occipital muscles, and the balance measured the tension in them. He then filled the maxillary antra with a substance of the same density as bone, and the balance promptly recorded a considerable increase in the tension of the hypothetical muscles—as, of course, he knew it would from a consideration of the mechanical moment of the added weight about the fulcrum on which the skull turns. In this respect at least, the part played by the sinuses in keeping our heads from nodding cannot be so easily dismissed.

On the floor above, in Prof. Geoffrey Hadfield's department of pathology, Dr. L. M. Franks showed how animal experiments have suggested that the anterior chamber of the eye is a promising site for heterologous transplants of malignant tumours; some tumours have survived and shown active mitosis after 10 weeks. Clearly, great advantages will be gained if this method can be extended to become a means of preserving and studying human tumours.

Prof. David Slome and his colleagues in the department of physiology and the research-workers at the Buckston Browne Farm also exhibited some of their work. For example, Dr. W. J. Dempster talked about experimental transplantation of the kidney; and Dr. I. K. R. McMillan illustrated his investigations into the action of the cardiac valves with a colour film in which post-mortem specimens were used to demonstrate the mechanics of normal and diseased aortic valves and the effect of operations designed to relieve stenosis or regurgitation. During the dinner technicians had been installing in the basement Dr. D. G. Melrose's new apparatus for maintaining an extracorporeal circulation in man. This pump-oxygenator of increased efficiency promises to give important help to the cardiac surgeon. Dr. Melrose suggested that the most profitable way of using the apparatus might be to combine it with a means of lowering the body-temperature and consequently the metabolic-rate; for under these circumstances complete cardiac arrest can be tolerated for long periods and the scope of surgery is correspondingly increased.

At the dinner the President, Sir Cecil Wakeley, was able to report that the worries of steel shortage no longer threatened to delay the first stage of the plan for the restoration and extension of the college. The great hall, the three Wellcome museums, the council room, exhibition hall, and cloakrooms come in the first part of the programme. Sir Cecil was hopeful that the progress of the next stage, which includes the building of the Nuffield College of Surgical Sciences, would soon be equally assured. The guests at the dinner included some distinguished visitors from America, and Sir Cecil told of the generous hospitality that they and their colleagues had given him during his recent travels. His toast brought responses from Prof. Howard Naffziger (San Francisco), Prof. Everett Evans (Richmond, Virginia), and Mr. M. J. Petty, F.R.C.S. (Buenos Aires).

THE MIDWIVES

THE old Central Midwives Board retired on March 31 of this year, and on April 1 the new board took over. This change, an outcome of the Midwives Amendment Act, 1950, and the new Midwives Act of 1951, has increased the size of the board from 14 to 16, and gives members three years of office instead of one. Our midwifery service has a very high tradition, and a vast membership. On March 31 of this year, according to the last report of the old board,[1] there were nearly 55,000 trained midwives on the roll, though, of course, only about a third of these (17,512) actually notified their intention of practising. The board are no longer under a statutory obligation to publish the complete roll for external circulation, and the only roll now published contains the names of practising midwives. As time goes on, the numbers on the roll decline of those who trained before 1939 when the present training rules came into action. They now represent less than half the total of midwives in practice.

The board were still inconvenienced, at the time of publication, by the fact that the Ministry of Health and the associations of local authorities had not yet agreed on a national arrangement for paying for the second period of training of pupil midwives. In some second-period training-schools the whole six months is spent on the district, and in those cases the local authority pays their fees without question. Usually, however, three months is spent on the district and three in hospital; and the hospital and local authorities have to settle the responsibility between them. Arrangements differ in different areas; and this makes some authorities cautious about opening districts for training. Births at home are getting scarcer, so if midwives are to get enough domiciliary experience new districts must be opened to them. The board think it urgent that some common system of payment should be arranged; and meanwhile ask local authorities not to let purely financial considerations prevent them from making their districts available for training.

The search for the perfect analgesic for use by midwives goes on. A new joint subcommittee, consisting of members of the analgesia in midwifery committee of the Medical Research Council, and of the anæsthetics committee of the Royal College of Obstetricians and Gynæcologists, with Dr. Albertine Winner of the Ministry of Health as secretary, has been appointed to direct clinical trials of new models of trichlorethylene inhalers. The board are represented on this subcommittee by Mr. Arnold Walker, F.R.C.O.G., their chairman. Meanwhile, pupil midwives, working single-handed, are allowed, when the teaching midwife judges them to have reached such a standard of competence as to be safely trusted with the responsibility, to administer nitrous-oxide/air analgesia.

OPINION ON PRESCRIBING

IN the view of Prof. David Campbell, president of the General Medical Council, prescribing in the National Health Service should be confined to official drugs and preparations. In an inaugural address at the School of Pharmacy, University of London, on Oct. 8, Professor Campbell suggested that such a policy would not impair but would in fact enhance efficiency, and it would be less expensive to the community. The danger now, he declared, was excessive and inaccurate medication; and this danger was not lessened by persistent advertisement in the form of quasi-scientific and clinical dissertations which were showered so freely on the medical profession by various manufacturing drug firms, often of the same drug under half a dozen or so different proprietary names.

"Many years ago," said Professor Campbell,[2] "Sollman maintained that one of the clamant needs of the medical profession in America was for some authoritative statement as to how to discriminate between good and bad in drug advertisement. That led to the establishment by the American Medical Association of the Council on Pharmacy and Chemistry and the annual publication of 'New and Non-Official Remedies' which tries to give reliable information as to the action and uses of new drugs. It may be that the National Formulary and the deliberations of the Cohen Committee will help to solve the problem in this country. But I doubt it. Now that we are to have a quinquennial publication of the British Pharmacopœia with Addenda in the years between, I suggest that it is worth considering whether, save for experimental purposes, prescribing in the National Health Service should be confined to drugs and preparations made official in the Pharmacopœia."

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[1] Report of the Work of the Central Midwives Board for the year ended March 31, 1952. Published for the board by Spottiswoode Ballantyne & Co., 1, New Street Square, London, E.C.4. Pp. 26.

[2] *Pharm. J.* Oct. 11, 1952, p. 261.

GENERAL PRACTICE TEACHING UNIT

The Rockefeller Foundation has made a grant of £25,000 to the University of Edinburgh for developing its general practice teaching unit. This unit, described in our columns two years ago by Dr. Richard Scott,[1] was created by the faculty of medicine to train senior medical students in general practice. It is a modern development of the dispensary training which has been a characteristic feature of the Edinburgh medical school for more than 150 years. The grant will be used to develop new techniques of training students, and to study the technical and clinical problems peculiar to general practice.

SUPPLIES OF TERRAMYCIN

A limited supply of 20 mg. vials of pure terramycin for sensitivity tests will shortly be available to hospital laboratories. Requests should be sent to the regional distribution centres from which terramycin is now supplied.

University of Oxford

Prof. T. Pomfret Kilner has been appointed to carry on the duties of the Nuffield professorship of surgery during Michaelmas term.

Prof. Dorothy Russell will deliver a Litchfield lecture at the Radcliffe Infirmary, Oxford, on Wednesday, Oct. 29, at 5 P.M. Her subject is to be Disturbances of Hypothalamic Function in Man.

University of Cambridge

On Oct. 1 Sir Lionel Whitby, master of Downing College and regius professor of physic in the university, was admitted to his second year of office as vice-chancellor.

University of St. Andrews

On Oct. 10 the degree of M.D. with honours was conferred on J. W. Smith.

Royal College of Surgeons of England

At a meeting of the council on Oct. 9, with Sir Cecil Wakeley, the president, in the chair, Mr. R. C. Davenport and Mr. F. C. W. Capps were admitted to the court of examiners to examine in ophthalmology and otolaryngology respectively for the fellowship. Sir Charles Symonds and Prof. Harold Dew (Sydney) were appointed the Sir Arthur Sims Commonwealth travelling professors for 1953. The first James Berry prize was awarded to Mr. R. H. C. Robins for his essay on the Treatment and Preservation of the Injured Hand. Dr. B. D. Wyke was appointed senior lecturer in the department of physiology. A Leverhulme Research scholarship was awarded to Mr. A. E. Kark (Witwatersrand). Mr. Brian Greenwood (St. Thomas's Hospital) was admitted as a Macloghlin scholar.

A diploma of fellowship was granted to G. S. Pestell and a diploma of membership to J. H. Swallow. The following diplomas were granted, jointly with the Royal College of Physicians, to the following candidates:

D.Phys.Med.—P. J. R. Nichols, J. G. Parish, R. C. Robb.

D.T.M.&H.—Soroj Kanto Ally, Georges Belios, K. H. Blaauw, Jo Bonne, Matilda J. Clerk, D. F. Clyde, K. R. J. Coates, K. J. Covell, J. C. Crook, J. S. Davis, Somabhai Chhakaddas Desai, S. S. Epstein, Henry Foster, D. G. Garrow, Anthony Gerada, S. R. S. Godkin, E. G. Hardy, J. R. Harries, Monica M. Hogben, Benson Okeke Igwebe, Gillian F. Jacob, P. A. H. Jenniskens, Elizabeth E. Johnson, Perin Kaikobad Jungalwalla, Tawfik Karadshy, Muhammad Khalaf, Muhammad Naim Khan, Abdel Razag Mubarak, Noi Panikbutra, Upali Kirthisiri Perera, Bhagwat Prasad, Sudhir Kumar Roy, Francis Saliba, W. B. Scale, D. H. Shennan, Shurvir Singh, A. W. Stinton, D. A. T. Tizard, R. A. R. Topping, Prasong Tuchinda, C. J. Xuereb.

D.C.H.—L. M. Armstrong, Harry Buckstein, J. F. J. Collins, June P. Cooper, Winifred Danaraj, B. M. Davies, Pamela Deas, G. L. de Silva, J. A. C. de Silva, Norman Feldman, Nellie P. Fernando, P. T. A. P. Fernando, Joan Ford, Yvette A. P. Franklin, O. P. Gray, Ruth F. Harris, W. L. F. Hatchuel, Frances M. Hill, Mary A. le C. Hills, Chandra Hooja, Pamela J. Houchin, W. W. Jones, Margaret Kennedy, Barbara Kilpatrick, C. W. Lankester, I. C. Lewis, Toan Keng Lim, Sampath Loganadan, Sudhindra Kumar Majumdar, Patricia A. Monk, E. A. Nieman, Olwyn K. Ockelford, D. J. A. L. Panditharatne, Dina Patuck, G. J. V. Perera, P. L. Pickering, Barbara M. Philpott, Quah Quee Guan, T. A. I. Rees, Frances L. J. Robinson, Pauline M. Seymour-Cole, Katherine A. H. Smith, Cheruvamky Srinivasan, June Stephenson, Gwendolyn R. Tapp, Frank Taylor, Nicolaas Van der Merwe.

D.I.H.—K. M. Basu, A. T. Halliday.

Yorkshire Association of Graduates of Glasgow University

The first post-war dinner of this association will be held in the Great Northern Hotel, Leeds, on Friday, Oct. 31, at 7.30 P.M., when Professor J. D. MacKie, LL.D., is to be the guest of honour. Further information may be had from the hon. secretary of the association, Dr. William MacAdam, 24, Park Square, Leeds.

Back Payments to General Practitioners

The Ministry of Health has asked executive councils "to make every endeavour to pay" on Nov. 28 the amounts of back remuneration due to doctors under the Danckwerts award (E.C.L. 77/52). Payment to doctors no longer on a council's list may be delayed, but it is hoped that all payments will be completed by March 31, 1953.

Charing Cross Hospital

At the annual prize-giving of the medical school on Oct. 10, Lord Inman, chairman of the board of governors, announced that the hospital had now signed the contract for its new site at Northwick Park, Harrow. The site had 47 acres, of which 34 were to be for the hospital and 13 for the medical school. "The plans are all ready," he continued, "and we hope it will not be long before the economic condition of the country will allow us to make a start on this great scheme for a new Charing Cross Hospital and its Medical School."

W.H.O. Regional Committee for Europe

This committee, which met in Lisbon on Sept. 25–27, has agreed that the main tasks in the next four years should be: (1) coördination of health policies and exchange of experience between national health administrations; (2) studies of existing health patterns and problems; and (3) an increase in the number of trained personnel in all categories of public-health work. The committee was informed of a "massive decrease" of venereal infection among the 80,000 boatmen on the Rhine River. The regional committee will hold its third session in Copenhagen in September, 1953. The regional office is to be provisionally maintained at Geneva for at least eleven months.

London Hospital Dinner

Sir John Parkinson, presiding over the old students' dinner on Oct. 9, began by speaking of some of the former Londoners who had died during the year—Hugh Cairns, Leonard Hill, Millais Culpin, H. E. Roaf, Garnett Passe, and Gordon Wilson. By retirement the hospital was regretfully losing S. P. Bedson and John Marrack, in whose chairs he welcomed C. F. Barwell and F. L. Warren. W. J. O'Donovan, who had achieved the seemingly impossible by proving himself as great a teacher as his predecessor Sequeira, had in turn been succeeded by Brian Russell; and other new appointments were those of S. D. K. Stride as assistant anæsthetist, and J. V. Crawford as assistant surgeon. Whether a hospital was governed by a house-committee or a board of governors, said Sir John, its essential workers were the doctors, who had been in existence before there was any kind of organisation and would outlast any of them. The reputation of the London was being extended not only by its teachers but also by the men in practice who take pride in their work and honour it by what they do. His own debt to the hospital could never be repaid: his pride in it was unbounded, and it had been to him a real and happy medical home. Sir Alun Rowlands, proposing The Chairman, conducted his hero from pastoral Lancashire (with side glances at the Universities of Liverpool on his right and Manchester on his left) via Bletchley (where he refrained from changing for Oxford or Cambridge), to Euston and so to University College. Continuing, after a year, his quest for the best of its kind, the young John Parkinson eventually reached the London Hospital, and proceeded to fulfil his early promise not only as a physician and leader in cardiology but incidentally as a painter in water-colours and a gardener of distinction. If, like the best novels, Sir Alun's narrative contained one or two extraneous characters and cheerful interpolations, these did not obscure the sincerity of his tribute. And both his respect and his friendship for the chairman were equally manifest in his audience.

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[1] *Lancet*, 1950, ii, 695.

Lloyd Roberts Lecture

Mr. Bernard Darwin will deliver the Lloyd Roberts Lecture at the Royal Society of Medicine, 1, Wimpole Street, W.1, on Wednesday, Oct. 29, at 8.30 P.M. He will speak on Dickens's Doctors.

Christian Medical Fellowship

Sir Henry Holland will deliver a lecture to this fellowship on Wednesday, Oct. 22, at 8.15 P.M., at the Royal Empire Society, Northumberland Avenue, London, W.C.2. His title of his address is to be The Doctor—has he a Faith ?

Epsom and Sutton Inter-Hospital Psychiatric Association

This association will hold a meeting at Banstead Hospital, Sutton, on Thursday, Oct. 23, at 8 P.M. The programme of papers and clinical demonstrations will be preceded by the election of officers for 1952–53.

London Medical Exhibition

The exhibition will take place this year at the new hall of the Royal Horticultural Society, Greycoat Street, S.W.1, from Nov. 17 to 21, from 11.30 A.M. to 6.30 P.M. Sir Cecil Wakeley, P.R.C.S., will open the exhibition at noon on Nov. 17.

Presentation to Sir William Hume

On Oct. 7, past and present members of the medical staff of the Royal Victoria Infirmary, Newcastle upon Tyne, entertained Sir William Hume to dinner in honour of the knighthood conferred upon him. In presenting Sir William with a television set, Dr. S. Whately Davidson, chairman of the medical board of the hospital, said the company wished to express their continued and growing affection for one who during the past 50 years had been a "father" to so many of those present. "But for the great opportunities which Sir William gave us to obtain a wide experience and develop a sense of responsibility, by seeing and doing things for ourselves, I doubt whether many of us would be where we are today."

King's College Hospital

At the opening of the 123rd session of the medical school on Oct. 3, Mr. St. J. D. Buxton presided, and the inaugural address was given by Dr. F. M. R. Walshe, F.R.S. In presenting his report, Dr. V. F. Hall, the dean, said that a scheme of interchanges had been introduced by which senior registrars will receive part of their experience at regional board hospitals with the object of widening the experience of the future consultant. The requirement under the Medical Act, 1950, that house-appointments must be held for a year before registration would not mean any great change at King's, where it had been the custom for many years for most students to hold resident posts. It was possible that in its early stages the machinery of the new Act might produce delays and difficulties which would involve the individual in hardship, but he had no doubt that the scheme itself was excellent. A number of rooms in the hospital would soon be converted into research laboratories, and Dr. Hall hoped that by next October this new research unit would be in full activity. In addition the school had already equipped a room as a neurohistological and gynæcological research laboratory. A new joint hospital and medical school research committee had been established to examine all new research proposals, and both the hospital and the school had made available some additional funds for research. The several benefactions the school had received during the year included £35,000 from the estate of Surgeon Captain A. D. Cowburn, lately H.M. Coroner for the Southern District of the County of London. This was for research in pathology, bacteriology, morbid anatomy, and allied subjects.

CORRIGENDA: *Prolongation of Action of Hypotensive Drugs.*—In Prof. F. H. Smirk's article last week (p. 695) fig. 4 was intended to show that the 8% M. & B. 1863 in 20% dextran solution with 1/2000 ephedrine prolonged the hypotension as compared with the 5% solution of M. & B. 1863 alone. The lettering on the two arrows at the top of the figure should be interchanged.

Streptomycin—P.A.S. Hypersensitivity.—The article by Dr. Kenneth Marsh in our issue of Sept. 27 (p. 606) contained a report of a sternal marrow biopsy; this report was by Dr. A. P. Peeney.

Progress in Clinical Medicine.—The price of the second edition of this book by Dr. Raymond Daley and Dr. Henry Miller, which was given incorrectly in our review (Oct. 11, p. 716), is 30*s*.

Diary of the Week

OCT. 19 TO 25

Monday, 20th

ROYAL COLLEGE OF SURGEONS, *Lincoln's Inn Fields, W.C.2*
3.45 P.M. Mr. P. H. Mitchiner: The Breast.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Dr. L. I. Woolf: Inborn Errors of Metabolism in Animal and Child.

HUNTERIAN SOCIETY
7 P.M. (Talbot Restaurant, 64, London Wall, E.C.2.) Dr. Basil Parsons-Smith: Cardiology—Old and New. (Presidential address.)

Tuesday, 21st

ROYAL COLLEGE OF SURGEONS
3.45 P.M. Dr. L. W. Proger: Blood Vascular Diseases.
5 P.M. Mr. K. W. Starr: Acute Postoperative Dilatation of Stomach. (Hunterian lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) *Prof. C. G. Douglas*, F.R.S.: *Control of Respiration.*

INSTITUTE OF DERMATOLOGY, *St. John's Hospital, Lisle Street, W.C.2*
5.30 P.M. Dr. J. P. O'Brien: Prickly Heat and Allied Disturbances *of Sweat Secretion.*

WEST END HOSPITAL FOR NERVOUS DISEASES, 73, Welbeck Street, W.1
5.30 P.M. Dr. Colin Edwards: Neurological demonstration.

EUGENICS SOCIETY
5.30 P.M. (Burlington House, Piccadilly, W.1.) Mrs. Margaret Pyke, Dr. H. A. Davidson: Family Planning.

SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Dr. John Yerbury Dent: Possibilities of Apomorphine in Treatment of Drug Addiction.

SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P.M. (Bolingbroke Hospital, Wandsworth Common.) Sir Arthur Porritt: Sport Injuries.

Wednesday, 22nd

INSTITUTE OF DERMATOLOGY
5.30 P.M. [illegible] Technique.

INSTITUTE [illegible]
3 P.M. [illegible] Road, W.12.) Prof. [illegible] In [illegible] ollowing Ultra-radical Surgery.

MIDLAND MEDICAL SOCIETY
8.15 P.M. Sir Allen Dal [illegible] Today.

SCOTTISH SOCIETY OF THE [illegible]
4 P.M. (Royal College o [illegible] Symposium on Plague.

Thursday, 23rd

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. H. F. Lunn: High Ligation of Neck of Sac in Inguinal Hernia. (Arris and Gale lecture.)

UNIVERSITY COLLEGE
5.30 P.M. Sir Geoffre [illegible] Prodromes to Cortical Localisation. [illegible] re.)

BRITISH POSTGRADUATE [illegible]
5.30 P.M. Prof. D. Keilin, F.R.S.: Metal Catalysis and Intracellular Respiration.

ROYAL SOCIETY OF MEDICINE
8 P.M. *Section of Urology.* Mr. J. G. Yates Bell: Hydronephrosis. (Presidential address.)

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. J. Hamilton Paterson: Neurological lecture-[illegible]

[illegible] IETY
[illegible] of Manchester.) *Section of Anæsthetics.* [illegible]: *Recollections not Confessions.* (Presidential address.)

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Dr. W. S. Shearer: *Radiographic Features of General* [illegible] the Skeleton.

[illegible] DREWS
[illegible] *hool, Small's Wynd,* Dundee.) Prof. J. C. [illegible] of Growth of Bones.

Friday, 24th

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. P. W. Brand: Reconstruction of the Hand in Leprosy. (Hunterian lecture.)

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Obstetrics and Gynæcology.* Mr. A. C. Palmer: Changing Practice in Obstetrics and Gynæcology. (Presidential address.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. W. Barber: Clinical demonstration.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION
8.30 P.M. (Royal Free Hospital School of Medicine, 8, Hunter Street, W.C.1.) Mr. Justice McNair: Organisation of the Law.

Saturday, 25th

CAMBRIDGE UNIVERSITY
10.30 A.M. (Addenbrooke's *Hospital.*) Postgraduate symposium on nervous diseases.

HEBERDEN SOCIETY
10 A.M. (B.M.A. House, *Tavistock Square,* W.C.1.) Lord Horder: Rheumatism—a National Problem. (Heberden oration.)

THE CAUSE AND TREATMENT OF LEG ULCERS *

S. T. ANNING
M.A., M.D. Camb., M.R.C.P.
ASSISTANT PHYSICIAN, DERMATOLOGICAL DEPARTMENT, THE GENERAL INFIRMARY AT LEEDS

LEG ulcers are common in this country, especially among women, and cause much pain and grave disability. Although sometimes the result of chilblains, tuberculosis, syphilis, or other conditions, they are more often caused by disease of the circulation, and it is this kind that I shall consider here.

My review will incorporate the results of personal observation of 715 patients (496 women and 219 men) suffering from the kind of ulcer which usually affects the lower third of the leg and is variously known as varicose, stasis, or gravitational.

The common leg ulcer is associated with chronic œdema, induration, sclerosis, and pigmentation; loss of hair and eczema of the leg are also often present. Varicose veins may or may not be found. These signs are evidence of a defective venous return of blood from the leg, and this has long been recognised.

HISTORICAL SURVEY

Hippocrates noted the association of varicose veins and leg ulcers (Adams 1849); but, until Harvey (1628) demonstrated the circulation of the blood, and for some time after, it was thought that ulcers were caused by humours. Derived probably from the humoral theory was the idea of menstrual ulcers: according to Ambroise Paré in 1579 (Johnson 1678), menstrual blood collected in the legs during pregnancy and became stagnant, causing ulceration; and even in the first half of last century Sir Astley Cooper (1837) and Critchett (1848) wrote of menstrual ulcers related to amenorrhœa from any cause. The idea that ulcers are caused by stagnation of blood in the leg seems to have persisted in the concept of venous stasis.

However, Harvey's discovery did have some effect on the views held about leg ulcers. Wiseman in 1676 wrote about venous thrombosis, the dilatation of veins, and the results of these conditions on the valves; he seems to have been the first to consider that ulcers might be the direct result of a circulatory defect.

Most of the 18th-century writers on the subject, such as Underwood (1783), Bell (1779), Baynton (1799), and Whately (1799), do not refer to varicose veins as a cause. But a new idea was growing: "the Indisposition of these Sores is in some measure owing to the Gravitation of the Humours downwards" wrote Sharp (1758): and Baynton (1799) declared that the disease arises "from the unfavourable situation of the parts which are placed at a remote distance in the human machine from the fountains of life and heat, and are obliged to return the venous blood and lymph to the heart under some peculiarly unfavourable and disadvantageous circumstances."

In the view of these 18th-century writers a leg ulcer followed a wound which failed to heal because of the erect posture and the resultant œdema. Everard Home (1801) believed that an ulcer was more difficult to heal if there were varicose veins, and Hodgson (1815) wrote of ulcers "which are generally situated near the ankle and are remarkably intractable. They appear to depend upon the varicose condition of the veins, for when the latter is relieved, the ulcers are as readily cured as ulcers in general." Other writers of last century (Brodie 1846, Chapman 1853, 1864, Astley Cooper 1837, Hunt 1859, Hilton 1861, Critchett 1848, and several more) placed the emphasis on varicose veins as the important cause, and the term "varicose ulcer," scarcely used since Wiseman (1676), became established.

Gay and Spender, two authors of outstanding books, both published in 1868, went much further: they thought that venous thrombosis also played a part. Indeed, Gay denied the validity of the doctrine of the varicose ulcer and believed, like Chapman (1853), that the term should be discarded.

Although Verneuil (1855a and b), in France, had made careful observations and dissections, Gay's work seems to have been the first scientific investigation of these conditions in this country. He pointed out, as did Nunn (1852), that severe varicosity may exist without ulceration—a useful observation neglected until recently (Lockhart-Mummery and Smitham 1951). He further noted that with superficial varicosity there may be other serious lesions affecting both arteries and veins, deep and superficial, which cannot be ignored, and he concluded that

> "ulceration is not a direct consequence of varicosity, but of other conditions of the venous system with which varicosity is not unfrequently a complication, but without which neither one of the allied skin affections [induration and bronzing] is met with, conditions which involve obstruction of the trunk veins, deep and superficial, either from impediments on the venous side, or incompetency on the arterial, or from both causes combined."

He introduced the term "venous ulcer" and was the first to describe the "arterial ulcer" caused by obliterative disease of the walls of arteries.

Since the time of Gay there has been little advance in our knowledge of these conditions. Many surgeons have remained obsessed with the primary ætiological importance of varicose veins and have directed their attention to injecting, tying, removing, or scarifying them. From the modern surgical textbook we learn little about the cause of ulcers, though the authors often write at length about the treatment of varicose veins. Dickson Wright (1930) did a great service when he redirected our attention to the essential problem, that of hydraulics. Bauer (1942, 1948, 1950a and b), Birger (1947), Haxthausen (1932, 1937), and other Scandinavians have done valuable work on the ætiology of these ulcers, and many American investigators have added to our knowledge of venous thrombosis and venous pressure.

What then is the present position?

NORMAL BLOOD-FLOW IN LOWER LIMB

The adoption of the upright posture was a great evolutionary advance, but man has had to pay dearly for the privilege of being two-legged. To return the blood from the lower part of the legs to the heart requires it to be raised about twice the height formerly necessary. How is this return accomplished?

> "In some parts of the body, the force of gravitation returns the blood to the heart; and it might seem, that elsewhere, as in the legs, the downward pressure of an arterial column serves to weigh against the inert column in the corresponding veins."

Thus wrote King (1837), and this conception of the hydrostatics of the lower limb is similar to that of Bauer (1950a). The vascular system of the lower limb, Bauer says, may be thought of as part of a large U-tube: if blood is introduced into one side of this U-tube, as happens each time the heart pumps blood into the aorta, an equal amount should flow out of the other end, from the vena cava into the right side of the heart, irrespective of the position of the body. Unfortunately for this analogy, however, the human U-tube does not have rigid or impermeable walls of glass or metal, and there

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* An address delivered before the Leeds and West Riding Medico-Chirurgical Society, on March 22, 1952.

are loops across the tube joining the two sides. If the capillary resistance is increased, or if there is any obstruction in the arterial or venous part of the most distal loop of the hypothetical U-tube—i.e., that in the lower limb—the flow there may be greatly reduced, though increased in more proximal loops. It is true that the venous pressure in the foot, when the person is standing at attention, is about equal to the weight of a column of blood extending from the point of measurement to the heart, with the addition of the capillary pressure present in the prone position which constitutes the vis a tergo. But many factors affect the venous pressure, as is shown in fig. 1, adapted from Landis and Hortenstine (1950).

The essential point is that, to maintain a satisfactory return of blood from the lower part of the legs in the erect posture, relay pumping is required to force the blood up to the heart. This is done effectively by the squeezing action of the calf muscles, together with the valves in the veins, especially in the deep veins of the calves and thighs, which prevent a reflux down the legs when the muscles relax.

Harvey (1628) described how the blood "is squeez'd out of the capillar veins into the little branches, and from thence into the greater, by the motion of the members and muscles." This was appreciated by Lower (1669), who wrote: "The blood is only driven upwards from the lowest part of the body with difficulty through the impulse of the arterial blood, and at times by the contraction of the muscles in exercise." Wiseman (1676) described the pumping action of the leg mucles aided by the venous valves, and King (1837) recognised its importance in driving the venous blood towards the heart; but until recently it has attracted little interest.

It was demonstrated by Carrier and Rehberg (1923) that even slight involuntary movements reduced the venous pressure in the dependent leg, and Warren et al. (1949) showed that, on walking, the pressure in the saphenous veins of normal people falls considerably. Other workers have found a similar fall of pressure in the leg (e.g., Smirk 1936, Pollack and Wood 1949, Hojensgard and Stürup 1949). It has been confirmed by Walker (1950), who found that the venous pressure in the foot in normal erect people standing still is 70–100 mm. Hg (100–140 cm. water), depending solely on the person's height, but falls to 0–30 mm. Hg (0–40 cm. water) on exercising the legs.

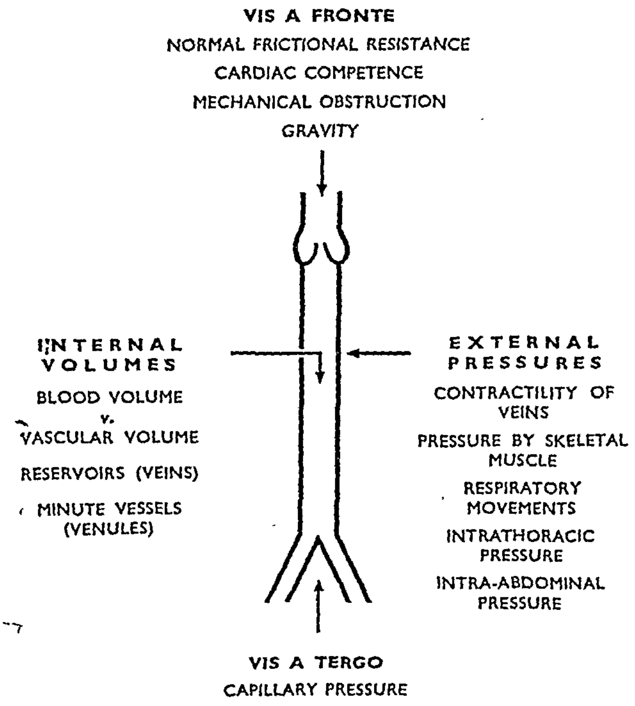

Fig. 1—Factors concerned in maintenance of venous blood-pressure (after Landis and Hortenstine 1950).

So effective is the leg muscle pump that in normal people there is no continued rise in venous pressure unless they stand for a long time in one position.

Some assistance to the return of blood to the heart may also be given, during inspiration, by the negative pressure in the thorax and the compression of the iliac veins by the increased pressure in the lower abdomen (Warwick 1931; cf. Franklin 1937).

CAUSES OF FAILURE OF LEG MUSCLE PUMP

Venous Thrombosis

Thrombosis may start in the veins of the foot or of the calf and spread upwards into the deep veins of the thigh. Some workers believe that it is useful to distinguish between phlebothrombosis, in which the thrombus is readily detached causing embolism, and thrombophlebitis with a primary inflammatory lesion in the vein (Ochsner 1946). Venous thrombosis of either type is more likely to develop in people with varicose veins or who have inherited a tendency to varicose veins (Anning 1950); in those lying at rest for some days, during which the blood-flow in the leg veins may be slowed; in conditions where the wall of the vein is injured; and where there is local infection. Thus we find thrombosis after childbirth (especially with pelvic infection), after certain illnesses—e.g., typhoid fever and pneumonia—after operations (particularly in the lower abdomen and pelvis), and after injury. The wall of a vein may be damaged by comparatively slight injury to the leg or by fracture, by operations on the leg, or by the injection of sclerosing solutions, which may pass from the superficial to the deep veins. Occasionally thrombosis occurs for no apparent reason (DeCamp et al. 1952).

According to Bauer (1942), a much greater quantity of blood normally passes through the deep veins than through the superficial. Because of the obstruction caused by thrombosis in the deep veins, a fresh route must be found for blood passing from the foot and leg to the abdominal veins. An enormously increased amount therefore flows through the superficial veins, which become dilated and may later become varicose. Varicosity following thrombosis is usefully described as secondary, and Curtis and Helms (1947) regard it as the commonest type.

Incompetence of Deep Valves

The valves of the deep veins may be absent, dilated, or destroyed. Congenital absence of valves in the deep veins has been described (Eger and Casper 1943, Curtis and Helms 1947), and the number of valves proximal to the saphenofemoral junction is often inconstant in adults.

Incompetence of the valves may result from dilatation of the vein. The tendency to varicosity may be inherited as a dominant character (Anning 1950), and in affected families dilatation of leg veins or hæmorrhoidal veins or veins elsewhere may appear after various periods of increased intravenous pressure, as produced in the leg veins by raised abdominal pressure from straining or coughing or by standing still at work—e.g., "standing too much before kings" (Marianus Sanctus Barolitanus 1555). Pregnancy is an important cause of this primary type of venous dilatation. These causes of varicosity of superficial veins are well recognised, but it is not always appreciated that the deep veins may also be dilated, although this was described by Verneuil (1855a and b) and Gay (1868), and has lately been demonstrated phlebographically by Moore (1951).

Destruction of the venous valves follows thrombosis, and recanalisation of the vein produces an irregular valveless tube (Homans 1917, Edwards and Edwards 1937, Bauer 1948).

Lack of Muscular Contraction

With long standing in one position, or with arthritis affecting the knees or ankles, contraction of the calf muscles may be so weak or intermittent that the leg muscle pump may fail.

RESULTS OF INEFFICIENCY OF LEG MUSCLE PUMP

If the leg muscle pump is inefficient and the venous return from the lower limb is consequently defective, the result will be œdema of the limb, and eventually pigmentation, induration, and ulceration. Where there is varicosity of the leg but the valves in communicating and deep veins are efficient, œdema does not develop more rapidly than in a normal leg, but the rate is significantly increased when these valves are incompetent (Holling et al. 1938).

It is worth consideration that in cardiac œdema, renal œdema, and œdema caused by lymphatic obstruction the complications just mentioned do not arise unless venous thrombosis or one of the other causes of venous insufficiency is also present.

In cardiac œdema the limb is pale and soft and pits readily. Acupuncture does not cause ulceration as it would certainly do in a leg with chronic venous insufficiency. The same remarks are true of chronic œdema from renal disease, the nephrotic syndrome. Furthermore, in the firm pale non-pitting œdema of the leg with lymphatic obstruction ulceration does not occur.

The reason for this difference between chronic venous insufficiency and these other conditions seems to lie in the venous and capillary pressures. In cardiac œdema the venous pressure is raised but the right auricular pressure is only, at most, 30 cm. water above the normal, and the valves in the deep veins protect the lower limbs against this rise except during systole of the leg muscle pump. Cardiac œdema is not caused by the rise in venous pressure but by reduced renal blood-flow with retention of salt and water (Brod and Fejfar 1950).

In chronic renal disease with œdema the venous and capillary pressures are not raised and œdema results from the reduction in the osmotic pressure of the blood owing to loss of serum-protein.

In lymphatic œdema too there is no rise in venous or capillary pressure. Fluid is retained in the tissues by lymphatic blockage and by the high protein content of the tissue fluid.

In chronic venous insufficiency, on the other hand, the venous, and therefore the capillary, pressure is greatly increased. During exercise the venous pressure in the foot is 50–110 mm. Hg (70–150 cm. water) instead of the normal 0–30 mm. Hg (0–40 cm. water) (Walker 1950). As a result there is considerable capillary damage with loss of fluid containing protein and red blood-cells (Massell and Kraus 1950). This fluid becomes organised with firm induration of the limb. Because of the capillary damage metabolic exchange is impaired and capillary thrombosis may take place, followed by necrosis. This, or failure of the tissues to heal after injury, produces ulceration, which is more common where the tissues are indurated. The area of induration may be localised, and through it a dilated superficial vein, left as a soft channel, may pass. Such an area may result from low-grade inflammation of the subcutaneous tissue, probably related to thrombosis of small superficial veins. When chronic venous insufficiency has been present untreated for a long time, lymphatic obstruction is probably also present.

The results of failure of the leg muscle pump are similar whatever the cause. Ulceration and other changes following venous thrombosis in the lower limb cannot be distinguished clinically from those caused by incompetent valves in the deep veins, whatever the reason. This view is also held by Lockhart-Mummery and Smitham (1951).

It will be noted that no mention has been made of venous stasis. Blalock (1929) found that, in patients with varicose veins of only one of the lower limbs, the oxygen content of blood from the femoral or from the saphenous veins was higher on the affected side. Moreover Holling et al. (1938) found no difference between the oxygen tension in the blood from normal leg veins, simple varicose veins, and varicose veins with ulceration. However, if an arteriovenous shunt is present in the leg after venous thrombosis, as demonstrated arteriographically by Brewer (1950), estimations of the oxygen content of venous blood from the leg may be misleading. Even so, Haxthausen's investigations on the temperature of ulcerated legs (1932) and on the circulation of dyes injected into varicose veins (1937) suggest that venous stasis is absent or unimportant—a conclusion also reached by Abramson and Fierst (1942) using plethysmographic methods.

Probably high venous pressure and the resulting capillary changes, and not venous stasis, are the essential causes of these leg ulcers. Although the rate of blood-flow through the lower limb may be reduced by failure of the leg muscle pump, and although the flow through dilated veins may be slow, tissue metabolism can only be affected by the capillary circulation and not by venous stasis, even were it present.

To sum up, chronic venous insufficiency may be brought about by thrombosis in the deep veins, with or without recanalisation; by primary varicosity of the deep veins usually accompanied by incompetent perforating veins and superficial varicose veins, causing true "varicose ulcers"; and by lack of muscular contraction, as with arthritis of the knees or ankles, or a job which involves standing. Often there is a combination of these causes, and in addition there may be arterial disease affecting the capillary blood-flow.

ARTERIAL DISEASE

Gay (1868) and Heller (1943) regarded arterial disease as an important cause of some chronic leg ulcers. Ulceration from arteriolar occlusion with hypertension was described by Martorell (1945) and Hines and Farber (1946). Arteriosclerosis obliterans (affecting larger vessels), with or without hypertension, may also cause ulceration (Shapiro and Nomland 1950), and it was this condition that Gay called "arterial ulcer."

Martorell (1945, 1950, 1951) has described "hypertensive ulcers" on the supramalleolar region, usually on the anterolateral aspect at about the junction of the middle and lower thirds of the leg. Ulceration is often bilateral and symmetrical. There is much pain which is not relieved by rest in bed. Œdema and other signs of disturbance of the venous circulation are absent. As there is usually no occlusion of the main arteries, pulsation may be felt in the lower limb. Histologically, obliterative changes similar to those found elsewhere in hypertensive people are found in the small arterioles of the legs. These ulcers are uncommon but are found more often in women than in men. Improvement is said to follow sympathectomy.

CLINICAL OBSERVATIONS

Fig. 2 shows the main cause of ulceration in 715 patients examined personally. In 15 patients venous thrombosis developed on two occasions from different causes. Hence, though 569 patients (79·6%) had post-thrombotic ulcers, thrombosis is shown in the figure of 584 ulcers. The large number of patients who had had either post-partum thrombosis (28·8% of the women) or traumatic thrombosis will be noted. As regards the non-thrombotic ulcers, 51 (7·1%) patients had true varicose ulcers, 8

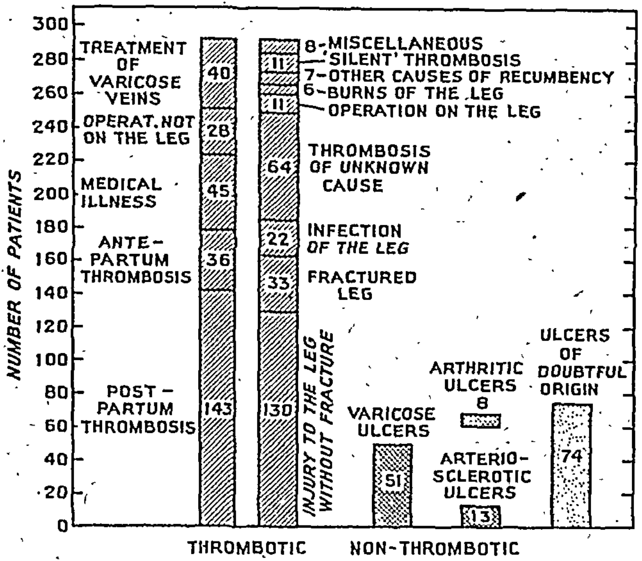

Fig. 2—Causes of leg ulcers in 715 patients.

(1·1%) had ulcers from arthritis alone, and in 74 (10·4%) the cause of venous insufficiency was doubtful. There were 13 patients (1·8%), 11 women and 2 men, with ulcers of the arterial type and hypertension: 3 of them had diabetes mellitus; 9 showed signs of arteriosclerosis obliterans, and 4 of these had calcification of large arteries shown radiologically; and 4 patients, all women, had gross hypertension and ulcers of the type described by Martorell (1945). In all 13 of these patients the feet were very cold.

HYPERTENSION

Besides the group of patients with arterial or hypertensive ulcers, a large proportion of those with post-thrombotic and varicose ulcers had hypertension (figs. 3 and 4). Comparison of 172 women patients with a large unselected group of American women showed that the proportion of ulcer patients with hypertension is significantly higher than in the control group (Anning 1949). Unfortunately no standard figures for blood-pressure readings of the English population seem to exist.

The relation between hypertension and ulceration from defective venous circulation is obscure. Kulwin and Hines (1950a and b) showed that, in patients with chronic venous insufficiency, there were hypertrophic and degenerative changes in the arterioles and venules of the lower limbs—sometimes in the absence of hypertension and in skin that appeared normal. These changes are similar to those reported by Gonin (1950) in patches of "white atrophy" of skin near the ankles, which patches often break down to form small painful ulcers resembling, apparently, those described by Corlette (1927). "White atrophy" usually appears in association with chronic venous insufficiency; it has been described by Critchett (1848) and Milian (1936).

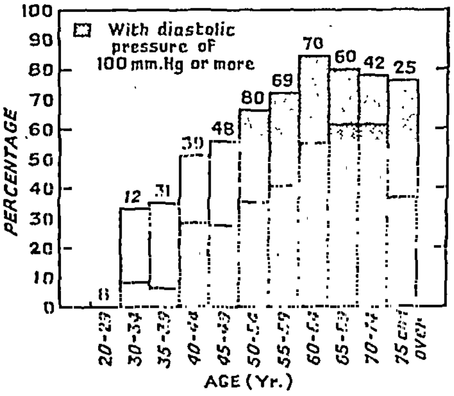

Fig. 3—Incidence of hypertension (diastolic blood-pressure 90 mm. Hg or more) in 484 women with leg ulcers. Numerals above histograms denote numbers of patients.

The cause of these arteriolar changes in the lower limbs of patients with chronic venous insufficiency is not known. It seems unlikely that they are merely secondary to arterial hypertension, because the changes were present in some of the patients of Kulwin and Hines (1950a and b) in the absence of raised blood-pressure. Is it possible that they are secondary to the rise in venous and capillary pressure? Furthermore, is it possible that the rise in blood-pressure found in so many patients with post-thrombotic and varicose ulcers may be secondary to the arteriolar changes in the lower limbs and to the resulting rise in peripheral resistance? Were this so, a relation might be expected between the duration of the venous defect (accurately determined when there is a history of venous thrombosis) and the blood-pressure. In the present series no such relation was found.

It is, of course, possible that hypertension and the presence of deep varicose veins or the predisposition to venous thrombosis might occur in the same families, but this seems unlikely. In the present series there is no relationship between hypertension and body-weight. Many of the lighter patients had a raised blood-pressure.

Perhaps hypertension with arteriolar changes is a coincidental finding which, in patients with a defective venous return from the lower limb, predisposes to ulceration.

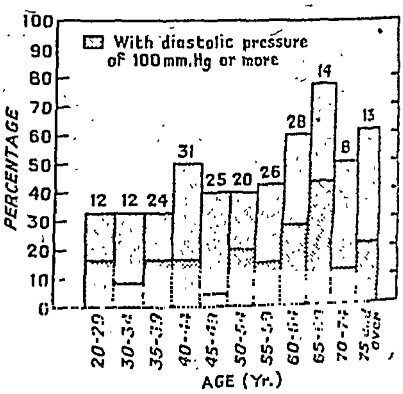

Fig. 4—Incidence of hypertension (diastolic blood-pressure 90 mm. Hg or more) in 213 men with leg ulcers. Numerals above histograms denote numbers of patients.

OBESITY

Of the 715 patients 684 (472 women and 212 men) were weighed. Though a small proportion were extremely heavy, 67% of the women and 64% of the men weighed 79 kg. (174 lb.) or less (fig. 5). Obesity, if present, seems to play a part in this condition but not a primary one, and weight reduction aids the healing of ulcers in heavy people. Thrombosis, according to Barker et al. (1941), occurs twice as often in those who weigh more than 91 kg. (200 lb.).

OCCUPATION

As regards occupation, 309 (62·3%) of the 496 women, being housewives, were on their feet most of the day, and of the remainder 148 (29·8%) stood at work in their employment as shopkeepers, as weavers, or otherwise. Only 24 (1%) of the 219 men had sedentary occupations.

TREATMENT

The prevention of ulceration is worth consideration, and here the prevention of venous thrombosis is clearly of paramount importance. I shall do no more than mention here the value of leg exercises in recumbent patients, especially when the limbs have been compressed from toes to groins (Ochsner 1947), and the postoperative use of anticoagulant substances in small dosage (Allen et al. 1947).

Chapman (1864) noted "the greater risk of Phlegmasia Dolens occurring in women who suffer much from varix during pregnancy." From a study of heredity in these conditions it can be said that where thrombosis is apt

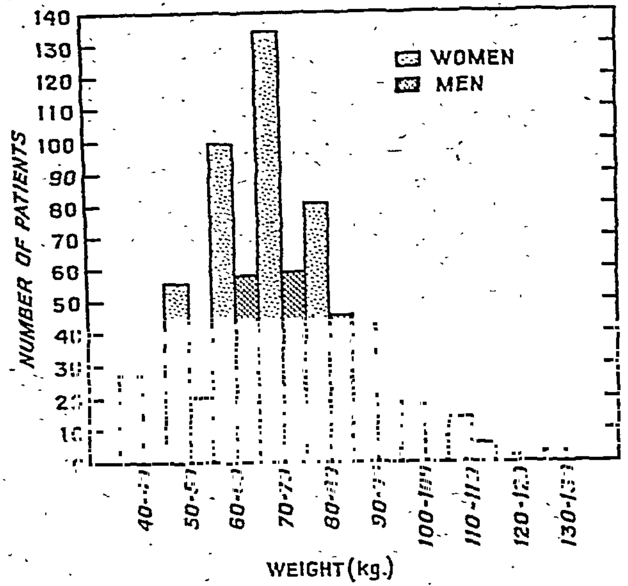

Fig. 5—Weight-distribution of 684 patients (472 women and 212 men) with leg ulcers.

to develop, as in parturient women, patients recumbent for medical or surgical reasons, and those with fractures of, or undergoing operations on, the leg, special efforts should be made to prevent it if there is a family history of varicose veins, thrombosis, or leg ulcers (Anning 1950).

When thrombosis has occurred, early treatment with anticoagulants is useful, and firm support for the limb will prevent the appearance of secondary varicose veins and control the œdema. When the acute phase has passed, massage by Bisgaard's (1948) method, together with continued elastic support, will prevent induration of the leg and subsequent ulceration.

The prevention of true varicose ulcers is a simpler matter. When there are early signs of chronic venous insufficiency adequate elastic support is sufficient. The value of the surgical treatment of superficial varices is doubtful; sometimes it precipitates ulceration.

Rest

Once ulceration has taken place, early treatment is important. The longer an ulcer remains untreated the more difficult is its cure. Except for ulcers of many years' duration with much induration, which may require rest in bed, it is only necessary to abolish the œdema and the ulcer will heal.

The value of rest has long been recognised. It was described by Bell (1779) as a material part of the cure, and by Cooper (1837) as indispensable, and Sharp (1758) emphasised the importance of rest in a horizontal position. However, a new approach was introduced by Underwood. In 1783 he published a treatise "proving that a Perfect Cure may generally be effected more certainly, without Rest and Confinement, than by the Strict Regimen in Common Use."

Compression

The cure of ulceration in a walking patient requires compression of the limb to abolish the œdema or to prevent its return. As Bisgaard (1948) pointed out, the massaging effect of the muscular contractions of a leg compressed by elastic bandages helps to remove the œdema, and the patient may be encouraged to walk.

The use of plaster bandages for leg ulcers was advised by Marianus Sanctus Barolitanus (1555). Paré (Johnson 1678) and de Marque (1618) recommended compressive bandages, but treatment by firm support does not seem to have been widely used until Wiseman (1676) introduced the laced leather stocking. Continental surgeons soon adopted this kind of stocking, one of which is illustrated by Dionis (1708). Wiseman also mentioned bandaging, but this does not seem to have come into general use for some time—certainly not by the time of Else (1771), who found that a tight roller bandage applied from the toes to the knees was much better than a laced stocking.

Underwood (1783) wrote in great detail of the treatment by bandaging and used "Welch flannel" because it was elastic. He considered that "the application of a bandage is no contemptible branch of our profession." The same view was taken by Hunt (1859), who said that the treatment of leg ulcers was so notoriously unsuccessful "mainly because the application of a bandage is looked upon as an easy and simple operation which may safely be entrusted to the nurse or the patient." He added that the bandage must be applied "in such a manner that every portion of the limb, from the toes to the knees (including especially the hollow between the heel and the inner and outer malleolus) shall receive equal and abiding support. If it be at all tighter round the leg, for instance, than round the foot, the foot and ankle will become swollen and œdematous." Spender (1868) also gave detailed instructions about bandaging.

The importance of good support in the treatment of leg ulcers must be emphasised whether or not surgery is used in addition. Firm elastic support is beneficial because it relieves the œdema, assists the pumping and massaging effects of muscular contraction, and compresses dilated veins.

Various types of support have been devised since Wiseman's leather stocking and Underwood's flannel roller. Baynton (1799) reintroduced the plaster bandage, and Dickson Wright (1930) demonstrated the value of the elastic plaster bandage. Most leg ulcers can be cured in a few months with such bandages, and preliminary painting of the leg with 1% aqueous solution of gentian violet greatly reduces the risk of 'Elastoplast' irritation. An elastic webbing bandage worn over stockinette provides excellent support, preferably when it stretches longitudinally only: bandages which stretch in two directions tend to become progressively narrower. Scott and Radakovich (1949) have introduced a stocking which allows controlled pneumatic pressure to be applied to the œdematous leg. Whatever method of compression is adopted, the patient should be encouraged to walk.

The Unna's-paste bandage or its convenient successor, the 'Viscopaste' bandage, is useful to support the limb after œdema has been abolished by other means. These bandages have no elasticity; but, if compression is required, elastoplast bandages may be applied over them.

The advantages to be derived from elastic support combined with deep massage were demonstrated by Bisgaard (1948). Deep massage is given to the sole and the hollows by the malleoli with the leg raised. Padding is next placed in the hollows, and the leg, from the toes to the knee, is covered with wadding, over which a firm elastic webbing bandage is wound. The patient is encouraged to walk. I have found Bisgaard's treatment valuable in the reduction of œdema and induration of the leg and in the healing of ulcers. I cannot compare the results of this method with those of other types of treatment, because I have had to limit its use to patients with severe induration and œdema or with intractable ulcers. However, several patients whose ulcers had resisted conventional treatment, surgical and other, were cured by Bisgaard's method. Patients treated in this way seem less prone to relapse.

Local Treatment

No mention has been made of infection of ulcers, for it plays no primary part in their ætiology. Inevitably an ulcer becomes secondarily infected with various organisms commonly present on the skin, but this rarely affects healing when treatment is based on the principles outlined above. If attention is directed to the circulation of the limb as a whole, the base of the ulcer and its flora may usually be ignored. Occasionally ulcers are seen which rapidly increase and become offensive and surrounded by erythema. On bacteriological examination *Pseudomonas pyocyanea*, proteus, or a virulent streptococcus may be found. Local treatment with a suitable antibiotic may be required for a few days. Penicillin and the sulphonamides are best avoided because the risk of sensitisation is great. Lassar's paste containing sodium bicarbonate 25% is effective in cleaning an offensive ulcer. Recently the unsaturated fatty acids have been advocated as a local application for ulcers, but they appear to have no beneficent quality other than as a soothing dressing.

Surgical Treatment

I do not intend to be so presumptuous as to discuss the surgical treatment of leg ulcers, but merely to make a few rather diffident remarks. The danger of thrombosis of deep veins after the injection of varicose veins with a sclerosing solution has been pointed out by several surgeons (Boyd and Robertson 1947, Kinmonth and Robertson 1949). The risk can be reduced by certain precautions but cannot be ignored. In the present series 48 patients had deep thrombosis after such injections, and in 32 (4·5%) the thrombosis was the direct cause of ulceration. Moreover the injection of secondary varicose veins—i.e., veins appearing after thrombophlebitis of deep veins—further embarrasses the venous return from the leg, even though another deep thrombosis is avoided.

About the results of ligation of the saphenous veins little can be said here. Such treatment may benefit temporarily a few patients with true varicose ulcers, but the seat of the trouble is in the deep and communicating veins, and relapse is common. After saphenous ligation in 48 patients ulcers became worse or appeared later, and in 8 other patients ligation was the precipitating cause of ulceration.

Ligation of the popliteal vein, introduced by Bauer (1948), seems to be successful in his hands in curing ulcers and relieving the bursting pain in the legs. On radiographic evidence, he thinks that reflux of blood down the femoral vein is prevented, and that the blood is driven by contraction of the calf muscles into the muscle veins of the thigh (Bauer 1950b). The patients are advised to wear elastic stockings after the operation. The results of this operation in the hands of British surgeons do not seem to have been reported, but de Takats and Graupner (1951) feel that ligation of the popliteal vein does more harm than good.

On theoretical grounds it seems that the rational surgical treatment would be the introduction, if thrombosis could be avoided, of an artificial valve (of plastic or metal) in the iliofemoral veins.

Sympathectomy seems to be indicated when arterial disease is present, if lowering of sympathetic tone is shown beforehand to be followed by vasodilatation. Ochsner and DeBakey (1949) believe that vasospasm is a common sequel of deep thrombosis, and that sympathectomy causes the œdema to disappear.

Excision of the ulcerated area, followed by grafting, is occasionally indicated where much sclerosis is present and the ulcer is bound down to deeper structures. However, unless combined with measures to control œdema, it is doomed to failure.

AFTERCARE

It is too often forgotten that the medical care of the patient with a leg ulcer should not cease with its cure. Unless aftercare is adequate, relapse is probable. Else (1771) recommended that "when the patients are well" they should "keep the leg constantly rolled tight in the day-time." This is good advice; for, unless return of the œdema is prevented by elastic stockings or firm bandages, ulceration will reappear.

To ensure that the patients are wearing adequate support for the legs, it has been found best to see them every three or four months after cure, so that fresh bandages or stockings can be ordered as required, and satisfactory support permanently maintained. As yet no surgical treatment can offer an alternative.

SUMMARY

The growth of knowledge of the ætiology of leg ulcers is reviewed historically.

The importance of an increase in venous and capillary pressure in the lower part of the leg is emphasised, the essential defect being shown to lie in the valves of the deep veins of the lower limb.

Of 715 patients the cause of such trouble was venous thrombosis in 80%, and varicosity of deep veins in 7%.

Ulcers due to hypertension are described, and the problem of arterial and arteriolar disease in relation to leg ulcers is discussed.

In addition to methods of prevention, treatment by rest, elastic support, massage, and surgery is considered.

Aftercare is necessary to prevent relapse.

It is a pleasure to acknowledge the kindness of Dr. John T. Ingram, Dr. F. F. Hellier, and other colleagues and practitioners who have referred patients to me. The help and skill of Sister Irene Gray and Sister Blanche Simpson have been invaluable in the treatment of these patients.

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VAGOTOMY IN THE TREATMENT OF PEPTIC ULCERATION

REVIEW OF 1524 CASES

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FASHIONS in the treatment of chronic peptic ulceration come and go, and the surgical problem remains unsolved. Virchow in 1855 stated that ulcers are caused by peptic digestion of devitalised tissue, and since that time speculation and experiments have centred on the causes preventing healing of these erosions. On the one hand, the lack of resistance of the stomach and duodenal lining is nearly as much a mystery today as it was fifty years ago. On the other hand, excessive secretion of hydrochloric acid has been found to be a factor more amenable to control than any other, and there is considerable clinical and experimental evidence to show that modification of the gastric acidity will favour healing of an ulcer.

The secretion of hydrochloric acid has long been attributed to two separate mechanisms: firstly, gastrin, liberated by food stimulation of the pyloric antrum circulates in the blood-stream and specifically releases hydrochloric acid from eosinophil cells in the stomach (Jory and Whitlow, cited by Wright 1940); secondly, stimulation of the vagus increases the secretion of acid. The central connections of the vagus nerves with the hypothalamus have been adduced as evidence that the emotional flow of acid is governed through these nerves. Much recent work (Wolf and Wolff 1943) has been directed towards correlating peptic ulceration with long-standing conditions of emotional strain. The rationale of resection of the vagus in the treatment of ulceration is obvious (Beattie 1949).

The operation was first used to any extent in Germany from 1914 to 1924 (Alvarez 1948). It fell into disuse and was never done again in the English-speaking countries until Dragstedt and Owens (1943) reintroduced it. The simplicity of the operation, the absence of mutilation, and its theoretical background formed a strong appeal, and many surgeons in the U.S.A. soon adopted it (Moore 1948, Grimson et al. 1949, Walters 1949).

Vagotomy was first adopted in this country in 1945 by Orr and Johnson (1949), and surgeons in many centres were soon using the operation. It was discovered that section of the vagus, if complete or nearly complete, produced an undesirable gastric atony with retention; and various drainage procedures were combined with vagotomy to overcome this effect. These varied from pyloroplasty and pylorectomy (Beattie 1950) to gastrojejunostomy and limited gastrectomy (Orr and Johnson 1949).

The present series comprises 1524 patients with peptic ulcer of the duodenum (1314 cases), stomach (127 cases), jejunum (82 cases), or œsophagus (1 case).

METHOD OF SELECTION OF CASES

After preliminary discussions and a pilot survey at the West London Hospital, leading surgeons in all the main centres in England, Scotland, and Wales were circularised. Where a reply indicated a series of more than 20 cases, that surgeon was visited and his coöperation sought. In no case was this refused. His series was then collected—usually by referring to the operation register in his hospital, but occasionally, when he had notes of all cases recorded at the time of the operation, by referring solely to this record. All the series were consecutive and included every case operated on up to the end of April, 1950. Cases were collected from Birmingham, Bridge of Earn, Bristol, Edinburgh, Leeds, Leicester, London, Manchester, Newcastle, and York.

745 patients (49%) have been interviewed; 632 patients (41·4%) have replied to a questionnaire; 19 patients (1·2%) had died within twenty-eight days of operation; 31 patients (2%) had died later; and 97 patients (6·4%) are untraced. No patient was regarded as untraced until he had failed to reply to three letters or until a letter was returned by the Post Office.

CRITERIA FOR OPERATION

These varied little from surgeon to surgeon and in general were the same as those for gastrectomy. Length of history and relapse after medical treatment were the commonest indications. Thus in the whole series 958 (63%) had an ulcer history of six or more years, and 470 (31%) one longer than ten years. 222 patients (14%) had previously perforated on one or more occasions, 193 (13%) had had one or more major hæmatemeses or melænas, 42 (3%) had both perforated and bled, and 127 (8%) had had a previous gastric operation for their ulcer. In 85 this was a gastrojejunostomy, in 24 a gastrectomy, in 11 a physiological gastrectomy, in 3 excision of an ulcer, in 3 repair of a gastrocolic fistula, and in 1 a pyloroplasty.

Vagotomy the Sole Operative Procedure

736 patients thus treated were studied (table I). 78 patients had died or were untraced, leaving 658 patients followed up from six months to four years. Of the 78 missing patients 10 (1·3%) died in the early postoperative period (1 of these died from hæmorrhage from his ulcer), 18 (2·4%) died later (none from the effects of an ulcer), and 50 (6·8%) were untraced.

40 patients were assessed from six months to a year after operation, 237 from one to two years, 265 from two to three years, and 116 from three to four years after operation. Only 18% were followed up longer than three

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TABLE I—PATIENTS TREATED BY VAGOTOMY ALONE

Male						Female					
D.U.		G.U.		J.U.		D.U.		G.U.		J.U.	
Total	Follow-up	Total	Follow-up	Total	Follow-up	Total	Follow-up	Total	Follow-up	Total	Follow-up
540	481	56	47	68	62	49	47	17	16	6	5

years. This detracts from the value of the investigation; nevertheless even within the short space of this follow-up there has been a considerable incidence of failure due to gastric retention and recurrent ulceration.

80 of these operations were done by the transthoracic route. The results were compared from the point of view of recurrence and retention, and differed in no way from those of abdominal vagotomy (except for pain in the thoracotomy incision). The two types are considered together.

FOLLOW-UP FINDINGS

Relief of Pain

In nearly every case this was immediate and complete. The mechanism of this relief is conjectural. It has been supposed (Grimson et al. 1947) that the vagus carries no sensory fibres, and that the relief of pain results from immediate gastric atony. On the other hand, Mr. Beattie tells me that on several occasions he has crushed the anterior vagal trunk under spinal anæsthesia and caused sharp epigastric pain. This contradicts the findings of Foerster (cited by Alvarez 1948), who produced nausea but no pain by such stimulation.

Recurrences of Pain

Many patients complained of occasional or frequent mild or severe abdominal pain. On the basis of relief of this pain by food and similarity to preoperative pain it has been called recurrent ulcer pain or recurrent pain (other causes). 167 patients (25%) have admitted to epigastric pain relieved by food at some time since operation. 240 patients (36%) have complained of other abdominal pain, usually taking the form of "wind," or colic, and sometimes associated with diarrhœa or with a sense of fullness.

Dysphagia

Mild difficulty in swallowing in the early days after vagotomy is very common. It sometimes persists and has necessitated dilatation of the cardia. In only 5 patients has it persisted longer than six months. It was remembered by 198 patients (30%). In the single case of œsophageal-hiatus sliding hernia with peptic ulceration and stricture of the lower œsophagus vagotomy was followed by an exacerbation of pain and dysphagia necessitating resection of the lower œsophagus.

Diarrhœa

This was an extremely common symptom, especially during the first six months after operation. It occurred in a mild form in 353 patients (53%) and in a severe form in 108 patients (16%). In 3 cases it contributed to death in the early postoperative period. Necropsy and bacteriological examination in 1 case threw no light on the mechanism of this symptom. In general, however, it was found that diarrhœa often, but not always, coexisted with gastric retention and foul eructations. It has been supposed to result from an enteritis due to gastric fermentation. On the whole this symptom caused little complaint—even some small pride in being a "bit too regular."

Foul Eructations

This symptom, not so common as the last—it occurred in 236 patients (36%)—was a source of great embarrassment. Description of the odour varied, but all the patients agreed that it was extremely unpleasant. Most often it was likened to a drain or to rotten eggs. One Scottish patient complained that he had to give up smoking because the gas he eructed was highly inflammable (cf. *Lancet* 1947). It was observed in performing test-meals that the gastric residue often smelt extremely foul. This symptom was closely bound up with gastric retention and ceased in every case as soon as that had been overcome.

Vomiting

238 patients (36%) had vomited on other than isolated occasions, and in 84 cases (13%) vomiting was severe or frequent enough to demand special treatment. The vomiting was characteristically foul and free from bile, typical of the retention syndrome. This symptom also responded rapidly to a gastric-drainage operation.

Fullness

An uncomfortable feeling of fullness in the abdomen after meals was noted in 406 patients (61%). It seldom caused much complaint itself, but it was often associated with pain, foul eructations, and diarrhœa.

Hypoglycæmia

Attacks suggestive of hypoglycæmia, coming on several hours after the last meal and responding to sugar, occurred in 208 patients (31%). On many occasions patients noted the similarity between these attacks and the hypoglycæmia induced by an insulin test-meal.

TABLE II—INSULIN TEST-MEALS IN 61 CASES WITH PROVED RECURRENT ULCERATION

Site of recurrence	Insulin test-meal			
	Strongly positive	Weakly positive	Negative	Unsatisfactory
Duodenal	7	4	—	11
Gastric	2	—	5	12
Jejunal	1	—	—	—
Uncertain	2	—	—	17

Weight

396 patients were weighed at the time of their interview, and their weight was compared with preoperative weight. 95 (24%) had lost weight, 80 (20%) had remained the same, 89 (22%) had gained 1–10 lb., 72 (18%) had gained 11–20 lb., and 60 (15%) had gained more than 20 lb.

Insulin Test-meals

The secretion of hydrochloric acid in response to hypoglycæmia has been recognised as a function of intact vagi (Hollander 1946). This phenomenon has been extensively used as a test for the completeness of vagal section. A dose of soluble insulin varying from 10 to 20 units was injected intravenously in a fasting patient. Samples of gastric contents were aspirated at intervals of ten to fifteen minutes for an hour and a half and titrated for "free" and "total" acidity. A test was accepted as satisfactory only if the following conditions were satisfied:

(1) Hypoglycæmic symptoms were noted. This usually coincided with a blood-sugar level, thirty minutes after the insulin injection, of less than 50 mg. per 100 ml. (Folin and Wu's method). A few cases of insulin sensitivity were found in which severe symptoms were produced and dextrose had to be given intravenously.

(2) No bile was present in most of the specimens.

(3) No food residue was present apart from the first two specimens.

(4) The test was continued for at least an hour.

In this series 450 insulin test-meals were available. 284 tests were made within the first six months after operation. 104 (37%) of these were unsatisfactory; 68 (24%) tests showed little or no rise in free acidity and

TABLE III—RESULTS OF VAGOTOMY RELATED TO INSULIN TEST-MEALS

Insulin test-meal	Excellent	Good	Fair	Poor	Failure	Total
Negative	7 (*10%*)	15 (*20%*)	12 (*15%*)	14 (*19%*)	26 (*35%*)	74 (*100%*)
Weakly positive ..	18 (*23%*)	10 (*12%*)	16 (*20%*)	13 (*17%*)	21 (*25%*)	78 (*100%*)
Strongly positive ..	21 (*23%*)	16 (*18%*)	14 (*15%*)	15 (*16%*)	27 (*28%*)	93 (*100%*)

were regarded as negative, 112 (39%) showed a rise, at 20–40 minutes, of at least 20 ml. of N/10 HCl (0·075% HCl) and were regarded as positive. 40% of these 112 showed a rise to more than 50 ml. of N/10 HCl (0·18% HCl) and were regarded as strongly positive.

166 tests were performed more than six months after operation. Only 16 (10%) of these were unsatisfactory, 47 (28%) were negative, and 103 (62%) were positive, of which 55 were strongly positive. The proportion of negative tests remained much the same, and most of the tests which were unsatisfactory soon after operation were positive later. No case was found in which an indisputably positive test later became negative or vice versa. In all, 330 satisfactory tests were performed on 245 patients. These patients are further considered below.

There is no doubt that some of the tests were positive because of incomplete section of the vagus, but in many cases both anterior and posterior vagal trunks had been sectioned and yet an insulin response was obtained. In these cases it has been assumed that additional vagal fibres have pursued anomalous courses, possibly within the muscle wall of the lower œsophagus (Weinstein et al. 1950).

Clinical results were not closely related to the results of insulin test-meals. Some retention was the rule in the early days after even an incomplete vagotomy, although it tended to recover more quickly than when the vagotomy was complete. On the other hand, symptoms suggesting recurrent ulceration were commoner in patients whose insulin test-meal was positive. Only 5 ulcers were proved to have recurred in the presence of a negative insulin test-meal, and these were all gastric (table II).

Table III shows the correlation of results of insulin test-meals with clinical grading in 245 cases of vagotomy.

When the causes of the failures ("poor" and "failure") were further examined, it was found that significantly more patients with a negative insulin test-meal developed severe gastric retention after vagotomy (sufficient to warrant a secondary drainage operation), and significantly more patients with a strongly positive insulin test-meal were suspected or proved to have a recurrent ulcer. This is shown in tables IV and V.

TABLE IV—ASSOCIATION OF STRONGLY POSITIVE INSULIN TEST-MEAL WITH PROVED OR SUSPECTED RECURRENT ULCERATION

Insulin test-meal	Proved or suspected recurrence	No recurrence	Proportion as percentage
Negative	14	60	23
Weakly positive ..	15	63	24
Strongly positive ..	30	63	48

Gastric Retention

This was present in nearly every patient soon after operation, but in the majority it disappeared within a year. In 98 patients retention was severe enough to demand a subsequent gastric drainage operation. Most of these patients had had a duodenal ulcer, and stenosis contributed to the retention. 21 patients had a normal duodenum, and in them retention was explained on the basis of gastric atony, pyloric spasm, or incoördination of gastric motility. It has been shown kymographically that gastric atony usually passes off within a year after operation (Moore et al. 1947). Pyloric spasm has been observed by Beattie (1950) at operation, but gastroscopically the antrum and pylorus have been seen to be widely open (Paulson and Gladsden 1949, A. M. Gill personal communication). Radiography has shown short-lived shallow ineffective peristaltic waves in these patients.

The drainage operation was gastrojejunostomy in 45 cases, pyloroplasty in 46, and gastrectomy in 7. The further history of these patients is considered below. Retention symptoms responded to operation in all the cases.

Recurrent Ulceration

167 patients (25%) complained of ulcer pain at some time after vagotomy.

X-ray evidence of continued or recurrent ulceration was found in 39 patients radiographed in the first year after operation, and in 26 patients after this time.

TABLE V—ASSOCIATION OF NEGATIVE INSULIN TEST-MEAL WITH SEVERE GASTRIC RETENTION

Insulin test-meal	Severe retention	No severe retention	Proportion as percentage
Negative	26	48	54
Weakly positive ..	19	59	32
Strongly positive ..	12	81	15

Proof of recurrent ulceration was accepted if hæmatemesis or melæna occurred and was unexplained on any other basis, or if an active ulcer was discovered at a subsequent operation. 27 patients had a subsequent hæmorrhage, 3 perforated, and 32 active ulcers were found at operation. Thus the total number of proved recurrences (table VI) was 62 (9·4%), only 2 of which were in women. Of 589 patients on whom vagotomy had been performed for duodenal ulcer 18 recurrent duodenal ulcers were found (3%) and 6 recurrent gastric ulcers (1%). In these cases of gastric ulcer there was evidence of gastric retention. In 12 cases (2%), where hæmorrhage had occurred but no laparotomy was done, the site of the recurrent ulcer was unknown.

In 73 patients whose vagotomy had been performed for gastric ulcer 11 recurrent gastric ulcers were found (15%), and in 2 cases the site of the ulcer was unknown (3%).

In 74 patients whose vagotomy had been performed for jejunal ulcer 4 recurrent duodenal ulcers, 2 recurrent gastric ulcers, and 1 recurrent jejunal ulcer were found, and in 5 cases the site of the recurrence was unknown. The total number of recurrences was 12 (16%).

The only patient with an œsophageal ulcer treated by vagotomy in this series had a proved recurrence of her ulcer.

TABLE VI—62 PROVED RECURRENCES AFTER VAGOTOMY

Vagotomy for	No. of cases	Site of recurrence				
		Duodenal	Gastric	Jejunal	Unknown	Œsophageal
Duodenal ulcer ..	589	18	6	—	12	—
Gastric ulcer ..	73	—	11	—	2	—
Jejunal ulcer ..	74	4	2	1	5	—
Œsophageal ulcer	1	—	—	—	—	1

GRADING OF PATIENTS

Each patient has been assessed and placed in one of five grades (modified from Visick 1948): grade I includes patients without gastric symptoms; grade II patients with minor symptoms which may be prevented with the exercise of care; grade IIIs patients whose complaints, though not amenable to prevention, do not interfere with their activities; grade IIIu patients whose symptoms prevent their enjoyment of a full life; and grade IV failures. Grades IIIu and IV are classed as unsatisfactory. The 658 patients followed up were graded as follows:

Grade I,	135 patients *(20%)*
Grade II,	115 patients *(17%)*
Grade IIIs,	123 patients *(19%)*
Grade IIIu,	122 patients *(19%)*
Grade IV,	163 patients *(25%)*

The total number of unsatisfactory results was 285 (44%).

Vagotomy Combined with Gastrojejunostomy

Of 511 patients thus treated 49 had died or were untraced, leaving 462 followed up (table VII). Of the 49 missing patients, 4 (0·8%) had died in the immediate postoperative period, 8 (1·6%) had died later (none from the effects of an ulcer), and 37 (7·6%) were untraced. The 45 patients whose post-vagotomy gastric retention was treated by gastrojejunostomy were included in this group, making a total of 507. These 45 patients were considered only from the standpoint of final assessment. Their *intermediate symptoms belong to the group of* vagotomy alone.

TABLE VII—462 PATIENTS TREATED BY SIMULTANEOUS VAGOTOMY AND GASTROJEJUNOSTOMY

Male				Female			
D.U.		G.U.		D.U.		G.U.	
Total	Follow-up	Total	Follow-up	Total	Follow-up	Total	Follow-up
456	408	10	9	43	43	2	2

It is only relative recently that it has been realised that all vagotomies, whether duodenal stenosis is present or not, should be combined with a gastric drainage operation. 78 patients have been assessed less than a year after operation, 215 from one to two years, 135 from two to three years, and only 34 (7%) for more than three years. This is a serious deficiency in the investigation since it is well known that the initial results of gastrojejunostomy alone are usually satisfactory. In this series, however, a higher proportion of unsatisfactory results was found during the first year after operation (15%) than later (8% during the second year, 13% during the third year, and 9% after the third year). This distribution is explained partly by slow recovery from operation and partly by gastric retention during the first year after operation. The incidence of recurrence was low at all times.

FOLLOW-UP FINDINGS

Relief of Pain

This was as striking as when vagotomy alone had been done. As with the vagotomy series, some patients complained later of recurrent abdominal pain. This was suggestive of peptic ulceration in 40 cases (8% of the total series of 507) and bore no resemblance to ulcer pain in 99 cases (20%).

Dysphagia

This occurred in 99 patients (20%) and usually did not last longer than a few weeks.

Diarrhœa

Mild diarrhœa was noted by 161 patients (32%) and severe diarrhœa by 12 (2%). It was much less frequent than in patients who had had a vagotomy alone, and the severe diarrhœa of the post-vagotomy retention syndrome was often cured by gastrojejunostomy. In a few patients there was X-ray evidence of gastric stasis even in the presence of a short circuit, but in most of the patients with mild diarrhœa there was no delay in the emptying of the stomach.

Foul Eructations

Only 19 patients (4%) noticed this symptom, and in each case there was collateral evidence of gastric retention in spite of the gastrojejunostomy.

Vomiting

Nausea and mild occasional vomiting of bile occurred in 130 patients (26%). It was of the same type as the bile vomiting after gastrectomy—i.e., a mouthful of bile without food would be vomited soon after a meal, with relief of nausea. Severe vomiting occurred in only 6 patients (1%).

Fullness

206 patients (41%) complained of uncomfortable epigastric fullness after meals.

Dumping Syndrome

Severe dumping (weakness, &c., immediately after eating) occurred in only 2 patients, but mild attacks of the same type were noticed by 38 patients (8%).

Hypoglycæmia

Attacks very suggestive of hypoglycæmia occurred in 108 patients (21%). These attacks of weakness, faintness, and sweating were quite distinct from the dumping syndrome, coming on, as they did, when the stomach was empty. They were relieved by sugar.

Weight

The weights of 267 patients before and after operation were known. Of these 47 (17%) lost weight, 48 (18%) remained the same, 64 (24%) gained 1–10 lb., 64 (24%) gained 11–20 lb., and 44 (16%) gained more than 20 lb.

Insulin Test-meals

By far the greater number of these were unsatisfactory owing to the presence of bile. 145 meals were studied. Of these 95 were unsatisfactory, 14 were negative, and 36 were positive (of which 17 were strongly positive). No correlation was found between clinical grading and the results of insulin test-meals.

Recurrent Ulceration

In only 40 patients (8%) was there any recurrence of ulcer-type pain. X-ray studies suggested recurrent jejunal ulceration in 5, and recurrent duodenal ulceration in 2, patients in the first year after operation, and jejunal ulceration in 1, and duodenal ulcer in 1, patient after the first year.

Recurrence was proved in 6 patients (1%). In 3 of these, subjected to gastrectomy, the ulcer was jejunal, and in the other 3, who suffered severe gastric bleeding, the site of the ulcer was not proved.

GRADING OF PATIENTS

The 507 patients followed up were graded as follows:

Grade I,	216 *(43%)*
Grade II,	132 *(26%)*
Grade IIIs,	99 *(19%)*
Grade IIIu,	45 *(9%)*
Grade IV,	15 *(3%)*

The total number of unsatisfactory results is 60 (12%).

Vagotomy Combined with Pyloroplasty or Pylorectomy

This was the definitive operation in 235 cases. Pylorectomy was performed by Beattie (1950) in all his recent cases. Pyloroplasty is impossible with a grossly deformed

TABLE VIII—220 PATIENTS TREATED BY SIMULTANEOUS VAGOTOMY AND PYLOROPLASTY

Male				Female			
D.U.		G.U.		D.U.		G.U.	
Total	Follow-up	Total	Follow-up	Total	Follow-up	Total	Follow-up
170	160	29	28	23	21	13	11

duodenum. Of the 235 patients 15 had died or were lost, leaving 220 followed up (table VIII). 46 patients whose post-vagotomy retention syndrome was treated by pyloroplasty or pylorectomy were included in this group, making a total of 266. Of the missing patients 4 (1·7%) died in the immediate postoperative period, 4 died later (none died from the effects of an ulcer), and 7 (3%) were untraced.

As with vagotomy combined with gastrojejunostomy, most of these patients were seen less than two years after their operation. Thus 93 (43% of the 220 cases) were assessed within a year, 97 (44%) between one and two years, 27 (12%) between two and three years, and only 3 (1%) longer than three years after operation.

FOLLOW-UP FINDINGS

Recurrent Pain

15 patients (6% of the total of 266 cases) complained of recurrent pain of ulcer type, and 75 (28%) of abdominal pain of other types.

Dysphagia

The incidence of this symptom was not affected by the additional procedure. 83 patients (31%) remembered having had some dysphagia for a few weeks after operation, and in 2 patients the distress lasted more than six months.

Diarrhœa

This was seldom severe. In fact in only 5 of the 70 patients who admitted to this symptom could it be called distressing. It generally came on soon after operation and seldom persisted for longer than six months. In many cases it coexisted with other signs of gastric retention.

Foul Eructations

14 patients (5%) reported belching foul-smelling gases. This symptom also was usually mild and temporary, and presumably reflected a gastric retention due to atony before the balance between propulsive power of the stomach and calibre of the pylorus and duodenum became established.

Vomiting

This was gratifyingly infrequent. 30 patients (11%) admitted to mild occasional vomiting, usually of food residues, and only 4 patients (2%) vomited frequently.

Fullness

65 patients (24%) complained of feeling full after meals. The reason for this feeling is unknown, but the feeling seems to differ in no way from that of the "small stomach syndrome" after gastrectomy.

Hypoglycæmia

Again this symptom was often noticed—in 92 patients (35%). Its cause is unknown.

Weight

189 patients were weighed and compared with their preoperative weight: 25 (13%) lost weight; in 47 (25%) the weight remained steady; 65 (34%) gained 1–10 lb.; 36 (19%) gained 11–20 lb.; and 16 (8%) gained more than 20 lb. These figures are comparable with those found in the other vagotomy series studied.

Insulin Test-meals

87 insulin test-meals were available for study. Of these 29 (33%) were unsatisfactory, 23 (26%) were negative, and 35 (41%) were positive, of which 19 were strongly positive. No correlation was found between clinical grading and the results of the insulin test-meals.

Recurrent Ulceration

In only 15 patients (6% of the series of 266) has pain suggestive of peptic ulceration recurred. In 1 patient during the first year a gastric ulcer was visible on radiography, and in 2 after the first year there was an appearance of duodenal ulceration on radiography. Recurrence was proved in 2 patients, both of whom had a severe hæmatemesis. In neither case was the site of the ulcer proved.

GRADING OF PATIENTS

The 266 patients followed up were graded as follows:

Grade I,	95 (*36%*)
Grade II,	84 (*32%*)
Grade IIIs,	50 (*19%*)
Grade IIIu,	28 (*10%*)
Grade IV,	9 (*3%*)

The total number of unsatisfactory results was 37 (13%). The figures are very similar to those of vagotomy combined with gastrojejunostomy.

Vagotomy Combined with Limited Partial Gastrectomy

Only 37 patients so treated were followed up, and no details will be given about this small series. Suffice it to say that the results were much more like those of gastrectomy than those of vagotomy, that undesirable side-effects were those associated with gastrectomy, that no instance of proved recurrent ulceration was discovered, and that the clinical grading was as follows:

Grade I,	13 (*34%*)
Grade II,	8 (*22%*)
Grade IIIs,	11 (*30%*)
Grade IIIu,	5 (*14%*)
Grade IV,	0

Summary and Conclusions

1524 cases were analysed, and they fell into two groups:

VAGOTOMY ALONE

Of 736 patients with peptic ulceration treated by vagotomy alone 78 (10·6%) died or were untraced.

Of the 736 patients 73 had been treated for gastric ulcer, with a proved recurrence-rate of 18%.

Of 74 treated for jejunal ulcer the proved recurrence-rate was 16%.

Of 589 treated for duodenal ulcer the proved recurrence-rate was 6%.

Many more patients had symptoms suggesting recurrent ulceration, but the recurrences were not proved.

44% of those studied fell into the "unsatisfactory" group (grades IIIu and IV).

Insulin test-meals revealed a high proportion of positive responses, many of which were probably due to incomplete section of the vagus.

The liability to recurrent peptic ulceration is higher when the insulin test-meal is positive, and the severity of gastric retention greater when the insulin test-meal is negative.

VAGOTOMY WITH DRAINAGE OPERATION

Of 788 patients treated by vagotomy, combined with some drainage operation, 69 (9%) died or were untraced.

Recurrence was proved in only 1% of these cases. Only in 7% were there symptoms suggesting recurrence.

The results were classified as unsatisfactory in 12% of these cases.

It is concluded that vagotomy alone is an unsatisfactory operation. Vagotomy combined with a gastric drainage operation yields much better immediate results;

but this procedure will stand or fall by the proved recurrence-rate over a number of years.

This investigation was suggested by Mr. H. W. Burge, M.B.E., F.R.C.S. It would have been impossible but for the generous coöperation of surgeons throughout the country, who have given me free access to their case-records and permission to follow up their patients. The work was done during the tenure of a Dan Mason research fellowship at the West London Hospital Medical School.

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CALCINOSIS UNIVERSALIS
TREATED WITH ADRENOCORTICOTROPHIC HORMONE AND CORTISONE

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DESPITE the infrequency of calcinosis universalis many papers on it have been published in the last forty years. Those of Brooks (1934) and Atkinson and Parkes Weber (1938) gave comprehensive reviews of earlier literature, the latter authors listing 78 publications before 1938.

The association of calcinosis with scleroderma was probably first noted by Meachen (1903). Atkinson and Weber (1938) concluded that this association occurred in about a third of all cases of calcinosis.

Numerous treatments have been used, including disodium hydrogen phosphate (Craig and Lyall 1931), heliotherapy (Schultze 1927), ammonium chloride with a low-calcium diet (Bauer et al. 1931), sodium nitrate and intravenous calcium (Roovers 1939), low-calcium diet (Brooks 1934), and thyroid extract (Weissenbach 1913). Sheldon (1936, 1938), described a spontaneous cure.

TABLE I—SERUM CHEMISTRY IN CASE 1

Date	Calcium (mg. per 100 ml.)	Phosphorus (mg. per 100 ml.)	Potassium (mg. per 100 ml.)	Sodium (mg. per 100 ml.)	Urea (mg. per 100 ml.)	Cholesterol (mg. per 100 ml.)
Before treatment with A.C.T.H.						
Aug. 25, 1951	10·5	4·7	Hæmolysed	320	25	140
1st course of A.C.T.H.						
Sept. 7, 1951	10·1	4·8	22·0	310	25	..
,, 21, ,,	10·0	..	20·0	328	22	..
Oct. 8, ,,	10·6	4·8	17·9	332	27	135
2nd course of A.C.T.H.						
Dec. 28, 1951	10·6	5·3	17·1	..	..	..
Jan. 10, 1952	9·6	5·3	21·0	..	..	..
,, 21, ,,	..	5 5	..	..	..	..

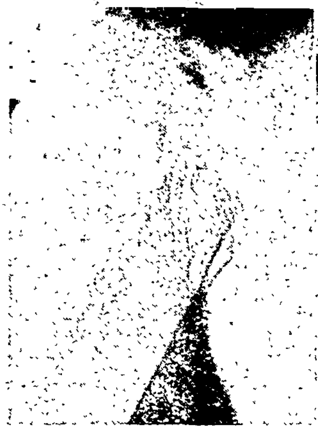
Fig. 1—Subcutaneous calcium deposits in region of shoulder before A.C.T.H. (case 1).

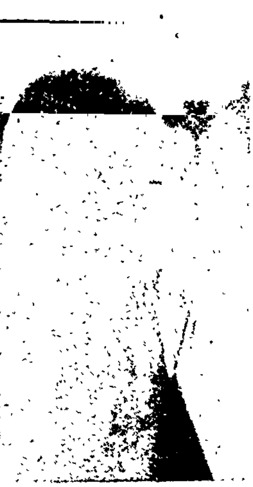
Fig. 2—Same shoulder as in fig. 1 after A.C.T.H. (a very small piece of tissue was removed for biopsy) (case 1).

In the two cases described below we used adrenocorticotrophic hormone (A.C.T.H.) and cortisone.

CASE-RECORDS

Case 1.—A girl, aged 4 years when first seen in 1949, had three weeks' history of stiffness of the arms, so that she could not feed or dress herself and had difficulty in walking and stooping.

Clinical Findings and Progress

On examination both her arms were swollen and her skin was shiny. There was obvious pitting œdema. Her face was violaceous. She had a well-marked reticular mottling of the face, limbs, and buttocks. There was some œdema of the lower limbs. Nothing abnormal was found elsewhere.

Dermatomyositis was diagnosed, and the patient admitted to hospital for biopsy, which confirmed the diagnosis and showed that the principal site of the lesion was in the muscle-fibres, which were degenerating. Radiographs taken at the time were regarded as normal, but further study of them later showed two small deposits of calcium, one in the right arm and one in the right loin.

During April, 1951, several small subcutaneous nodules, which felt calcareous, began to appear around the shoulders (fig. 1) and thighs. The patient was readmitted, and further radiography showed the presence of considerable deposits of calcium, chiefly in the subcutaneous tissues of the neck, shoulders, and buttocks, and in the fascial planes of the gluteal muscles and the adductor and abductor muscles of the thighs.

Another biopsy showed that calcium was present in the superficial layer of the skin (fig. 7) in close association with several collagenous masses. Foamy cells were present in small crypts between the collagenous and calcified areas. There appeared to be a transition between the collagen and calcified material which was not an inflammatory change.

The use of adrenocorticotrophic hormone was considered, but it was decided to delay this until the child had been observed for a further period of six months to determine whether the condition would progress, remain stationary, or resolve. At the end of six months it was evident both clinically and radiologically that her condition was worse. She was less mobile, more nodules had appeared on her elbows and in her neck, and a flexure contracture of her right tendo Achillis had developed. Radiography showed a considerable extension of the deposits in the interfascial planes (figs. 3 and 5).

Treatment with A.C.T.H.

The patient received A.C.T.H. between August and October, 1951. The dosage was 100 mg. on the first day, 50 mg. on the second, and 30 mg. on the third, followed by 20 mg. daily. Each daily total dose was given intramuscularly in divided amounts six-hourly. The total dosage was 1000 mg. As a result of this treatment the eosinophil-count fell from 510 per c.mm. to 38 per c.mm. in seven days. No change was noted in the serum chemistry, the serum-calcium and

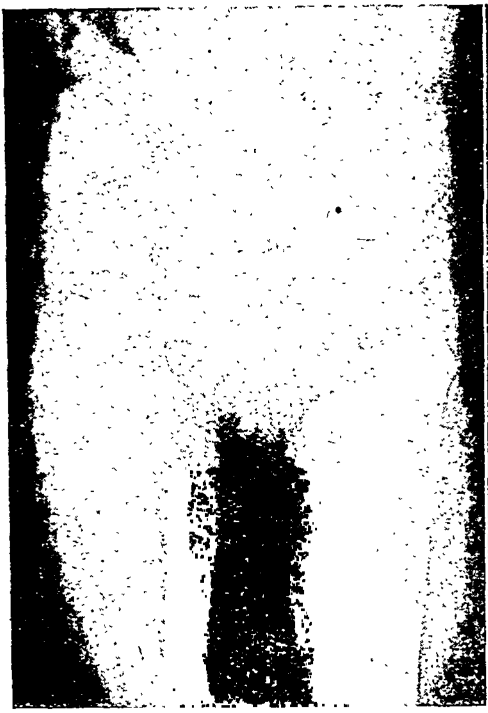

Fig. 3—Deposits of calcium in tissues of lower limb before A.C.T.H. (case I).

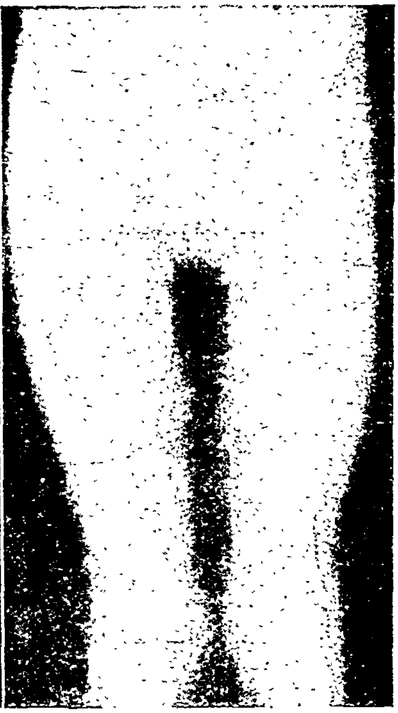

Fig. 4—Lower limbs after A.C.T.H. (case I)

serum-phosphorus levels remaining normal (table I). During the second week of treatment she became unwell, and her subcutaneous lesions became inflamed but did not break down. After five days she improved and her subcutaneous lesions were found to have become softer and smaller. Radiography at the end of the course showed considerable improvement had occurred, with clearing of large areas of calcium deposits, especially around the pelvic girdle. Another skin biopsy confirmed the disappearance of calcium and a regression of the collagenous material previously present.

Although the response to the first course of A.C.T.H. was striking, the calcium deposits had not entirely disappeared. Because of this it was felt that a further course of the hormone was essential if the condition was to be cured. A.C.T.H. therapy was begun again in December, 1951. The hormone was given in divided doses four times a day by the intramuscular route to a total of 2000 mg. in six weeks. Radiography at the end of the course (figs. 4 and 6) showed that almost all the calcium deposits had now disappeared.

The girl is being followed up in the outpatient department and has so far remained well. In October, 1952, nine months after treatment was completed, X-ray studies showed no further deposition of calcium.

Biochemical Findings

The results of the biochemical estimations are summarised in table I.

Calcium-balance estimations while the patient was on a known dietary intake were carried out before and during the courses of A.C.T.H. On a low-calcium intake of 65 mg. a day before treatment with A.C.T.H. the patient was in negative balance. During the course of A.C.T.H. the result on the same diet was almost identical. From a study of these balances no evidence of increased loss of calcium in the urine could be detected. Unfortunately further estimations of calcium balances on a normal calcium intake before and during the second course of A.C.T.H. were technically unsatisfactory.

Case 2.—A girl, aged 13, was well until 1942 when, after an attack of mumps, several small swellings were noted in the skin overlying her popliteal fossæ. Shortly afterwards others appeared in the skin over her shoulders, elbows, buttocks, and groins.

Clinical Findings and Progress

She was seen at the Children's Hospital in 1943, and the diagnosis of calcinosis universalis was confirmed by radiography. The lesions were both subcutaneous and in the fascial planes of her limbs and buttocks. They were extensive around her shoulders, elbows, pubis, thighs, and ankles. During 1943–44 she began to have episodes in which subcutaneous nodules became red and indurated. Later they broke down and discharged a creamy white substance and left sinuses which tracked down to the deep fascial layer. These episodes have persisted with increasing frequency, leading to severe scarring and contractures, as a result of which she cannot stand unaided. Throughout 1942–52 the deposits of subcutaneous calcium and the plaques in the fascial planes have steadily increased.

Treatment with Cortisone

She was admitted to the Children's Hospital in 1951, and a course of cortisone was begun on Oct. 31. The hormone was given orally: 250 mg. on the first day, 200 mg. on the second, 100 mg. on the third, and thereafter 50 mg. daily. Her general condition remained unchanged, and her serum chemistry did not alter. Her eosinophil response was

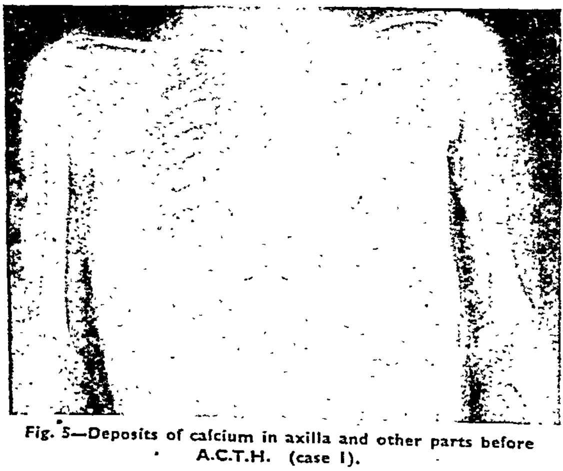

Fig. 5—Deposits of calcium in axilla and other parts before A.C.T.H. (case I).

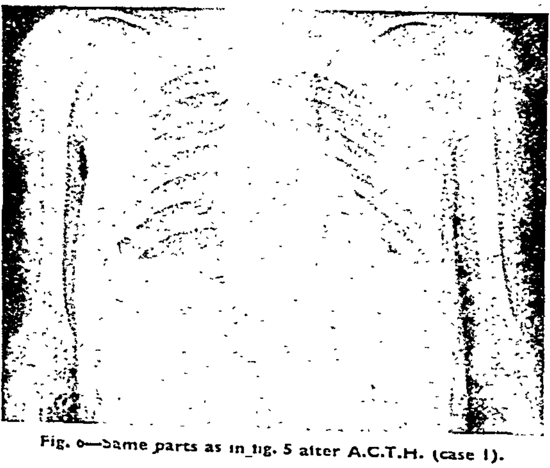

Fig. 6—Same parts as in fig. 5 after A.C.T.H. (case I).

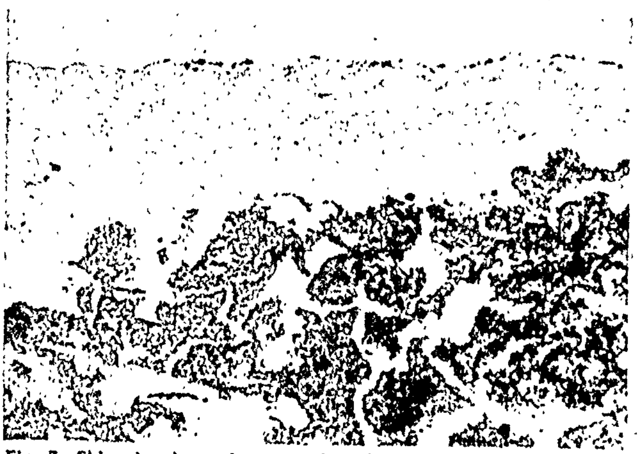

Fig. 7—Skin showing calcareous deposits, shown in black (case 1) (Von Kossa).

unsatisfactory. At the end of a course of 2425 mg. there was no apparent improvement in her clinical state, and further radiography showed that the calcium deposits were unchanged.

Treatment with A.C.T.H.

On Dec. 8, 1951, an intramuscular course of A.C.T.H. was begun. The dosage was 200 mg. on the first day, 100 mg. on the second, and thereafter 50 mg. daily. The eosinophil-count fell from 63 to 6 per c.mm. in five days. Slight insignificant variations occurred in the serum-calcium, serum-phosphorus, and serum-alkaline-phosphatase levels. When the patient had received 1075 mg. of A.C.T.H., there was no clinical or radiological evidence of improvement. She is being followed up as an outpatient, and her condition is slowly deteriorating.

Biochemical Findings

Table II summarises the biochemical investigations.

The daily urinary output of calcium was estimated for a week before and during the course of hormone therapy (table III). The diet was kept constant. Although the figures do not cover the whole period of therapy they suggest that, after an initial decrease in calcium excretion during treatment with cortisone, there was a rise during the third week. During the first week of A.C.T.H. therapy the urinary calcium output was increased to three times that seen during the week before any hormone treatment.

TABLE II—SERUM CHEMISTRY IN CASE 2

Date	Calcium (mg. per 100 ml.)	Phosphorus (mg. per 100 ml.)	Potassium (mg. per 100 ml.)	Sodium (mg. per 100 ml.)	Phosphatase (mg. per 100 ml.)	Urea (mg. per 100 ml.)
Before treatment						
Oct. 31, 1951	10·5	4·8	17·7	..	..	22
On cortisone						
Nov. 14, 1951	10·5	3·9	19·0	324	13·6	..
„ 21, „	10·3	..	..	..	..	..
„ 28, „	9·8	3·6	17·2	324	15·3	18
Before A.C.T.H.						
Dec. 10, 1951	9·5	2·6	19·4	305	12·5	20
On A.C.T.H.						
Dec. 14, 1951	9·5	4·1	17·4	320	11·5	..
Jan. 21, 1952	10·1	5·4	17·5	..	9·6	24

DISCUSSION

It is always difficult to assess the use of a drug in conditions in which spontaneous cures are possible. Spontaneous cure of calcinosis universalis however, is exceedingly rare, and in case 1 there had been a progressive deposition of calcium for two years. In the last six months of this period we took serial radiographs at intervals to be sure that the calcium was not disappearing spontaneously. These films showed undoubted evidence of increasing deposition of calcium. After this long period of observation, A.C.T.H. was given, and within two or three weeks there was an obvious reduction in the size of the subcutaneous nodules, and the clinical impression that improvement was taking place was amply confirmed by radiography. At the end of the first course of A.C.T.H. the radiographs showed a striking disappearance of the calcareous deposits. The girl was next observed for a further two months, and during this period there was no further clinical or radiological evidence of the disappearance of the deposit. After a second course was completed the further improvement was just as striking as before, with the result that the calcium had almost completely disappeared. Though one cannot be certain, the evidence is very strong that the disappearance of calcium was the direct result of the A.C.T.H.

There was no evidence of any improvement in case 2. The failure of A.C.T.H. in this girl may perhaps have been related to the long duration of the disease before treatment was started.

It is unfortunate that the biochemical investigations do not throw any light on the processes involved in the course of calcinosis under A.C.T.H. treatment. There seemed to be a transitory increase of calcium excretion in case 2 under cortisone and under A.C.T.H., but we are not satisfied with this evidence. It is particularly unfortunate that biochemical data are lacking in the second course of A.C.T.H. in case 1. We fully realise that the balance studies in both cases are inadequate, but we felt that they should be summarised because they may be of interest to others studying similar cases.

TABLE III—URINARY CALCIUM OUTPUT IN CASE 2

Weekly periods	Total calcium (mg.)
Before therapy	656·2
1st week cortisone	344·1
2nd week cortisone	353·4
3rd week cortisone	911·7
4th week cortisone	Insufficient data
5th week cortisone	Insufficient data
1st week A.C.T.H.	2881·5
2nd week A.C.T.H.	350·0
3rd week A.C.T.H.	Insufficient data
4th week A.C.T.H.	Insufficient data

SUMMARY

Two cases of calcinosis universalis were treated by A.C.T.H.; one had had a previous course of cortisone.

One of these cases, in which the calcinosis followed dermatomyositis, appeared to respond dramatically to A.C.T.H., almost all calcium deposits disappearing during the course of treatment. The second case, of many years' duration and unrelated to dermatomyositis, did not respond.

We wish to thank Dr. J. L. Emery for the histological studies, and Miss E. Finch for the biochemical investigations.

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"... *It is a peculiarity of our present civilisation that the average educated person will be ashamed to admit that a work of art is beyond his comprehension although, in the same breath, he will proclaim not without pride his complete* [illegible] *which make his electric-switch work, or* [illegible] *of his offspring. Our whole higher* [illegible] *designed to foster this lopsided mentality, to create indifference toward the laws of nature, a deficiency comparable to myopia or colour-blindness.*"—ARTHUR KOESTLER, *Observer*, Oct. 12, 1952, p. 9.

ANTIGENIC EFFICIENCY OF FLUID AND PRECIPITATED DIPHTHERIA PROPHYLACTICS

IN VERY YOUNG BABIES AND LAMBS

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It was shown by Barr, Glenny, and Randall (1950) that babies could be successfully immunised by two doses, each 0·5 ml. (25 Lf doses), of alum-precipitated toxoid (A.P.T.), if the level of their maternally conferred antitoxin had fallen below 0·04 unit per ml. at the time of the first injection. Among babies with levels below 0·02 unit per ml. at this time, the response to immunisation seemed better among those first injected when 6–13 weeks than in those first injected after the age of 6 months. This was attributed to the dose of prophylactic per body-weight being greater, and the total circulating passive antitoxin less, in the younger babies in relation to antitoxin titre per millilitre. Very young babies were not investigated. Vahlquist (1949), however, showed that infants born without any passively conferred antitoxin could be immunised at birth with 1 ml. (45 Lf doses) of A.P.T., though the response might be somewhat delayed. It is probably now generally accepted that failure to immunise very young babies is due rather to interference by maternally conferred antitoxin than to their physiological inability to respond.

IMMUNISATION OF BABIES

We have now investigated the effect of immunisation of very young babies born with passive maternally conferred antitoxic titres below 0·02 unit per ml.: most of these titres were below 0·001 unit per ml. One group received two intramuscular injections, each 0·5 ml. (25 Lf doses), of A.P.T. separated by an interval of 8–9 weeks. The other group had three intramuscular injections, each of 25 Lf doses, of purified toxoid, separated by intervals of a month. This toxoid, prepared by Dr. Linggood, contained about 1800 Lf doses per mg. of nitrogen. The first injection was given to all the babies when they were 6–10 days old. Blood samples were taken 7–10 (usually 8) weeks after the last injection and were titrated for antitoxin content by the guineapig intracutaneous method (Römer and Sames 1909) as modified by Glenny and Llewellyn-Jones (1931). Titrations were made at approximately twofold differences and titres recorded, for example, as 0·02 unit were over 0·02 but under 0·05 unit per ml. In the calculation of geometric means of groups each value was taken as the geometric mean of the limits between which it lay.

The results of these tests are shown in table I, which includes the titres of a group of older babies immunised with two doses of A.P.T. given intramuscularly at an interval of 6–9 weeks; these figures have been taken from the earlier work of Barr et al. (1950). Also included in this table are the titres of six babies, immunised with purified toxoid, who received the first dose when 7 months of age or older. Two facts are at once evident from this table: first, that the response of babies first injected with A.P.T. when 6–10 days old was as good as that of babies first injected at the age of 6 weeks or more; and, secondly, that the response of very young babies to three injections of toxoid was definitely inferior to that of babies of the same age to two injections of A.P.T. At least two factors might contribute to this result: very young babies may not respond well to unprecipitated prophylactics, and the intervals between the injections of toxoid may have been ill chosen.

We have been unable to test the first of these suggestions adequately, but it is perhaps significant that none of the very few babies immunised with toxoid at the age of 7 months or more (group D in table I) failed to produce any detectable antitoxin. Nearly half the very young babies had titres below 0·01 unit per ml. at the time of sampling; none of the six older babies had such low titres. It is clearly impossible to draw any definite conclusions on such small numbers, but the results suggest that age at the time of the first injection may have a considerable effect on the response to immunisation with fluid purified toxoid. Further work is needed.

So far as we are aware, no careful study has been made to determine the best procedure to adopt in a course of primary immunisation involving three injections. It is clear on theoretical grounds that the optimal intervals between the first and second and between the second and third doses must depend on the degree of basal immunity established by the first injection. If this were poor, it might be advisable to use the second injection as a reinforcing primary stimulus and inject it 7–10 days after the first; the third injection might then be delayed for 4 or more weeks. A procedure of this kind was suggested for the immunisation of adults by Barr and Glenny (1951). It appears probable that the basal immunity established by the first injection of toxoid in the young babies of group C was of a low order.

IMMUNISATION OF GUINEAPIGS

Good immunity was produced in guineapigs by only two injections of this batch of purified toxoid. Table II shows the antitoxin titres of guineapigs 10 days after the second of two subcutaneous injections of A.P.T. and of purified toxoid, given 28 days after the first. Slightly better immunity was produced by two injections each of 1 Lf dose of A.P.T. than by two injections of the same amount of purified toxoid. The difference between the means of the logarithms of the titres in the two groups is not significant ($t = 1{\cdot}599$, $P = 0{\cdot}1$–$0{\cdot}2$), but the scatter of titres among the animals immunised with toxoid was considerably greater, and some failures might therefore be expected in the immunisation of a large population of animals with this material. It is nevertheless clearly evident that the difference between the responses of

TABLE I—ANTITOXIN TITRES OF BABIES 7–10 WEEKS AFTER IMMUNISATION

Group	Age at 1st injection	No. of babies and antitoxin titres (units/ml.)										Total	Geometric mean
		<0·005	0·005	0·01	0·02	0·05	0·1	0·2	0·5	1·0	2·0		
A	6 weeks or more	..	..	..	1	5	9	22	6	..	..	43	0·237
B	6–10 days	..	..	..	2	0	4	10	7	..	..	23	0·286
C	6–10 days	6	2	1	2	1	1	2	..	..	..	15	..
D	7 months or more	..	..	2	1	0	0	1	1	0	1	6	0·128

Groups A and B received two injections, each of 25 Lf doses of A.P.T., and groups C and D three injections, each of 25 Lf doses of purified toxoid.

TABLE II—ANTITOXIN TITRES OF GUINEAPIGS 10 DAYS AFTER SECOND INJECTION OF DIPHTHERIA PROPHYLACTIC GIVEN 28 DAYS AFTER FIRST INJECTION

Type of prophylactic	Size of dose	No. of guineapigs and antitoxin titres (units/ml.)									Geometric mean
		0·1	0·2	0·5	1·0	2·0	5·0	10	20	50	
A.P.T.	1 Lf	..	..	..	1	2	17	8	2	..	8·44*
Toxoid	1 Lf	1	1	1	0	4	6	4	1	1	5·17*
Toxoid	2·5 Lf	..	..	..	1	5	7	15	1	..	14·13

* t = 1·599, P = 0·1–0·2

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0·004	1	..	..	..	0	1
0·01	2	..	..	..	0	1
0·02	2	..	..	..	0	2
0·05	1	1	..	..	1	1
0·1	2	7	..	..	3	3
0·2	1	1	..	..	0	..
0·5	..	0	2	..	1	..
1·0	..	1	2	1	0	..
2·0	..	..	4	3	1	..
5·0	..	..	1	3	..	..
10	..	..	..	3	..	..

Much work could profitably be done, especially on the optimum intervals between injections of different types of prophylactic. Little is known of the duration of immunity in babies after primary immunisation, and antitoxic titres 2 or 6 months after the second injection of the course may give a false idea of the amount of permanent antitoxin produced by the course. The effect of rapid growth on permanent production is unknown: possibly the rate of production may only become constant when body-weight remains constant, or antitoxin-producing cells may increase during growth.

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SUMMARY

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Babies given a first injection of purified toxoid at the age of 6–10 days, and two other similar injections at monthly intervals thereafter, developed poor immunity. Better results were obtained in a very few babies given the first injection of three at the age of 7 months.

Two doses of 1 Lf of purified toxoid given at an interval of 4 weeks produced similar titres in guineapigs to those following two injections of 1 Lf of A.P.T. The scatter of titres after toxoid was, however, considerably greater.

Sheep injected with 250 Lf doses of A.P.T. produced higher antitoxic titres than newborn lambs 28 days after injection. This result was also obtained 10 days after a second similar injection.

After three injections of purified toxoid given at monthly intervals newborn lambs tended to have higher antitoxic titres than sheep, but the antitoxin titres were widely scattered.

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MEASUREMENT OF IODIDE-CONCENTRATING POWER AS A TEST OF THYROID FUNCTION

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It has been shown that, even after synthesis of thyroid hormone has been prevented by the administration of thiouracil, the thyroid gland of the rat can still concentrate iodine (Taurog et al. 1947, Vanderlaan and Vanderlaan 1947). Under these conditions the iodine is concentrated as iodide, the amount contained by the gland at any given moment being proportional to the plasma-iodide level at that time. Between the thyroid gland and the plasma there is a gradient for iodide which remains constant over a wide range of plasma-iodide levels.

Stanley and Astwood (1948), producing evidence that the same holds true for man, have suggested that the amount of radioactive iodine accumulated by the thyroid gland after a dose of the antithyroid drug 2-mercapto-imidazole might be used as a measure of thyroid activity. Foss and Herbert (1952), using a modification of Stanley and Astwood's technique, found it, as a test for thyrotoxicosis, as useful as the thyroid iodide clearance.

Childs et al. (1950), investigating in man the effect of increasing amounts of inert iodide "carrier" on the behaviour of a tracer dose of radioactive iodine, showed that amounts of about 5–10 mg. of sodium iodide modified the uptake of radio-iodine by the thyroid gland in a similar way to thiouracil. The radio-iodine, being accumulated in the form of iodide, could be almost completely discharged from the thyroid gland by a dose of sodium thiocyanate. Sodium iodide in doses of this order appears to inhibit the binding of iodine to protein without saturating the iodide-concentrating mechanism of the gland.

This paper sets out the result of 86 tests done by a method similar to that of Stanley and Astwood.

METHOD

86 subjects were tested in two groups. The first group totalled 32 and comprised 12 normal volunteers between the ages of twenty and sixty-five with no history or evidence of thyroid disease, 7 patients with clinical thyrotoxicosis, and 13 patients referred for testing as possible cases of thyrotoxicosis. To these methylthiouracil 400 mg. was given by mouth four hours or more after their last preceding meal, followed an hour later by an oral dose of 35 μC of carrier-free radio-iodine.

The second group totalled 54 cases and comprised 10 normal people, 12 patients with thyrotoxicosis, and 32 patients referred for diagnosis. To these the tracer dose of 35 μC of radio-iodine was given intravenously together with 10 mg. of sodium iodide in a volume of 2 ml.

After the tracer dose counting-rates over the neck and thigh were followed until the highest count was reached, and usually for longer.

The neck was counted at a fixed distance of 20 cm. from the skin over the cricoid cartilage to the central wire of a G10 Pb counter (20th Century Electronics Ltd.) enclosed in a lead collimator 2 cm. in effective thickness. A window with an aperture 6×11 cm. at a distance of 6 cm. from the central wire exposed the whole length of the cathode to gamma rays.

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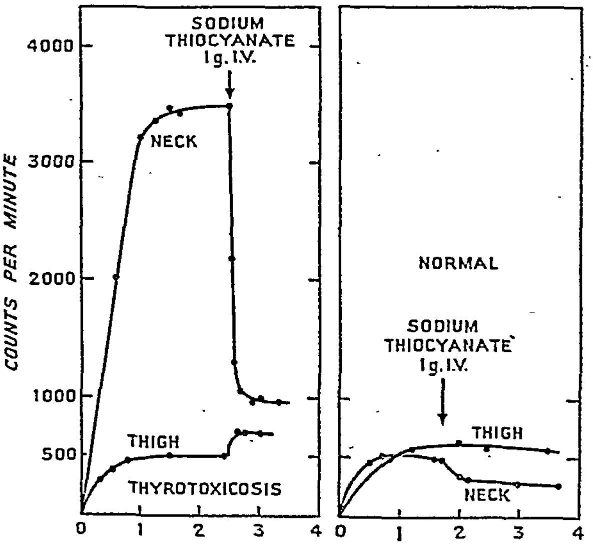

Fig. 1—Neck and thigh counting-rates for 1 thyrotoxic patient and 1 normal person after an oral dose of carrier-free radio-iodine. Methylthiouracil 400 mg. was given an hour beforehand in each case.

TABLE II—ANTITOXIN TITRES OF GUINEAPIGS 10 DAYS AFTER SECOND INJECTION OF DIPHTHERIA PROPHYLACTIC GIVEN 28 DAYS AFTER FIRST INJECTION

Type of prophylactic	Size of dose	No. of guineapigs and antitoxin titres (units/ml.)									Geometric mean
		0·1	0·2	0·5	1·0	2·0	5·0	10	20	50	
A.P.T.	1 Lf	..	..	..	1	2	17	8	2	..	8·44*
Toxoid	1 Lf	1	1	1	0	4	6	4	1	1	5·17*
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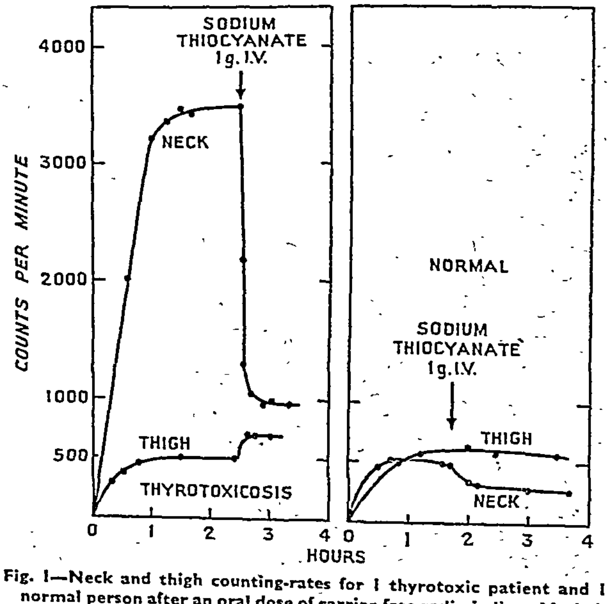

Fig. 1—Neck and thigh counting-rates for 1 thyrotoxic patient and 1 normal person after an oral dose of carrier-free radio-iodine. Methylthiouracil 400 mg. was given an hour beforehand in each case.

of a considerable amount of radio-iodine from the thyroid into the blood-stream. The amount of radio-iodine discharged from the normal thyroid gland is too small to affect the thigh count appreciably.

In fig. 2 the corresponding curves obtained after an intravenous dose of radio-iodine and sodium iodide are shown for one patient in the second group with mild thyrotoxicosis. The counting-rate over the neck reaches a maximum within twenty minutes, after which time there is a steady fall in neck and thigh counting-rates. In most of the normal people tested the counting-rate over the neck reached a maximum within a few minutes.

In view of the finding of Taurog et al. (1947) that the amount of iodide concentrated by the thyroid gland depends on the amount in the blood at any given time, it seemed desirable to express the thyroid uptake of radio-iodine in terms of the blood-iodide level measured at the same time. Childs et al. (1950) have suggested the use of the following fraction:

$$\frac{\text{Percentage of dose taken up by thyroid}}{\text{Percentage of dose per litre of plasma}}$$

This they term the "thyroid iodide space," to express the iodide uptake of the "blocked" thyroid gland. The measurement of the fraction of the dose taken up by the thyroid gland involves the use of corrections for backscatter, &c., and makes the method unnecessarily complicated. The use of the ratio of neck count to thigh count at a chosen time avoids the need for those corrections and for a plasma sample and gives an index of thyroid activity which correlates well with the thyroid iodide space. In 28 cases both indices were measured and the coefficient of correlation was found to be 0·98 (fig. 3).

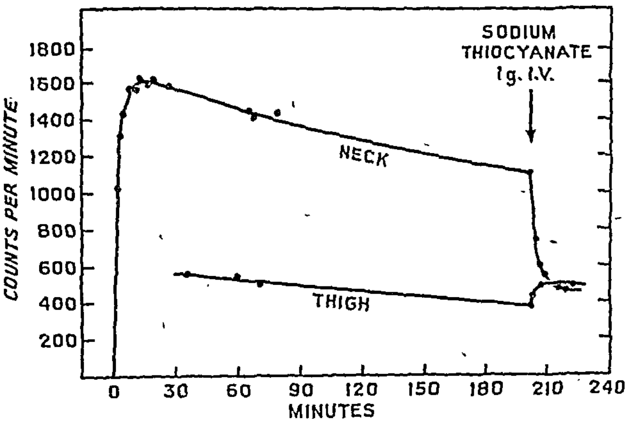

Fig. 2—Neck and thigh counts after intravenous injection of radio-iodine with 10 mg. of sodium iodide as "carrier" in mild thyrotoxicosis.

In people given an oral dose of tracer the ratio was measured after the highest thigh count had been reached and the blood and tissue levels of radioactivity were more closely in equilibrium than during the phase of rapid increase of counting-rates. After this time the thigh counts can be shown to reflect more faithfully the radioactivity of the plasma.

In the remaining cases in which the dose was given by intravenous injection, the neck/thigh ratio was always measured after thirty minutes because the neck count had reached its highest by then. The diffusion of radio-iodine into the thigh tissues is not yet complete by this time, but the choice of a constant time-interval allows a constant relation between the thigh count and blood level of radio-iodine to be assumed, although this is only strictly true if the rate of diffusion of radio-iodine is the same in different people.

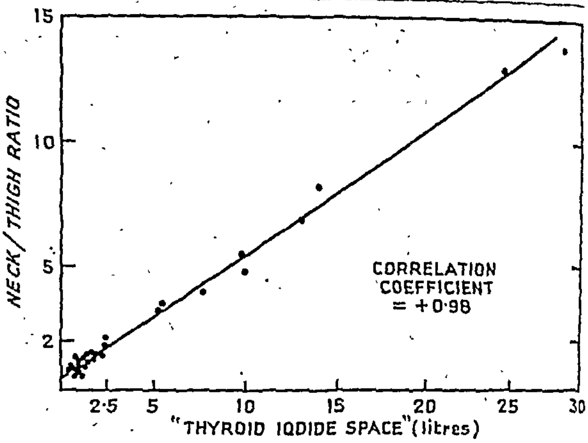

Fig. 3—Correlation between neck/thigh ratio and "thyroid iodide space" in 28 cases.

The 12 normal people in the first group gave neck/thigh ratios of 0·78–1·88 (mean 1·13, S.E. 0·09), and the 10 normal people in the second group had ratios of 0·9–1·8 (mean 1·3, S.E. 0·08). For these two series $t = 1{\cdot}29$, which gives a probability of more than 20% that the difference between the two is a chance one. It has been assumed that there is no significant difference between the two groups, and all the results have been considered together.

In 19 clinically thyrotoxic patients the ratios lay between 2·7 and 26·0, and the remaining 45, for whom the diagnosis was not definite, had ratios of between 0·8 and 4·4. These results are shown in fig. 4. It will be noted that the normals are separated by an interval from the cases of thyrotoxicosis; but, as would be expected, the patients referred for diagnostic testing overlapped both ranges.

These cases were, so far as possible, diagnosed as thyrotoxic or euthyroid without reference to the radio-iodine test, this diagnosis being indicated in the figure. The diagnosis was based on clinical assessment, sleeping pulse, basal metabolic rate, and, in some cases, response to treatment. It will be seen that, with one exception, all the cases with neck/thigh ratios of less than 1·9 were judged on other grounds than the radio-iodine test to be euthyroid. All those with ratios greater than 2·2 were similarly judged to be thyrotoxic. In 8 cases the ratios lay between 1·9 and 2·2; 3 of these patients were considered on clinical grounds to be euthyroid and 5 mildly thyrotoxic.

The single exception was a woman, aged 62, with a neck/thigh ratio of 1·4. She showed many features

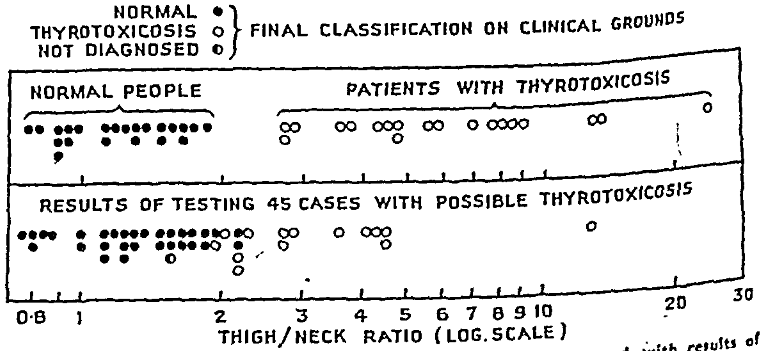

Fig. 4—Neck/thigh ratio in normal and thyrotoxic people compared with results of tests on 45 cases referred for diagnosis. Clinical diagnosis is indicated in each case.

suggesting thyrotoxicosis but also had mild rheumatoid arthritis. Treatment with thiouracil was refused, and no final diagnosis was reached.

DISCUSSION

The only figures for this kind of test so far available are those of Foss and Herbert (1952), and further results are needed to compare its value with that of the more usual "unblocked" tests of thyroid activity. While it was not practicable to make this comparison by carrying out several different tests in every case investigated, in 3 cases measurements of thyroid iodide clearance were also made by the method of Myant et al. (1949):

The first patient had an anxiety state, and gave normal results to both tests, having a neck/thigh ratio of 1·6 and a thyroid iodide clearance of 45 ml. per minute.

The second was judged clinically, and by her subsequent response to thiouracil, to have mild thyrotoxicosis. Both tests gave intermediate results—a neck/thigh ratio of 2·1 and a clearance of 75 ml. per minute.

The third had ophthalmopathic Graves's disease with a normal clearance of 35 ml. per minute and, two days later, a definitely raised neck/thigh ratio of 3·2. This patient had taken several doses of an expectorant medicine during the previous four days, each dose containing about 0·3 g. of potassium iodide, and this explains the apparent disagreement between the two results, the blocked uptake test being much less likely to be falsified by an increase in iodine intake than the thyroid iodide clearance.

The fact that this test remains relatively unaffected by large increases in iodine intake is its main advantage. Foote and Maclagan (1951), using an "unblocked" radio-iodine test in 100 subjects, mention that falsely low results were obtained in 3 cases as the result of high iodine intake. A dose of about 10 mg. of sodium iodide administered with the tracer dose will greatly modify protein binding and therefore give misleading values for thyroid iodide clearance but will not affect the "blocked" uptake.

A further advantage is that the greater part of the radio-iodine taken up by the thyroid gland leaves it within twenty-four hours, thus subjecting it to less radiation than it would receive if protein binding were allowed to occur.

Sources of inaccuracy in this type of measurement have been discussed by Foote and Maclagan (1951); but, besides those which they mention, two further errors may be introduced by using a "blocking" agent. Firstly, some of the radio-iodine is bound to protein, in spite of the use of methylthiouracil or sodium iodide. This finding, which varies from patient to patient, causes the amount of radio-iodine in the thyroid gland to be overestimated to some extent. To allow for this by measuring the residual radioactivity in the neck twenty-four hours after the dose would complicate the test unduly and require the assumption that this radio-iodine had all become protein-bound by the time of the measurements on the previous day.

In this connection it is worth noting that the neck/thigh ratio of the case shown in fig. 2 is 2·7 at 30 minutes, and 2·8 if measured at 180 minutes, after the intravenous injection. In this case very little protein binding of radio-iodine has taken place, but in other cases in which it has not been so effectively prevented the ratio will be found to increase with time, since the protein-bound radio-iodine does not leave the gland as the blood level of radio-iodine falls. For this reason it is desirable to measure the ratio as early as possible after the highest counting-rate has been reached, so as to diminish the error introduced by protein binding.

Accuracy of measurement is also affected by the fact that "blocking" the thyroid gland diminishes the uptake of radio-iodine considerably. Thirty minutes after an intravenous injection of radio-iodine the "blocked" uptake is about half as much as the "unblocked" uptake and correspondingly lower in comparison with the radioactive background provided by the other tissues of the neck, which fact must to some extent diminish the accuracy of measurement. Unlike the "unblocked" uptake of radio-iodine, the radioactivity in the thyroid gland falls in parallel with that in the other neck tissues, and accuracy cannot be increased by delaying measurements until tissue radioactivity has fallen to a low level.

Values found for the "thyroid iodide space" in 10 normal people varied between 0·5 and 2·4 litres, with a mean of 1·26 litres. Assuming the normal thyroid gland to weigh 25 g. it appears to concentrate iodide about fiftyfold, when 1 g. of thyroid tissue is compared with 1 ml. of plasma. In 5 thyrotoxic patients the weight of the thyroid gland was estimated from the weight of tissue removed at operation. By using this and the previously measured values for the "thyroid iodide space" figures for iodide-concentrating power were obtained which varied between 120 and 325 times. Vanderlaan and Vanderlaan (1947) obtained values of 25–50 times for the normal rat thyroid gland and about 250 times when the gland was made hyperplastic by prolonged treatment with propylthiouracil.

There is evidence that iodide-trapping takes place to the same extent in the "unblocked" thyroid gland, merely being thrown into prominence by the use of drugs such as thiouracil which prevent this function from being overshadowed by that of hormone synthesis. Lein (1943) showed in rabbits that the radio-iodide content of the thyroid gland rose rapidly to a peak ten minutes after an intravenous injection of radio-iodine and thereafter slowly fell. The protein-bound (acetone-insoluble) radio-iodine continued to rise steadily for some hours. Franklin et al. (1944) found that slices of sheep's thyroid contained similar quantities of inorganic iodide whether protein-binding was prevented by thiouracil or allowed to take place freely. In some people it appears that protein binding may be blocked spontaneously. Stanbury and Hedge (1950) describe several cretins with large goitres in whom the iodide-concentrating mechanism was intact but not the ability to bind iodine to protein and thus synthesise thyroid hormone.

It will be seen that the measurement of the neck/thigh counting-ratio an hour after an intravenous injection of carrier-free radio-iodine, as suggested by Pochin (1950), is probably to some extent a measure of iodide accumulation. At this time about a third of the radio-iodine in the thyroid gland is likely to be in the form of iodide, although the relative proportions of iodide and protein-bound iodine may not remain the same in glands of differing activity. The present results do not indicate whether the advantages gained by preventing protein binding of iodine are outweighed by the fact that the binding is not completely arrested but is still able to take place to a variable extent.

SUMMARY

The uptake of an oral dose of radioactive iodine by the thyroid gland was measured in 32 people after a dose of 400 mg. of methylthiouracil. To a further 54 people the radio-iodine was given intravenously together with 10 mg. of sodium iodide. Using either method the radio-iodine was accumulated mainly in the form of iodide and was not fixed by the gland.

The two methods appear to give equivalent results, but the second is more rapidly completed, the concentration of radio-iodine by the thyroid gland reaching a maximum within twenty minutes of an intravenous injection.

The ratio of the counting-rate over the neck to that registered over the thigh was used as an index of the iodide-concentrating power of the thyroid. By using this ratio it was possible to make a definite diagnosis in 38 out of 46 cases referred for diagnostic testing.

This test is rapidly completed, is unlikely to be affected by variation in dietary iodine, and subjects the thyroid gland to less radiation than do methods using "unblocked" uptake.

I wish to thank Prof. W. M. Arnott for his encouragement and advice, and the physicians of the United Birmingham Hospitals for access to their patients. Some of the work in this paper has previously been submitted as part of a thesis for the degree of M.D. of the University of Cambridge.

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SUCCINYLCHOLINE IN THE TREATMENT OF TETANUS

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IN tetanus the well-known dangers of exhaustion, dehydration, and infection of the lungs are largely consequences of the muscle rigidity and spasms. The use of hypnotic drugs to lessen muscle spasm increases the danger of respiratory infection. The peripherally acting muscle relaxants therefore promised to be of value in treating tetanus. Since West (1936) described the benefit of curare this drug has often been used (Cole 1951, Frank 1951); and more recently cases have been treated with other muscle relaxants, such as mephenesin (Boles and Smith 1951, Bandi 1951, Davison 1951, Godman 1951, Nilsson 1950, Newhouse et al. 1950, Belfrage 1947) and decamethonium (Keir 1950). These three drugs, however, act comparatively slowly; they cannot follow the rapid fluctuations in muscle tone which are characteristic of tetanus. With succinylcholine, on the other hand, the degree of muscle relaxation can be varied widely in a matter of seconds, and the dose can be continuously adapted to the requirement of the moment.

This paper records experience with a continuous infusion of succinylcholine for three and a half days in a patient with tetanus.

CASE-RECORD

A spinster, aged 58, underwent an operation for removal of nasal polypi on June 3, 1952. No catgut was used, and the postoperative course was uneventful except for slight but persistent bloodstained nasal discharge. During the week June 22–29 the patient toured Scotland by motor coach and at times she was driven through clouds of road dust. On July 4 her jaws became painful and stiff and she had difficulty in chewing her food and in swallowing. Next day she could not open her mouth or swallow her saliva; her neck and shoulders became stiff and painful. She was admitted to hospital on the night of July 7.

On examination on July 8 there were an obvious risus sardonicus and trismus—she could separate her teeth by about $^1/_8$ inch. There was continuous rigidity of the neck and upper back muscles; the abdominal muscles were becoming firm, and all tendon-jerks were grossly exaggerated. There was no cranial nerve paralysis. An attempt to examine her mouth caused a severe spasm, which involved the larynx as well as the neck and shoulder muscles, and the patient became deeply cyanosed and lost consciousness for about a minute. No wound was found, and no sepsis was discovered at the site of the nasal operation. Swabs from the nose grew *Staphylococcus aureus* but no *Clostridium tetani*.

Treatment.—Antitetanic serum 100,000 units was given intramuscularly and repeated three days later; procaine penicillin ('Distaquaine') 900,000 units was given daily for ten days. A Ryle's tube could not be passed, the attempt causing an alarmingly prolonged spasm. It was decided to postpone tracheotomy until the effect of succinylcholine was seen.

Effect of Succinylcholine.—The patient's response to succinylcholine was first assessed by intravenous injections of different doses. 10 mg. caused complete flaccidity for about three minutes and necessitated artificial respiration with oxygen. Two doses of 2·5 mg. two minutes apart caused decrease in respiratory excursion without abolishing trismus. On these findings the patient was given an intravenous drip of isotonic saline solution containing 3 mg. per ml., the rate being varied to deliver between 1·5 and 3 mg. per minute. On this régime the patient was more comfortable and free from major spasms for several hours, but she could not swallow or clear her throat. When the drip was discontinued, a severe spasm with cyanosis developed in three or four minutes. By making minor alterations in the rate of infusion it was possible to steer the patient between mild overdosage (diplopia, shallow respiration with cyanosis) and underdosage (painful spasms of the neck and back, together with laryngeal spasms).

July 9.—During the day the patient became worse and the laryngeal spasms could not be controlled without causing so much respiratory paralysis that there was cyanosis. The dosage of succinylcholine needed to produce this flaccidity was between 1·0 and 1·5 mg. per minute. The patient was also becoming embarrassed by retained material in her pharynx; so tracheotomy was done under local anæsthesia. Thereafter the trachea and posterior nasal space were sucked out at short intervals. This procedure naturally caused laryngeal and generalised spasms; but these could be prevented, or rapidly abolished, by boosting the dosage of succinylcholine so that 5 or 10 mg. was given in a few seconds; during the resulting paralysis the patient could be sustained by inflating the lungs with oxygen through the tracheotomy tube.

July 10.—It was again possible to steer the patient between paralysis and spasms for most of this day; but this entailed almost constant medical supervision. At times it was necessary to give oxygen by artificial respiration; only light pressure on the oxygen bag was needed. The patient however, had slept very little. She was becoming exhausted and her pulse-rate was rising steadily. After 16 ml. of paraldehyde in oil per rectum at 11 P.M. she slept. Succinylcholine had to be given continuously, otherwise painful spasms occurred and woke the patient. The optimal dosage fell so that by 2 A.M. only 0·2 mg. per minute was required; with this dose respirations were so shallow that continuous oxygen was needed to prevent cyanosis.

July 11.—After about eight hours' almost uninterrupted sleep the patient woke refreshed. Succinylcholine was stopped for five hours, except for short periods to cover aspiration of the trachea and pharynx. During most of this time spasms occurred every five to fifteen minutes; during these bouts the patient became cyanosed and needed oxygen for a few minutes after each. For these reasons the succinylcholine drip was started again at 1.30 P.M. and was given for another eight hours, after which it was finally discontinued. The patient was given 16 ml. of paraldehyde rectally and slept in snatches afterwards.

July 12.—The spasms became less frequent, about one every hour; and they were less severe, causing little cyanosis. Improvement thereafter was gradual.

Progress.—Spasms stopped on July 16; rigidity went more slowly; and stiffness of the jaws persisted until July 25. Some lumbar œdema and basal râles were present on July 12, and remained for a week.

The intravenous fluids given during the first five days were equivalent to $3^{1}/_{2}$ litres of isotonic glucose and $2^{1}/_{2}$ litres of isotonic saline solution.

DISCUSSION

There is little doubt that succinylcholine contributed to this patient's recovery. The continuous infusion reduced the muscle rigidity and the severity of the spasms. It would have needed large doses of hypnotic drugs to achieve equivalent relaxation. This would clearly have endangered the already embarrassed respiratory system. By increasing the rate of drip of succinylcholine the patient could be made flaccid while the nasopharynx and trachea were aspirated, while penicillin was injected, or while attention to the back or other nursing manœuvres were completed. This sometimes gravely weakened the patient's respiratory muscles, but anoxia could easily be avoided by inflating the lungs with oxygen. Likewise, the combination of paraldehyde with succinylcholine, continuous oxygen, and, when need be, artificial respiration seemed to be of decisive value when the patient needed sleep during the critical stage of her illness.

Though the use of muscle relaxants is clearly logical in tetanus it complicates the therapeutic problem. The aim is to abolish exaggerated muscle tone without seriously weakening the respiratory apparatus. Though this can be done in patients with a normal neuromuscular system it cannot always be done in patients with tetanus (Adriani and Ochsner 1947, Woolmer 1949). Even when it can be done, the dose required will vary from minute to minute. The degree of muscle tone (which is an expression of the balance between acetylcholine and cholinesterase) depends on many factors. The most important of these are sensory stimuli and tetanus toxin, which increase it, and sedatives and antitoxin, which decrease it. Since these factors vary widely, muscle tone cannot be expected to remain constant, and therefore the dose of relaxant that is right at one moment will at the next be either insufficient to prevent spasms or enough to cause respiratory paralysis. If complete control is the aim—and by this is meant the achievement of a *continuous* balance between muscular relaxation and respiratory paralysis—it is clearly an advantage to use a method, such as continuous succinylcholine, which is capable of minute-to-minute adjustment.

The variation in required dosage was well illustrated in this patient. At first 2·5 mg. a minute caused some relaxation without affecting breathing; later 0·2 mg. a minute caused decreased respiration and cyanosis. The change was presumably due to the fact that, as time went on, more toxin was being neutralised by antitoxin, and the acetylcholine-cholinesterase balance was moving in the direction of decreasing muscle tone. It is also possible that some cumulative action was being exerted by the succinylcholine. Serum-cholinesterase estimations might be of interest in future cases (Evans et al. 1952).

Because of the flexibility of the method, a nearer approach to complete control was attained in this case than in any other in our experience. In practice, however, the need to vary the dosage and the need to give oxygen with artificial respiration mean that this form of treatment entails virtually continuous medical attention, day and night, for several days.

SUMMARY

Succinylcholine was given for three and a half days by continuous intravenous drip to a patient with tetanus.

Administration needed practically constant medical supervision.

Succinylcholine given in this way seemed to be a valuable contribution to recovery.

Our thanks are due to Mr. Angell James for doing the tracheotomy.

References at foot of next column

FATAL POISONING IN CHILDREN FROM ASPIRIN, QUININE, AND ANTHISAN

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OWING to the comparative rarity of accidental poisoning in children, the following three separate cases may be considered of interest.

ASPIRIN POISONING

Case 1.—A girl, aged 1 year 6 months, healthy and active, was found by her mother playing with an aspirin bottle a quarter full of tablets, there being pieces of tablets on the floor. This bottle was usually kept in a drawer within reach of the girl. The child seemed quite well and remained so until she went to bed at 6 P.M. At 10.30 P.M. the mother woke up and gave her some milk and water and, thinking she was cold, took her into bed, when she was sick. Her cot was brought into the mother's room, and the child went to sleep again. At 3 A.M. next morning she was sleeping peacefully, but at 8 A.M. the mother found her with blue lips and no sign of life and sent for the doctor, who found the child was dead.

Necropsy findings 33 hours after death. The cerebral vessels were congested. The stomach contained only a small quantity of thin yellow fluid, and the mucosa was sodden and intensely congested in places. The thymus was congested, with many small petechial hæmorrhages. The lungs were deeply congested with blood. The heart was congested, with subpericardial petechial hæmorrhages. The kidneys showed a few small subscapular hæmorrhages. The liver was yellowish brown, soft, and with large hæmorrhagic areas. The viscera contained salicylic acid, the decomposition product of aspirin; the stomach and its contents contained gr. $^{1}/_{20}$, and the liver gr. $1^{1}/_{10}$. From these figures it was calculated that about eight tablets, each of gr. 5, had been consumed.

At no time after playing with the bottle of aspirin tablets was the girl seen to perspire or to be flushed. About 7 hours elapsed before she vomited. Death occurred suddenly, about 15 hours after ingestion, possibly in a convulsion; no early signs or symptoms of aspirin poisoning were noted by the mother. In adults death has followed the taking of gr. 150, but a more usual fatal dose is gr. 300–450. Calculated from the smallest recorded fatal dose the equivalent for a child of the patient's age would be gr. 20; but it was estimated that she had taken gr. 40.

QUININE POISONING

Case 2.—A healthy and active girl, aged 1 year 9 months, was seen to swallow a pill at 10.30 A.M. Her mother therefore gave her a dose of syrup of figs. The child did not vomit, and half an hour later the doctor could find nothing wrong with the child and prescribed syrupus ipecacuanhæ. At 12.45 P.M. the child died in convulsions.

Necropsy findings 26 hours after death. The face was cyanosed, and the cerebral vessels were intensely congested. The stomach and small intestine contained a little thick and slightly blue matter. The lungs were intensely congested with blood and rather œdematous. The right auricle and ventricle were congested. The viscera contained a con-

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DR. WOOLMER, DR. CATES: REFERENCES

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siderable quantity of quinine sulphate and iron. The stomach and its contents contained gr. 3 of quinine sulphate together with three undecomposed pills. The liver contained gr. $^3/_4$ of quinine sulphate, and the urine gr. $^1/_{40}$ of quinine sulphate. The pills were of iron and quinine, containing gr. $^1/_5$ of quinine sulphate. They did not contain any strychnine.

Before general protoplasmic poisoning sets in, there is a preliminary short stage of excitation, and convulsions may develop. The quinine alkaloids cinchonine and cinchonidine present in quinine sulphate are convulsants. Quinine can be similar to strychnine in its convulsant effects. The respiratory centre is first stimulated, causing fast, shallow, inefficient respirations, and later paralysed. There is also a fall of blood-pressure and direct cardiac depression.

The maximal *B.P.* therapeutic dose of quinine sulphate for an adult is gr. 10; so that for a child aged 1 year 9 months would be gr. $1^3/_4$, which dose was greatly exceeded. Smith (1938) states that the toxic dose is difficult to estimate in adults, being recorded as between gr. 27 and gr. 240. The proportionate toxic dose for a child aged 1 year 9 months would be gr. 3–4. More than this was found in the child's body. Sollmann (1949) states that in an adult recovery has followed the taking of gr. 450. Fatal cases in children are uncommon. Bamford (1947) states: "Children have been fatally poisoned by swallowing tablets." Willimott (1931) reported a case of fatal poisoning in a child, aged $2^1/_2$ years, following ingestion of 26 tablets, each of gr. 5. Nelson (1950) describes the premonitory symptoms preceding coma and death but does not say what is a fatal dose.

ANTHISAN POISONING

Case 3.—A healthy and active girl, aged 1 year 4 months, was found at noon putting her hand to her mouth, with a small white box, which contained tablets of 'Anthisan' (pyranisamine maleate), lying open on the floor. This box had been in a drawer 2 ft. above the ground. Soon afterwards the child began retching, but only vomited a little after some warm tea had been given. Her colour was good, and she was put in a chair but fell off in a convulsion, the time of onset of which was not noted. Before leaving for hospital at 1.30 P.M. the child was almost certainly dead, being very white and still. Death was certified at 1.50 P.M.

Necropsy findings 21 hours after death. The cerebral vessels were congested. The stomach contained a little mucoid material with flecks of blood. The blood-vessels were congested, as were the intestines. There was thick bluish-green fluid in the small intestine. The larynx, trachea, and bronchi were clear and pale, and their inner surface was covered with thin watery fluid. The lungs were acutely emphysematous and congested. The left ventricle appeared to be in systolic contraction.

Histology.—The only organs to show any changes of note were the lungs, where there was congestion of the capillaries with irregularly loculated areas of collapse, associated with interstitial and intra-alveolar œdema. The stomach contents contained gr. $^1/_{14}$ of anthisan, the contents of the small intestine gr. $^1/_4$, and the liver gr. $^1/_2$.

Each tablet contained about gr. $1^1/_2$ of anthisan equivalent to about gr. $1^1/_4$ of pyranisamine. Hence the child had consumed up to six anthisan tablets. Such a dose would undoubtedly be fatal in a small child.

Possibly the toxic effect of the quinidine-like action on the heart caused the fatal convulsion by producing heart-block, ventricular fibrillation, or inhibition of the whole heart (Sollmann 1949).

Few deaths have been reported in children, and the smallest fatal dose in children is not established.

COMMENTS

These three cases bear similarities, although the drugs were so different, in that the children were healthy, were of similar ages, and had found the tablets which were put away within their reach.

In cases 1 and 2 there were no immediate symptoms and it was uncertain whether the tablets had been consumed, but in case 3 symptoms came on quickly, the child being seen putting tablets in her mouth. Death took place suddenly in each case, in convulsions with anthisan and quinine and possibly so with aspirin.

Absorption was probably hastened in case 2 by syrup of figs and in case 3 by warm tea.

When there is a strong possibility without definite evidence that a child has swallowed possibly poisonous tablets, it should be assumed that this has happened, rapid action should be taken to empty the stomach, and nothing should be given by mouth that could hasten absorption.

I wish to thank Colonel E. Laverack, H.M. coroner for the Howdenshire district; Mr. E. T. Heap, H.M. coroner for the West Riding; and Colonel I. N. Ware, O.B.E., H.M. coroner for York for allowing me to make extracts from their depositions in these cases. I am also grateful to Mr. L. C. Nicholls, director of the Metropolitan Police Laboratory, for the chemical analyses.

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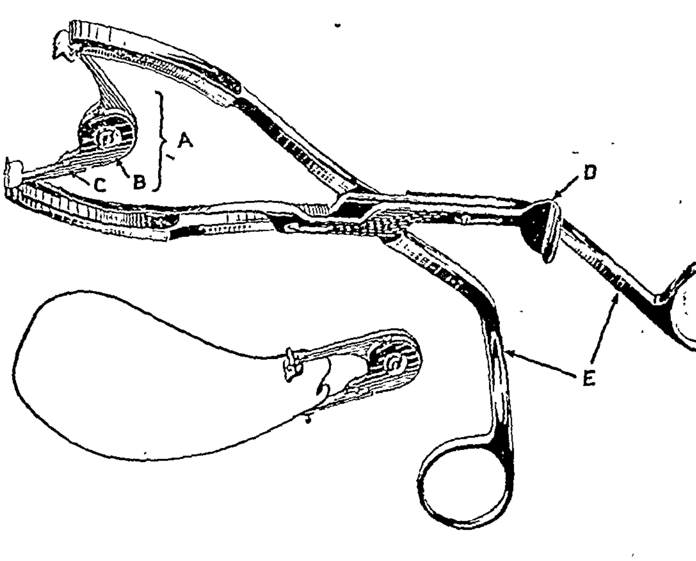
New Inventions

A CERVICAL OCCLUSIVE CLAMP

As a preliminary to total hysterectomy for carcinoma of the body of the uterus, it is an agreed and logical practice to occlude the cervix by some means in order to prevent malignant cells escaping during the operation. The relative frequency with which the growth recurs in the vault makes this procedure rational, and encourages the use of any simple measure which will limit local recurrence even further.

Such measures as packing the uterus with spirit or formalin-saline solution have been used either alone or combined with suturing of the cervix. This by no means produces a watertight or cell-tight seal, and, since this type of growth is commoner in nulliparous women, it is often very difficult to suture the cervix perfectly.

The purpose of this clamp is to occlude the cervix more tightly than has been found possible by any other means. Its efficiency has been tested extensively in



benign cases by filling the uterus with indigo-carmine solution before total hysterectomy; there has never been any escape of fluid.

In the accompanying figure, the clamp unit (A) consists of sharp toothed upper and lower jaws, supported by strong arms converging at a hinge $1\frac{1}{2}$ in. distant; the opening and closing of the jaws is controlled by a rachet mechanism (B) neatly located in the hinge. The control lever (C) of the rachet lies parallel to the arm of the lower jaw, where it may be disengaged readily by a simple device (D) on the carrier forceps (E) when the clamp is approaching the cervix in the vagina. This allows the clamp to be introduced in the closed position through the narrow introitus of the nulliparous patient, and then to be opened when the roomier vagina is reached so that it can grip and compress the cervix. Immediately before the final compression of the cervix, the rachet on the clamp is allowed to come into action merely by operating the disengaging lever (D) on the carrier forceps. Full compression is thus securely maintained. The carrier forceps are then easily slipped off the clamp by a slight opening movement of the handles.

The clamp, which is made in two sizes (standard and large), takes up very little room in the vault and in no way interferes with the hysterectomy. In fact it acts as a very convenient landmark which identifies the base of the portio vaginalis. The clamp and carrier forceps are easily dismantled for cleaning.

This clamp should be capable of modification to suit temporary occlusive procedures in other operative fields.

The instrument may be obtained from Heaton Grogan Co. Ltd., 21, Bowling Green Lane, Clerkenwell, London, E.C.1, to whom much credit is due for its final production.

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Reviews of Books

Non-Pulmonary Tuberculosis of Bovine Origin in Great Britain and Northern Ireland

GRAHAM SELBY WILSON, M.D., F.R.C.P., D.P.H., director, public health laboratory service, Medical Research Council; J. W. S. BLACKLOCK, M.D., F.R.F.P.S., professor in pathology, St. Bartholomew's Hospital Medical College, London; LILIAN VIOLET REILLY, B.SC., M.D., D.P.H., bacteriologist, Northern Ireland Tuberculosis Authority. London: National Association for the Prevention of Tuberculosis. 1952. Pp. 108. 16s.

IN this volume three papers dealing with findings for England and Wales, Scotland, and Northern Ireland have been brought together, and a general discussion of the English and Welsh and the Scottish reports has been added. The distribution of human and bovine bacilli is analysed in detail according to types of disease, age of patient, contact history, milk-drinking history, and region of domicile of patient. The calculation that in Great Britain as a whole in 1944 there were 1600 deaths from non-pulmonary tuberculosis due to bovine-type bacilli has already had the full publicity it deserves. This volume contains the evidence needed to demand that all milk for human consumption should be made safe by efficient heat treatment, unless it is known to be derived solely from a herd of non-reactors to tuberculin. The evidence that the number of such herds should be increased as rapidly as possible is equally strong.

The Metabolic Response to Surgery

FRANCIS D. MOORE, M.D., Moseley professor of surgery, Harvard Medical School, Boston, Mass., and MARGARET R. BALL, A.B. Metabolic diagrams by MILDRED B. CODDING, A.B., M.A. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 156. 55s.

To show how the human body responds to injury, Professor Moore and his team have arranged the results of some of the metabolic balance studies they have made during the last six years. The effects of surgical operations of varying severity in different types of patient, and of starvation, immobilisation, and changes in endocrine secretion, on nitrogen, sodium, and potassium metabolism, are discussed and evaluated.

The writers illustrate the disturbances associated with multiple operations and with large extrarenal losses of body-fluids accompanying intestinal fistulæ, and the changes associated with burns and bilateral adrenalectomy. They also discuss how much the normal effects of injury can, or should, be disturbed by treatment, giving case-histories (which are an important part of the book) and describing the value of protein supplements such as albumin, whole plasma, and solutions containing amino-acids or protein hydrolysates. The importance of adequate provision of calories with amino-acid and hydrolysate preparations, and the slow rate of turnover of albumin and whole plasma, are emphasised. They mention the difficulty of interpreting metabolic balance studies in which materials are pooled for periods of three, four, or even seven days. Difficulty also arises when the preoperative period of study is too short for the existing plane of metabolism of the patient to be assessed. The last chapter summarises the evidence and recommendations, and a useful appendix gives the detailed composition of diets and intravenous infusions suitable for the various stages of treatment.

Here is described in detail the stuff the sick are made of. The essential normality of the metabolic changes after injury is emphasised and enthusiastic claims to have reversed such reactions, by overwhelming the urea ammonia mechanism with hydrolysed protein, are disarmingly discounted. This book should have a profound effect on the postoperative treatment of all patients and especially those whose convalescence is complicated by infection, wound disruption, or leakage from fistulæ.

Understanding Heredity

An Introduction to Genetics. R. B. GOLDSCHMIDT, professor emeritus of zoology, University of California. New York: John Wiley. London: Chapman & Hall. 1952. Pp. 228. 30s.

ENCOURAGED by the public interest in the Lysenko controversy, Professor Goldschmidt has written a book setting out clearly and simply the principles of genetics. He does not directly refute Lysenko's views: but he shows that the main outline of mendelian segregation fits so well with the observed behaviour of the chromosomes that the reader will be convinced that the chromosomes are the main bearers of heredity. The later chapters, covering more difficult topics—gene collaboration, multifactorial inheritance, multiple alleles, and physiological and biochemical genetics—are well written but less convincing. Here the reader without special knowledge of genetics must take Professor Goldschmidt on trust as a reliable guide. Medical practitioners will be pleased to note his full account of mutations; many doctors find it difficult to appreciate that where a condition seriously affects health, even though it is determined by a single dominant hereditary factor, most patients will have a "negative family history."

Isotopes in Biochemistry

Ciba Foundation Conference. Consulting editors: J. N. DAVIDSON, M.D., L. H. GRAY, PH.D., A. S. MCFARLANE, M.B., A. NEUBERGER, M.D., F.R.S., G. POPJÁK, M.D., and C. RIMINGTON, PH.D. Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, M.B. London: J. & A. Churchill. 1951. Pp. 288. 27s. 6*d*.

AN informal international meeting of workers with isotopes in the biochemical field was held in London in March, 1951, under the auspices of the Ciba Foundation. The proceedings, consisting in communications followed by discussions, are published with a foreword by Sir Charles Harington, F.R.S. The speakers were concerned on the whole less with technique than with the results obtained with isotopes in various branches of biochemistry, but the extent to which procedures such as chromatography, ionophoresis, and infra-red spectrometry are being used in isotope work clearly emerges. Six fields were covered: steroids; hæmoglobin and metabolic derivatives; the use of tracers in the study of biological effects of radiation; nucleic acids; proteins and amino-acids; and carbohydrate and fatty acid metabolism. All the subjects discussed had an indirect, and some also a direct, reference to medicine.

C. P. Leblond emphasised the excretion of steroids in the bile, and K. Bernhard, after studying a spleen of high cholesterol content in a case of splenic tumour, suggested that cholesterol is synthesised by this organ. A. Neuberger pointed to discrepancies between the isotopic and agglutination methods of measuring the life span of the human red cell; the hæmoglobin may not be so completely locked up in the cell as was thought. A. Hollaender, G. E. Stapleton, and W. T. Burnett reported that *Bacterium coli* is protected from X-ray damage by a variety of compounds, especially thiols and carboxylic acids. E. Hammersten's findings indicate that synthesis of nucleoproteins precedes, and is necessary for, synthesis of proteins. From studies of fatty acid synthesis in the mammary gland, G. Popják concluded that it proceeds by stepwise addition of two-carbon units, and suggested that the glycerol supply may sometimes be rate-limiting in fat synthesis. In the discussion S. Gurin stressed pituitary-pancreas antagonism in fat synthesis from acetate.

Sodium Metabolism in Health and Disease

DOUGLAS A. K. BLACK, M.D., F.R.C.P., lecturer in medicine, University of Manchester. Oxford: Blackwell Scientific Publications. 1952. Pp. 79. 9*s*. 6*d*.

OUR knowledge of the physiology and the functional pathology of the electrolytes in man is advancing so rapidly that few who are not working in this field can keep pace. Many of the published reviews consist largely of diagrams and are difficult to follow or digest. This small monograph, which was awarded the Rogers prize of the University of London in 1951, reviews the highly complex problems of sodium metabolism, covering work published up to eighteen months ago. In a surprisingly small space Dr. Black covers such diverse subjects as the excretion of sodium, its distribution in the body, its metabolism in the infant, the clinical effects and treatment of sodium depletion and retention, and the rôle of the adrenal cortex. This is a really readable introduction to a difficult subject. A companion volume on potassium would be equally welcome.

Clinical Pathology of the Eye

BERNARD SAMUELS, M.D., emeritus clinical professor of ophthalmology, Cornell University Medical College; ADALBERT FUCHS, M.D., E.O. professor of ophthalmology, University of Vienna. London: Cassell. 1952. Pp. 420. £7. 7*s*.

THE opening chapter of this work deals with the general pathology of the eye, and the 7 succeeding chapters with the different ocular structures. The last 6 chapters cover myopia, tuberculosis, syphilis, post-operative pathological findings, injuries, and tumours. Unfortunately the text as a whole deals more with morbid histology than with the wider aspect of pathology, and thus fails to live up to its title. The illustrations leave nothing to be desired; but the supporting text is uneven, the technical revolution through which histology is passing at present is overlooked, the descriptions tend to be confined to individual entities, and the teaching is not always up to date. The significant work of Callendar and Wilder on the histology of choroidal melanomata is ignored in favour of a rather obsolete interpretation, and the pathology of phlyctenular ophthalmia is discussed in almost meaningless terms. Sympathetic ophthalmia is firmly, and perhaps rightly, ascribed to virus infection. The great experience of the authors in the morbid histology of the eye lends authority to many specialised accounts scattered throughout the text, but this cannot be regarded as an adequate presentation of the current teaching in ophthalmic pathology.

The Human Blood-groups

P. H. ANDRESEN, M.D., chief, municipal blood bank, Bispebjerg Hospital, Copenhagen. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 114. 25*s*. 6*d*.

THIS book deals mainly with the medicolegal applications of blood-grouping. It gives adequate detail about the distribution and heredity of the blood-groups and the application of this information in cases of disputed paternity: it also deals with the use of blood-group methods for the identification of blood stains, semen, and saliva. Actual techniques of blood-grouping are hardly mentioned at all, and the author seems satisfied with the slide method. A former chief of the serological department in the Copenhagen University Institute of Legal Medicine, Dr. Andresen has had more experience of this kind of work than anyone in Europe; in fact, only A. S. Wiener in New York has had comparable numbers to deal with. In Denmark the courts can make compulsory orders for blood-group tests in suitable cases, and at present about 2000 disputed paternity cases are settled annually. The courts, moreover, can have these tests done at the University Institute, which is not run by the police and accepts no fee from the plaintiff. Apparently the Danish Medicolegal Council still relies on the use of the ABO, A_1A_2, and MN systems. Dr. Andresen consequently gives most space to these; but he does deal quite adequately with the Rh system and the "secretor" phenomenon, and he mentions briefly the other blood factors such as P, S, and the Lewis groups. He does not commit himself on the question of the Rh group nomenclature, and it is unfortunate that apostrophes have often been substituted for dashes in the symbols of Wiener's nomenclature (e.g., Rh' for Rh′). This book, however, fills a gap in the literature and Dr. Andresen's wide experience allows him to point out the difficulties and limitations, as well as the possibilities, of blood-group techniques.

Mind: A Social Phenomenon

Illustrated by the Growth of Medical Knowledge. F. S. A. DORAN, M.A., M.D., F.R.C.S., clinical demonstrator in anatomy, University of Manchester. London: Watts. 1952. Pp. 182. 10*s*. 6*d*.

To say anything new about the mind-body problem calls for genius: even to restate the issues arrestingly demands exceptional freshness of outlook. Dr. Doran is a painstaking and thoughtful man who writes clearly, but does not manage to grapple with the complexities of his theme or the stronger arguments of the dualist. As a simple statement of the view that mind is an expression of brain function, and a rapid résumé of the history of medical thought, the book is interesting and would give a useful turn to a medical student's reflections.

Méconnaissances et hallucinations corporelles

Intégration et désintégration de la somatognosie. H. HÉCAEN and J. DE AJURIAGUERRA. Paris: Masson. 1952. Pp. 382. Fr. 2300.

THIS interesting monograph from the Paris school of neurology deals with problems common to neurology and psychiatry which have recently attracted renewed interest. The theme of the book is disturbances of the body-image; and phantom limbs, anosognosia, constructive apraxia, the Gerstmann syndrome, "hallucinations of the self," and other aspects are discussed in detail. The authors give many personal case-records with, in some cases, detailed pathological reports; and these are correlated with previous work on the subject. The production of the book is good, but the price seems high for a paper-bound volume.

Architectural Principles in Arthrodesis (2nd. ed. E. & S. Livingstone. 1952. Pp. 196. 42*s*.).—The second edition of Mr. H. A. Brittain's well-known monograph has been largely rewritten, and expanded in various ways. It is a craftsman's manual, not pretending to any wide discussion of the indications for arthrodesis as opposed to any other procedure in a given case, and it has the advantages and disadvantages of this type of book. He is a persuasive advocate of the operations he describes, many of them the result of his own original thoughts and methods. The principles he expounds so clearly are those essential for the embodiment of the graft, which he considers the mainstay of all arthrodeses. He does not attempt any wide description of other methods of arthrodesis, and the book is therefore of greater value to the surgeon of some experience than to the student.

Brittain's ischiofemoral arthrodesis has come to stay; over the last ten years the experience of surgeons in many parts of the world has proved the soundness of this procedure. He now adds a description of his more recently designed V-arthrodesis of the hip. Whether this will become equally popular remains to be seen: an incidence of nearly 10% of fractures of the femur as a complication of its early stages is rather disquieting. In view of the present surge of feeling towards arthroplasty, it is perhaps healthy to be reminded of the advantages of arthrodesis by someone as expert and enthusiastic as Mr. Brittain.

THE LANCET

LONDON: SATURDAY, OCT. 25, 1952

Congenital Tuberculosis

Some medical conditions are truly rare; others, once thought to be rare, prove less uncommon when rigorously sought. This second group would seem to include congenital tuberculosis. In 1935 Beitzke[1] found reports of 61 proved cases of congenital tuberculosis with morbid anatomical lesions, and of a further 40 in which tubercle bacilli were recovered from the fœtus without any apparent histological change. Hughesdon,[2] surveying the period 1935–45, found an additional 11 proved cases and 15 "probables"; and the total of acceptable case-records is now around 130.

The main source of infection is the placenta, bacillary thrombi developing in the intervillous space because, in Loewenstein's[3] words, "circulation in these lagoons is very slow." After direct invasion of the fœtal blood-stream via the umbilical vein a primary complex may be established in the liver and the glands of the porta hepatis or, if the bacilli by-pass the liver via the ductus venosus, in the lungs and hilar glands. The fœtal tissues being in the first instance non-allergic, simultaneous primary infection of liver and lung can also occur; hence the finding of primary complexes in both organs. When a tuberculous placental focus ruptures into the amniotic fluid the fœtus may either swallow tubercle bacilli and develop mesenteric lesions or inhale the bacilli during the course of labour, so that multiple primary foci develop in the lungs and hilar glands[4]; bacilli may also be aspirated into the eustachian tube and middle ear, again causing lesions of primary type. A further possible source of infection, after the membranes have ruptured, is material from a tuberculous endometrium. The various routes and modes of infection can thus give rise to a disease-pattern of considerable complexity, which may be further complicated by direct droplet infection from the mother's breath after birth. The clinical course of the illness is generally disastrous; the infant soon fails to thrive, and generally dies within two months from miliary tuberculosis. One important factor in the accelerated postnatal progress of the disease is the increased level of tissue oxygenation compared with that in the fœtus, which depends entirely on the placental blood-supply for its oxygen. Vorwald[5] demonstrated in the fœtal guineapig high resistance to tuberculous infection even after injection of the bacilli directly into the fœtal tissues in utero. The expansion of the fœtal lungs at birth, before the umbilical cord is tied, may also flood the newly opened pulmonary circulation with tubercle bacilli, leading to miliary foci throughout these organs. After birth, as Rich[6] points out, the abundant oxygen supply to the lungs, combined with the facts that the blood-supply to the liver is largely venous and that much of the available oxygen is consumed by the hepatic cells themselves, may favour the more rapid development of the pulmonary lesions, so that by the time of death these may be much the more prominent.

Placental tuberculous infection does not necessarily result in invasion of the fœtal circulation, nor is such invasion inevitably followed by tuberculous disease; organisms are sometimes recovered from the fœtal heart blood with no evidence whatever of disease in any organ. Indeed, the possibility of occasional recovery from congenital tuberculous disease cannot be discounted; certainly survival up to the age of 26 months has been recorded by Hughesdon; and presumably there can be slight, as well as severe, intra-uterine infections, according to the number of bacilli released. Most earlier accounts have described or assumed the presence of extensive disease in the mother. As Harris and Trenchard[7] indicate, however, there is a strong likelihood that the early hæmatogenous dissemination of organisms after primary infection may result in infection of the placenta. The finding by Choremis and Pantazis[8] of positive bone-marrow cultures in a high proportion of cases with a recent primary complex supports this view. Such a dissemination occurs more freely before allergy develops, and the initial implantation of bacilli in the placenta may even take place within the first few weeks after entry of the organisms into the mother's body. Certainly the plea that women who develop any significant primary or early post-primary tuberculous lesions during pregnancy should be carefully supervised is amply justified, and probably such patients should receive chemotherapy as well.

Congenital tuberculosis is one of the conditions awkwardly placed on the frontiers of various specialties. The chest physician, obstetrician, pædiatrician, and pathologist are all more or less concerned. Combined effort should ensure, however, that no gap exists where the frontiers meet. Measures that might be considered include routine radiographic examination of the chest of all pregnant women; bed rest and chemotherapy for those found to have active lesions (including primary infection with visible pulmonary or glandular foci, erythema nodosum, and particularly pleural effusion); routine pathological examination of the placenta of tuberculous mothers; and culture for tubercle bacilli of the lochia and of blood from the umbilical vein where the mother has, or has recently had, active tuberculous disease. A suspected infant should have a tuberculin-jelly test and perhaps a chest radiograph at weekly intervals, since early chemotherapy might be life-saving.

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1. Beitzke, H. *Ergebn. ges. TuberkForsch.* 1935, 7, 1.
2. Hughesdon, M. *Arch. Dis. Childh.* 1946, 21, 121.
3. Loewenstein, E. *Beitr. Klin. Tuberk.* 1935, 87, 57.
4. Pagel, W., Hall, A. S. *Tubercle*, 1946, 27, 153; *Ibid*, 1948, 29, 32.
5. Vorwald, A. J. *Amer. Rev. Tuberc.* 1937, 35, 260.
6. Rich, A. R. Pathogenesis of Tuberculosis. Springfield, Ill., and Oxford, 1951: p. 75.
7. Harris, W. C., Trenchard, H. J. *Tubercle*, 1952, 33, 273.
8. Choremis, C., Pantazis, S. *Lancet*, 1952, i, 748.

Dental Treatment of Children

UNDER the Dentists Bill the new General Dental Council would be enabled to follow the New Zealand precedent and allow ancillary workers to perform simple dental operations, under professional supervision, in the public-health services. The British Dental Association has sought to prove that such a step is not only undesirable in the public interest but also unnecessary. The dental profession has always argued that it could treat satisfactorily the "priority classes" of the community, and that the reduced demand for treatment after the imposition of charges under the National Health Service would free enough dentists to restore the school dental service, which has virtually broken down since the health service began in 1948. Many more young dentists, it was contended, would wish to enter the local-authority dental services, since they would find fewer openings as assistants in private practice; while the reduced demand on practitioners would enable them to devote more time to the treatment, in their own surgeries, of school-children and expectant and nursing mothers.

The increase in the number of recruits to the local-authority health services has turned out to be much smaller than was expected by some prophets; for it has made no significant impression on the staffing problem of the school dental service, and there are still very few parts of the country with a full complement of school dentists. The British Dental Association has accordingly sent a questionary to all practising dentists throughout the country asking them whether they are willing to treat children in their practices and, if so, how many hours each week they are prepared to set aside for this purpose. From the replies it appears that private practitioners are between them prepared to devote 10,000 hours a week to treating children; which, according to the association, would suffice for the treatment of a million children per annum. It would be more accurate, however, to say that, working for fifty weeks in the year, these practitioners would set aside annually one million half-hour sessions for the children. Thus each year one million children could each be seen once, for half an hour. But very few children can have all the dental treatment they need in a single half-hour session each year. The average number of visits to the dentist by every child who needs dental care is at least four each year; and little of permanent value can be done if each session is shorter than half an hour. Thus, on the most optimistic estimate, the returns suggest that an additional 250,000–300,000 children could be properly treated. Any scheme based on the willingness of dental practitioners to devote 10,000 hours weekly to their child patients can obviously reach only an insignificant fraction of the 6–7 million school-children in the country, of whom at least 80% require continuous dental care. Far from supporting the case against the legalisation of dental ancillaries for simple routine dentistry, the results of the British Dental Association's initiative seem to show that these ancillaries are essential if dental treatment for the vast majority of our children is to go beyond the emergency extraction of teeth for the relief of toothache.

It is perhaps not surprising that of the 10,000 or more practising dentists in the country, more than four-fifths have indicated their unwillingness to treat school-children. The work is mainly routine and holds little interest for the highly trained dental surgeon. For this reason, the proposal to train ancillaries specifically for simple operations, and to employ them in clinics under professional supervision, must seem to the unprejudiced observer of the neglect of our children's dental health an unexceptionable development. The British Dental Association's investigation demonstrates that without this step the neglect will continue. In the Parliamentary session that is now ending the Bill passed through all stages in the House of Lords[1]; but unfortunately, in the press of business, it did not come before the House of Commons. We hope that in the new session the Government will not forget it.

New Views on Bronchiectasis

THE pathogenesis of bronchiectasis has long been a favourite subject of medical controversy: LAENNEC considered that the bronchi were dilated by their retained secretions; STOKES, of Dublin, taught that the condition arose when the bronchial walls were weakened by inflammation; and others have since attributed the dilatation to fibrosis or to congenital defects in the bronchi. In the last twenty years, largely as a result of the work of LEE LANDER and DAVIDSON,[2] the importance of peripheral collapse of the lung has received a great deal of attention. It is argued that mucus is aspirated into the peripheral bronchi, leading to collapse of the affected area of lung, and that this collapse increases the negative pressure in the pleural space and causes dilatation of the bronchi proximal to the obstruction. This explanation has been widely accepted, but it was challenged by ROBERTS and BLAIR [3] on the grounds of their work on pulmonary collapse in primary tuberculosis; among 77 children with collapse they found 31 in whom there was no suggestion of bronchiectasis and no increase in the pleural negative pressure, though this was not measured in all cases. They considered that in the children who did have bronchiectasis the important factors were retention of secretion and inflammation of the bronchial wall. The wheel has thus come full circle.

The latest contribution to the discussion comes from WHITWELL.[4] He has examined 200 bronchiectatic lungs removed at operation, and he has explored the bronchial tree by serial histological sections, by direct dissection, and by the preparation of neoprene casts. Believing that bronchiectasis is not one disease but several, he has tried to correlate the pathological findings with the clinical picture, and to some extent he has succeeded. He distinguishes three types of bronchiectasis, the atelectatic, the saccular, and the follicular, but even so he was unable to classify a large proportion of his material. The atelectatic type was the least common, accounting for only 10% of his specimens, and it was the only type in which all the bronchi to a lobe were involved; in the other types bronchial involvement was patchy. Here the

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1. Lancet, 1952, i, 363.
2. Lee Lauder, F. P., Davidson, M. Brit. J. Radiol. 1938, 11, 65.
3. Roberts, J. C., Blair, L. G. Lancet, 1950, i, 386.
4. Whitwell, F. Thorax, 1952, 7, 213.

whole lobe was collapsed and airless, and the right middle and lower lobes were the ones most commonly affected. This type was usually found in children, but it also occurred in adults. On section, obvious alveolar collapse was seen throughout the affected lobe, and fibrosis and hæmorrhage into the alveoli were common, but, on the other hand, active inflammation was comparatively rare. Whitwell attributes these changes to compression of the lobar bronchus by lymphatic glands which have been enlarged either by tuberculosis or by the adenitis that sometimes develops in measles or whooping-cough. The obstruction was proximal rather than peripheral, and the peculiar vulnerability of the middle-lobe bronchus to this kind of blockage has been stressed by Brock.[5] The term "saccular bronchiectasis" covers the pathological appearances in another and slightly larger group described by Whitwell. Bronchography had usually shown saccular changes, but he is careful to point out that X-ray signs do not correspond closely to pathological findings, and are not a satisfactory basis for classification. On this point he confirms the opinion of Ogilvie,[6] but differs from that of Reid.[7] Saccular bronchiectasis often developed later in life than the other two types, usually after the age of 15, and, in sharp distinction to the atelectatic group, the disease was found in the left lower lobe in three-quarters of the lungs examined. The distribution of the lesions was patchy, segments rather than entire lobes being affected. The saccules showed considerable squamous metaplasia, and chronic inflammatory changes were an outstanding feature, but there was no lymphadenopathy. The saccules did not arise at the periphery of the bronchial tree, but between the first and third branches of the segmental bronchi. They ended blindly and the branches beyond them were obliterated. The pathogenesis of this type is uncertain: there is no direct association with measles or whooping-cough, but about half the cases followed bronchopneumonia; and most of the others began insidiously, though it is impossible to rule out a mild aspiration pneumonitis as the start of the trouble. Whitwell himself suggests that they began as a chronic inflammation in the walls of the medium-sized bronchi.

The third and largest group is the most interesting. This Whitwell calls "follicular bronchiectasis"—a name chosen because the most prominent histological feature is an excess of lymphoid tissue in the follicles and nodes in the walls of the affected bronchi and among the surrounding alveoli. This type follows acute viral infection of the lungs in early childhood, usually after measles, whooping-cough, or bronchopneumonia. Again the disease is spread in patches, and affects mainly the left lower lobe. The dilated bronchi commonly, but not invariably, appear cylindrical on bronchography. In both the follicular and the saccular types, the affected lung is usually well aerated, in spite of the fact (noted by Reid[7] in Australia and Duprez[8] in Belgium) that the affected bronchi end blindly because their distal ends have been destroyed. It has been observed both experimentally and during operations that occlusion of a main lobar bronchus produces collapse of the lobe, which, as the air is absorbed, fills up with its own secretions. On the other hand, when a segmental bronchus is occluded, collapse does not usually follow, though the segment may retain its own secretions just the same, giving the radiological appearances of segmental collapse. If, for any reason, the secretions do not accumulate or are absorbed, the segment will become re-aerated by the collateral circulation of air from neighbouring segments, even though the bronchus is still occluded. This phenomenon was first demonstrated twenty years ago by Van Allen and his colleagues,[9–11] but its importance has only lately been realised, by Churchill[12,13] in America and by Baarsma, Dirken, and Huizinga[14,15] in Holland. Incidentally, this collateral circulation of air provides strong evidence of the existence of Kohn's alveolar pores, which have provoked such controversy in the past. Churchill argues that the collateral air drift cannot serve any respiratory function except that of filling space, because the air that enters the obstructed segment will already be in equilibrium with the blood. A further point to which he draws attention is that the bronchial arterial supply to a segment seems to be increased when the segmental bronchus is occluded. This, he thinks, may establish a pressure gradient great enough to prevent the shunting of pulmonary arterial blood into an area of lung where it would be physiologically useless.

Whitwell's conception of these three types of bronchiectasis as separate clinical and pathological entities of different ætiology may represent a real advance in this difficult subject. Clinically, however, the distinction between his saccular and follicular groups seems to involve little that could not be accounted for by the different age at which the events leading to the bronchiectasis take place. The clinician, who would welcome an explanation which takes greater account of the bronchographic changes, may, for this reason, be attracted by Reid's suggestion that the difference between saccular and other types of bronchiectasis lies in the level at which the dilatation begins and in the degree of peripheral bronchial obliteration.

The Patient's Favour

In his Harveian Oration to the Royal College of Physicians on Oct. 17 Lord Moran recalled that when the college was founded in 1518 its primary purpose was to suppress unlicensed practitioners. It had shown more aptitude for repression than for getting to the root of the trouble—which was that people go to the quack because they think he is better than the doctor. One remedy was to educate the public as to what a good doctor could do, and another was to purge medicine of its elements of humbug. But the real remedy, he thought, was to make it unnecessary to win the patient's favour, and he welcomed the evolutionary process by which, in hospital practice, the fortunes and advancement of the doctor now depend less and less on the patient's likes and dislikes, and more and more on the verdict of his colleagues. The danger in this, Lord Moran said, is that in the cultivation of his science the physician may neglect his art. In the address which we publish on p. 820 Sir Heneage Ogilvie draws attention yet more forcibly to the danger that science may come to be preferred to the patient.

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5. Brock, R. C. *Ibid*, 1950, 5, 5.
6. Ogilvie, A. G. *Arch. intern. Med.* 1941, 68, 395.
7. Reid, L. M. *Thorax*, 1950, 5, 233.
8. Duprez, A. *J. franç. Méd. Chir. thor.* 1951, 5, 442.
9. Van Allen, C. M., Jung, T. S. *J. thorac. Surg.* 1931, 1, 3.
10. Van Allen, C. M., Lindskog, G. E. *Surg. Gynec. Obstet.* 1931, 53, 16.
11. Van Allen, C. M., Lindskog, G. E., Richter, H. G. *J. clin. Invest.* 1931, 10, 559.
12. Churchill, E. D. *J. thorac. Surg.* 1949, 18, 279.
13. Churchill, E. D. Obliterative Bronchitis and Bronchiectasis. Alex Simpson-Smith lecture delivered at the Institute of Child Health, University of London, on Oct. 19, 1951. London, 1952.
14. Baarsma, P. R., Dirken, M. N. J. *J. thorac. Surg.* 1948, 17, 238.
15. Baarsma, P. R., Dirken, M. N. J., Huizinga, E. *Ibid*, p. 252.

Annotations

RAPID DIAGNOSIS OF INFLUENZA

THE clinician and the epidemiologist, who have been spoiled by the speed of modern bacteriological diagnosis, are still not reconciled to the unhurried laboratory diagnosis of virus diseases. They should be heartened by a report[1] describing how to determine within three days the type of virus responsible for a case of influenza. Throat washings from the suspected case are inoculated amniotically into fertile hen's eggs from which the amniotic fluids and membranes are harvested two to three days later. These are at once used as antigens in a complement-fixation test to determine the serological type of the influenza virus. Refined techniques can then be applied at leisure if the epidemiologist requires more precise information about the serological subtype.

Much more rapid, although less complete, information is yielded by a test designed by Fazekas de St. Groth[2] and based on experimental studies of influenza in mice.[3] The respiratory mucus of normal mice contains an inhibitor of influenza-virus agglutination which disappears during influenza infection, probably as a result of enzymic action of the virus. Human nasal secretions also contain an inhibitor of influenza-virus agglutination, but its concentration varies greatly between normal people. Fazekas[2] found, however, that the inhibitory titres of nasal secretions for three different strains of influenza virus showed a characteristic pattern which was significantly altered by influenza infection. It is claimed that the test will give an answer within an hour, although it tells only whether infection with influenza virus is present. This test deserves further study; it may be most useful in selecting specimens likely to give positive isolations of influenza virus. Also, under certain circumstances it might help public-health authorities who wished to decide rapidly whether a suspected case was of influenza.

One reason for the long delays in the diagnosis of virus diseases is that the virologist, unlike the bacteriologist, has no single broth on which all but the most fastidious of organisms will feed contentedly. Instead, the laboratory which sets out to isolate different viruses must house many types of laboratory animals in addition to fertile hen's eggs and the paraphernalia of tissue culture. Recently, however, tissue-culture techniques have been applied very successfully to the cultivation[4] and serological identification[5] of the poliomyelitis viruses, which were originally thought to be much more specific in their dietetic requirements than they now appear to be. It may not be too much to hope that further research will one day provide a general tissue-culture technique for growing many different types of viruses which could later be identified by simple serological tests. We might then look forward to the time when cultures will be reported after a couple of days "bacteriologically and virologically sterile."

PARTIES TO ADOPTION

ONLY twenty-five years have elapsed since the first *legal* adoption took place in England and Wales. The first Adoption Act was passed in 1926, and the first adoption orders—2967 of them—were made the following year. Northern Ireland followed suit with an Adoption Act in 1929, and Scotland did the same in 1930; but the Republic of Eire has not yet legalised adoption—a fact which causes social workers here some difficulties. In England and Wales in 1949 the number of adoption orders was 17,331.

There are four ways nowadays in which a child can be [illegible]ered adoption society, through [illegible] of a local authority, through a third person, or directly by the mother or father. Doctors are often concerned in the third of these, as are also nurses and almoners. Margaret Kornitzer, the author of a new book on adoption,[1] regards both the third and fourth methods as very undesirable; and as she is clearly an observer of experience and wide knowledge, and shows herself in most matters tolerant and unprejudiced, her views must command respect, even though she herself is closely associated with registered adoption societies. She regards as the essence of successful adoption the unhurried placing of a child, whose background is fully known, with adopters whose temperaments, motives, and material surroundings have been carefully studied—the careful matching, in other words, of child to adoptive parents, with the interests of the child always pre-eminent. This careful study, she thinks, requires experience and objectivity; and she has found doctors, who are usually deeply concerned with the interests either of the natural mother or of the adopters, insufficiently aware of the dangers to the child of an unsuitable adoption as well as of the infinite unhappiness it may bring to all concerned.

"A gynæcologist dealing with a distraught or bereaved woman patient," she says, "must often be sorely tempted to get her a baby somehow, without thinking what it means to the child. It is unfortunately not unknown for doctors to scour the maternity wards and the nursing homes, and if the search is unsuccessful, importune the local authorities and adoption societies on behalf of an unhappy creature who, 'if she doesn't get a baby soon will be in a mental home.'"

"*It is only fair to say that many doctors are fully aware of the dangers of promiscuous adoption placements and never prescribe as medicine another woman's child.*"

"But there does seem to be a case for educating the medical world in some of the factors that go to making adoption placement a success or a failure and for inculcating a greater sense of responsibility towards the child."

These views deserve serious thought. We have heard of a woman doctor complaining about an adoption society which had refused to provide a baby for a woman with recurrent depressive episodes, just out of a mental hospital. The doctor had taken steps to find a child herself, and was well satisfied with her success. Yet if this therapeutic adoption failed, the child would be irrevocably linked to a melancholic.

Nevertheless Miss Kornitzer's picture is incomplete. Many doctors believe that adoption by affectionate people, even if they are imperfect, exposes a child to fewer risks than does life in an institution. All recent studies suggest that the child's primary need is for direct personal love—which, indeed, appears to inoculate him against many emotional disasters. Better, these doctors would argue, that he should feel much, even painfully, in a place where love is, than starve emotionally in impersonal surroundings. Is it not possible that here we are dealing with a case where the best is the enemy of the good? They might point out, too, that the adoption societies are in the enviable position of having to look after the interests of only one party to the transaction: their concern is solely for the needs of the child. But does that mean that the needs of prospective parents should count for nothing at all? The doctor is obliged to take the welfare of all parties into consideration. His opinion that an emotionally disturbed woman may be helped, sometimes even to lasting recovery, by having a child to look after, is not always, or necessarily, ill founded. The adoption societies say that they have so many applicants and—relatively—so few babies, that it is their duty to select the parents carefully. But this means that parents who do not care to submit to inquiry look elsewhere for a baby—and generally find one. Until e have emptied our institutions and orphanages, we annot pretend that adopters outnumber children; and may be that by insisting on a high standard for the ew the adoption societies are standing in the way of an verage home life for the many.

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[1] Hummeler, K., Kravis, L. P., Sigel, M. M. *J. Bact.* 1952, 64, 253.
[2] Fazekas de St. Groth, S. *Nature, Lond.* 1951, 167, 43.
[3] Fazekas de St. Groth, S. *Lancet*, 1950, i, 1101.
[4] Enders, J. F., Weller, T. H., Robbins, F. C. *Science*, 1949, 109, 85.
[5] Svedmyr, A., Enders, J. F., Holloway, A. *Proc. Soc. exp. Biol., N.Y.* 1952, 79, 296.

[1] *Child Adoption in the Modern World.* London: Putnam. 1952. Pp. 403. 16*s*.

Their principles, however, should certainly carry great eight with all doctors given to arranging adoptions. childless couple, a lonely spinster, a mother bereaved f a child may all be legitimate objects of sympathy; ut they are full grown, and unlikely to change much. he child is growing and vulnerable: he needs to be iven a fair chance. The doctor about to arrange an doption might pause to consider whether he would hink the home appropriate if the child were his own.

ACTION OF INSULIN ON THE LIVER

THE apparently differing effect of insulin on the liver f normal and of diabetic animals has long been a uzzle. In diabetic animals formation of liver glycogen eems to be increased by insulin, whereas in normal nimals it seems to be decreased. Macleod[1] drew ttention to this anomaly in 1934. Soskin[2] suggested hat any insulin administered to the normal animal was an excess over the optimal amount already present and caused hypoglycæmia; this in turn brought into operation a compensatory hepatic glycogenolysis. The adrenaline mechanism very probably mediates this glycogenolysis in the liver, since removal or denervation of the adrenal glands prevents depletion of liver glycogen following hypoglycæmia.[3] [4] In some experiments with perfused livers,[5–7] however, where hepatic glycogenolysis followed the administration of insulin, adrenaline played no part. In these experiments only certain samples of insulin showed glycogenolytic effects, although all were therapeutically active. Bridge[8] even demonstrated depletion of hepatic glycogen after injecting insulin into normal animals which were protected from hypoglycæmia by glucose infusions or which had been previously adrenalectomised; but he used a brand of insulin later shown by de Duve et al.[9] to contain the glycogenolytic factor, glucagon. Bouckaert and de Duve[10] reinterpreted Bridge's results in the light of this knowledge and concluded that with glucagon-free preparations of insulin Bridge would have observed an increase in hepatic glycogen proportionate to the dose of insulin, provided that the blood-sugar had been kept fairly normal by regulating the glucose infusion. Work by the Louvain school[10] has confirmed the relative preponderance of the hepatic action of insulin over its peripheral action—a theme previously developed by Soskin.[2] With small doses of insulin the ratio of hepatic action to peripheral action is up to 2 to 1, but with very heavy doses it reaches 8 to 1 in favour of the liver. This predominant localisation of the action of insulin in the liver is further illustrated by recent isotope studies on lipogenesis in the liver of the rat. Chernick and Chaikoff,[11] using glucose labelled with C^{14}, have shown that insulin stimulates the incorporation of glucose into glycogen, carbon dioxide, and fatty acids, the stimulation of lipogenesis exceeding that of carbon dioxide formation. It is thus possible that glycogenolysis in the normal liver after the administration of insulin does not necessarily represent increased glucose production, but may be due, at least partly, to increased formation of fatty acids.

Sherlock and her collaborators,[12] who have studied "normal" and diabetic patients by hepatic-vein catheterisation, conclude that the liver is largely, but not wholly, responsible for the fall in the blood-sugar level after an injection of insulin. In normal persons there was a correlation between the diminished hepatic output and increased peripheral utilisation of glucose; but this was not apparent in diabetics, in whom two types of response could be distinguished. In one group, corresponding to the elderly obese diabetic often with cardiovascular complications, the effect of insulin was mainly an increase in peripheral utilisation of glucose but with a relatively slight fall in blood-sugar; whereas the other group—the young thin diabetic with minimal complications—responded to insulin by a large drop in the capillary glucose level, mainly due to diminished hepatic production. Aspiration biopsy of the liver showed normal liver cells in the hepatic-sensitive group and fatty change in the hepatic-insensitive group.[13]

It now seems possible to have a unitary conception of the action of insulin in normals and diabetics; for insulin has been shown consistently to stimulate formation of liver glycogen, if freed from the opposing effects of hypoglycæmia with release of adrenaline and of contaminating glucagon derived from the pancreatic α cells.

HEALTHY DOCTORS

SHOEMAKERS' children are said to be ill shod; and, if the truth were known, their fathers' boots are probably often in a worse condition than theirs. Undaunted by this legend of occupational hazard, however, Dr. Cuthbert Dukes, in his search for the causes of good health, boldly addressed an informal questionary to some of his colleagues. His confidence was justified, and in his presidential address to the Medical Society of London on Oct. 13 he was able to describe the reasons given him by 50 doctors, including 23 fellows of the society, for their own good health. As his controls he chose 50 non-medical men of the same age-group and social grade. He had intended to include 50 women to complete his series of controls, but he gave up this project when still 10 short of the mark, because he found that women attributed their good health to such irrelevant and non-masculine reasons as having a baby, the use of the paint-box, or an unsympathetic husband.

Having accordingly abandoned the female sex, Dr. Dukes restricted his analysis to the straightforward replies of the men. Most of them attributed their good health to five reasons: open-air physical exercise, such as walking, gardening, or golf; congenial occupation (this was mentioned by several doctors and seldom by the lay controls); some precaution adopted after a former illness; temperate habits in smoking, drinking, and eating; and successful emotional adaptation to the strain of life, which they usually described by some such phrase as "learning to take life the right way." Dr. Dukes did not claim that these answers were new or unexpected, but his researches did suggest that an inquiry into the private precautions which people adopt to keep fit might yield interesting results.

In the *Shorter Oxford Dictionary* health is defined as "soundness of body, that condition in which its functions are duly discharged." But Dr. Dukes would like to extend this definition to read "discharged harmoniously"; for harmony in his view is an essential characteristic of health especially when we think "in terms of body, mind, and spirit." Indeed he wondered whether perhaps we gave ourselves enough credit for our own good health. We were apt to forget the struggle some of us had had to make the "stubborn body become a willing servant to the spirit." But those who had learnt the lesson "enshrined in ancient wisdom and confirmed by modern

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12. Bearn, A. G., Billing, B. H., Sherlock, S. *Clin. Sci.* 1952, 11, 151.
13. Bearn, A. G., Billing, B. H., Sherlock, S. *Lancet*, 1951, ii, 698.

science that body and spirit are not two but one," had, he believed, achieved true health. He was the more surprised that only one of the doctors answering his questionary had spontaneously spoken of the importance of religion in relation to health. But Dr. Dukes is convinced "that the little working bit of a man's religious faith, not his outward professions or his theological creed but his inward secret convictions—these must ultimately influence his health to some extent, and might, if given more scope for expression, often improve it."

OXYGEN THERAPY

THE use of high concentrations of oxygen is now well established in the treatment of many conditions; and owing to advances in technique a continuous supply of this gas at concentrations of 60% or more can be assured. This improved efficiency in administration should give rise to further thought on the indications and dangers of the agent. Hitherto there has sometimes been a tendency to regard oxygen as a harmless physiological substance which "if it does no good, at least will do no harm." It is increasingly clear, however, that oxygen therapy must be applied with circumspection.

In chronic pulmonary disease, and notably emphysema, there is commonly a considerable accumulation of carbon dioxide in the arterial blood. If oxygen is then given the pulmonary ventilation diminishes owing to the cessation of anoxic impulses from the carotid body; further retention of carbon dioxide results from the hypoventilation, and toxic levels may be reached. This train of events has been noted in the course of normal oxygen therapy.[1] Bouterline-Young and Whittenberger[2] suggest that where anoxæmia is accompanied by hypercapnia effective pulmonary ventilation must be maintained by artificial respiration while oxygen is being administered.

Storstein[3] submitted three groups of patients to cardiac catheterisation and measured their respiratory and circulatory responses to the inhalation of 97% oxygen for one hour. His first group comprised healthy people rendered acutely anoxic by the inhalation of low-oxygen mixtures. His second group was composed of patients with chronic pulmonary disease; this group was divided into those with evidence of cardiac failure (cor pulmonale) and those without past or present signs of heart-disease. The last group consisted of patients with various chronic heart lesions. The respiratory responses tended to confirm the observations of other workers; and as the experimental conditions were not ideal for respiratory stability Storstein concentrated on the circulatory findings. By measuring the pulmonary arterial pressure he found that pure-oxygen breathing reversed the pulmonary hypertension induced in healthy people by administering low-oxygen mixtures. Where, however, anoxia had long been present, as in his chronic lung-disease group, the lowering of pulmonary arterial pressure was far less striking. He suggests that with chronic anoxia early and efficient oxygen therapy might prevent the pulmonary vascular changes from becoming irreversible. Calculation of the cardiac output and work of the right ventricle in his three groups showed that not only was the work of the right ventricle greatest in the cor-pulmonale group but that it was actually increased by the administration of 97% oxygen. This undesirable effect was due to an increase in cardiac output without compensatory reduction in pulmonary arterial pressure. Chronic anoxæmia is a persistent stimulus to high cardiac output even in the presence of cardiac failure; and when irreversible pulmonary hypertension is present long-continued administration of oxygen will place an increased strain on the already over-burdened right ventricle.

The administration of oxygen in high concentrations to the premature newborn infant has become a routine in many nurseries. That this measure may not be wholly beneficial has been demonstrated by Jefferson,[4] who has shown that the incidence of retrolental fibroplasia in premature infants is closely related to the fashion of oxygen therapy. Incidence was greatest among infants who had been suddenly removed from an atmosphere containing 60% oxygen to room air. When removal from the oxygen atmosphere was made more gradual, the incidence of retrolental fibroplasia was lower. Equally striking is her success in treating babies with early signs of the disease by replacing them in high concentrations of oxygen for a long time before gradually reducing the concentration.

INCIDENCE AND PREVALENCE

WHEN medical statistics were concerned mainly with mortality, problems of terminology were few. Death is an unequivocal fact, and it comes only once to each person. The epidemiology of acute diseases is also fairly straightforward, in that the affected can usually be clearly distinguished from the unaffected, and the outcome—recovery or death—is apparent within days or weeks. But the epidemiology of more chronic disorders may be complicated by a gradual onset, so that a person who regards himself as in normal health may be shown to be in the early stages of serious disease. Furthermore, the patient may remain affected for a long time; and this complicates surveys and the terminology in which their results are expressed.[5]

One of the chief trouble-makers is "incidence." Some years ago Hogben[6] objected to the practice among medical writers of using this word when "frequency" was meant. A record of the number of cases in age and sex groups is a "frequency" distribution. To justify the use of "incidence" it is essential to know the size of the population from which the cases are drawn, so that the result may be expressed "per 1000" or "per cent." But even then "incidence" may be used in any one of three different senses: (*a*) for the number of cases per 1000 examined at a given time; (*b*) for the number of cases per 1000 examined, developing during an unspecified time in those known to have been normal originally; (*c*) for the number of cases developing during a known period in those known to have been normal at the beginning of the observation period, expressed as, for example, "per 1000 per annum."

The third of these is more usually known as an "attack-rate." To the first—namely, the number of cases per 1000 examined at a given time—American workers apply the term "prevalence"; and this has much to commend it. To most people "incidence" conveys the idea of the onset of some new condition; but a mass-radiography survey, for example, includes cases that have existed unknown for many years, and the term "prevalence" seems etymologically more justifiable than "incidence." Stocks[5] recognises this, and defines "monthly prevalence-rate" as the "number of illnesses present in the population at any time during the month, regardless of when they began, per stated number of population." If "prevalence" were to be generally adopted for the results of surveys applied once only to populations of known size in which the time of onset cannot be known, and "attack-rate" were used when both the population and the duration of risk are known, then "incidence" with its ambiguities could largely lapse, or be restricted to the second meaning—i.e., new occurrences in a known population during an unspecified time.

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4. Jefferson, E. *Arch. Dis. Childh.* 1952, **27**, 329.
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one method of treatment, the more is his general education wasted, the more he approximates to a technician—in fact, the more easily he can be replaced by a technician. Many of the laboratory tests that were introduced by doctors and that were formerly performed by doctors, are now handed over to technicians. Blood-counts, sedimentation tests, estimation of blood-groups, urine analyses, blood-pressure readings, the taking of electrocardiograms and of X-ray films, these are now done for the most part by technicians. A doctor is in charge and does the final interpretation, but the technicians are constantly improving their education and taking an increasing interest in the uses to which their work is put; they often make their own interpretation, they often think their opinion is as good as the doctor's, they are often right.

In many foreign clinics all the anæsthetics, even those for severe and long operations, are given by technicians; a qualified anæsthetist sits in a central office nominally in charge, and ready to appear in any theatre if the technician presses an alarm signal, but he is seldom needed. In New Zealand much of the work of dentists has been handed over to nurses, and in Britain a Bill has been introduced allowing such a scheme to be tried here. It is easy to see how a ruthless Minister of Health, determined to reduce the cost of the service and to break the cartel of doctors, could set about to dilute labour. An optician would see all cases referred to ophthalmic outpatients, keeping only the unusual ones for the ophthalmologist. A nurse, given a course in the use of specula, could, with the help of a welfare worker, deal with two-thirds of the otolaryngological outpatients. A chiropodist with a box of Scholl's supports would lighten the work of the orthopædic surgeon at outpatients, and a plaster technician would do the same for him in the theatre. In general surgery the meticulous but tedious work of opening and closing wounds could be handed over to an unqualified assistant, allowing the surgeon to do twice as many operations in a session. Fantasies can come true. The Erewhon of today may become the Erehwemos of tomorrow.

HEALING OR SCIENCE?

Had we asked ourselves twenty years ago "What is the purpose of medicine?" we should have answered "to heal the sick." The patient then regarded his own doctor as one to whom he could bring all his troubles and from whom he could seek advice in all his difficulties. He respected the consultant, and he was willing to attend hospital to undergo tests and be informed of the result. But only if the verdict was confirmed by his own doctor, the man who knew his virtues, his failings, and his idiosyncrasies, and who understood him as an individual, was he willing to accept the advice and to act upon it.

How have we departed from this relationship? Possibly in two ways, in the ideal for which we are working and in the place we hold in our patients' regard. Were we to ask modern students "What is the purpose of medicine?" none would answer "to heal the sick"; that is too Biblical, too Victorian, too sentimental. They would say "to prevent illness" or "to discover the cause of disease," a scientific rather than a humanitarian ideal. In becoming scientists rather than healers, in making the centre of our interest the laboratory rather than the bedside, in organising ourselves and our work on a nation-wide basis, we are losing that personal contact which has characterised medicine since prehistoric times. In handing over each aspect of disease to a specialist, we have removed the doctor from his age-old rôle of friend and adviser. The patient, taught by the journalist in search of copy and the manufacturers looking for increased sales to demand the newest form of treatment, is prone to look on the general practitioner merely as a supplier of the commodities he desires, and a fixer of appointments with the specialist of his own choice. Whereas formerly he came to his general practitioner saying "I am sick, I want your help," he now says "I have a pain, I want an X ray; I have fever, I want 'Chloromycetin'; I have rheumatism, I want cortisone."

Dr. F. M. R. Walshe, speaking seven years ago on the Integration of Medicine, drew the distinction between physiology, which he described as a liberal profession because it pursues knowledge for its own sake alone, and medicine which is a useful profession because its activities are directed to an end, the health and well-being of the community. Our present tendency is to transform medicine from a useful to a liberal profession, from an applied to a pure science; to seek knowledge for its own sake rather than to attempt the application of knowledge already acquired for the good of the patient; to look on sickness as an intellectual rather than a human problem. In this trend we find another influence undermining the relation of mutual trust that has always existed between the doctor and his patient. If the patient is coming to look on the doctor as a man in a white coat behind the counter of Welfare Incorporated, Universal Providers, picking the right remedy out of the right drawer, wrapping it up and handing it over, the doctor is coming to look on his patients as customers, on disease as an intellectual problem for solution, and on the sick man as experimental material to be studied in the search for knowledge rather than as a fellow human being in need of help.

The science of experimental medicine is something new, and, to those brought up in the Hippocratic tradition, something sinister; for it is capable of destroying in our minds the old faith that we are the servants of the patients whom we have undertaken to care for, and in the minds of the patients the complete trust that they can place their lives, or those of their loved ones, in our care, knowing that we will help them *if it is in our power to do so. To the exponent of experimental* medicine the patient may no longer be the most important person in the room. In the search for knowledge, we may lose something far more precious.

Experiment is not new. Harvey, Hunter, Jenner, and Lister were all experimenters. The man who in his work comes across a question new to medicine to which he must find an answer, can do so only by experiment. What is new is the cult of the experimental method for its own sake, not to find the answer to a specific question but in the hope that by experimenting with sufficient persistence some questions will be stirred up, not as an intellectual discipline for those who are likely to become *investigators*, but as a routine exercise for all students. What is new is research by fraud, the performance on patients who have come to us in good faith for the cure of their ailment of any number of tests and investigations, many of them unpleasant, some of them dangerous, all of them unnecessary for the diagnosis or treatment of their ailment, but performed in a general search for information, or merely as a bit of practice in technique.

THE PLACE OF RESEARCH

The discovery of the cause of disease and the prevention of disease are admirable aims that we must pursue as vigorously as we can; but the treatment of disease is the immediate problem for which we have been trained and which we must tackle, and it will not wait. If practical medicine and scientific medicine are indeed in competition for money, material, and man-power, practical medicine must have first claim on available funds and prior place in the training of the medical student, and research must do the best it can with what can be spared for it. The efficacy of treatment is largely dependent on the money spent upon it: the efficacy of research is not, for the most important discoveries have usually been made by humble men working in garrets with home-made apparatus. Further, treatment is local and personal, benefiting those whose labour pays for it. Research is global, impersonal, and available to all the world alike. Penicillin is distributed among the nations, not in proportion to their contribution to its discovery, but in proportion to their ability to buy the finished product. Pure science is a luxury, and, like all luxuries, must be paid for by production of commodities.

How then should we divide our resources between research and treatment, in order to get the best from each? Is not the first necessity to employ scientists to investigate and clinicians to treat, and to abolish the clinico-scientific Pooh-Bah? We find it a little difficult to assess research at its true worth, because of the box-office glamour with which it is at present associated. The novelist or the film-script writer cannot hope to make a doctor the hero unless he is employed in research. The dying financier makes his peace with both worlds by leaving his money to research. The dean of a university can be hard-hearted to any appeal for further expenditure unless it is intended for research. The man in a white coat who talks a jargon unintelligible to his fellows is looked on as a superior being. But what is research? Constant inquiry, the striving to shine the light a little further into the darkness, the quest for truth; a little touch of genius and a lot of hard work. But the genius and the hard work are very seldom contributed by the same man. Originality cannot be discovered by appointment committees or attracted by grants; it will reveal itself in spite of discouragements and make opportunities where none are offered it. And genius and originality are a very small part of research, merely the spark that sets the machine in motion. The greater part of research work is done by dull, unambitious yes-men, who do not need the training of the clinician because their work is limited to a narrow field, who do not need the brains of the clinician because they follow a programme planned for them from step to step and repeat the same observation day after day, who do not need the courage of the clinician for they lock up the laboratory at five every evening and draw their pay, results or no results.

We must treat research as something vital and not, as we tend to do today, as a parlour trick. Even though the scientific discoveries of the whole world are as open to us as ours are to them, we must still conduct research within the limits of our budget, even if it have no higher purpose than an intellectual stimulus, a flag that must be kept flying. But how shall medical research be organised?

I recently spent a week with a member of the senate of a young and progressive university with a medical school. He had to deal with a number of enthusiasts, each of whom wanted a research department, and on the surgical side alone there were at least six groups who had plans ready for approval—the general surgeon (who had an ambitious programme for the study of gastric function), the vascular surgeon, the ophthalmologist, the otorhinologist (who proposed a joint project with the endocrinologist), the orthopædic surgeon, and the urologist. Each had a group of problems to be solved, each had a team of juniors eager to solve them. Should each department be given its own research unit? if so, how much space would each need in the enormous laboratory building that would arise; how could duplication of apparatus and technicians be avoided; and what would happen when the problems of any particular group were solved and no fresh ones were propounded, when the enthusiastic junior who had been the driving force of the investigation left to take a chair elsewhere?

I ventured to bring forward the view I have held for many years, that research is too important to be entrusted to a doubly unqualified amateur with a foot in both camps. Research demands a long and arduous training
that is almost wholly divorced from that of the bed
a devotion that is lifelong. I suggested that in e
medical faculty there should be at any rate four c
equal in status and salary—of medicine, surgery, g
cology, and clinical research. The research prof
would be a scientist with a medical degree rather th
doctor with scientific leanings, and his department w
be closely linked with the others. He would attend
rounds and give regular lectures in the clinical co
Every registrar would serve at least a year under
to gain an insight into the scientific method. The p
lems that arise every day in the wards would be t
straight to him and not shrugged aside as they are
and he would give perhaps a straight answer, sugg
few experiments that could be carried out in the w
or plan a research project that would be carried ou
his department and under his supervision by mem
of the department concerned.

LIBERTY AND OPPORTUNITY

Chief among our aims in medicine should be
restoration of that liberty of action and equalit
opportunity which is every man's birthright, and w
alone can ensure that the profession makes its
contribution to the welfare of the State. No lo
must the first step in medical practice be final
irrevocable, but each man should have the opportu
to develop his work in the direction that his ambi
leads him and to rise to a position that his ability just
The best should be able to get to the top by merit,
not so good should not drift to the top by seniority al
The general practitioner should be relieved of such o
work as is not medical, and for his medical work
should be rewarded for its quality rather than by
number of patients on his list. He should have ac
to hospitals, to libraries, and to laboratories, and
allowed to keep in touch with his patients in t
serious as well as their minor ailments. He should
able to study intensively aspects of medicine in w
he is interested and for which he shows an aptitude,
eventually to take higher degrees; but he should
be eligible for merit awards on the quality of his gen
practice alone.

The specialist, no less than the general practitio
should have the opportunity to develop according to
talents and to grade himself according to his ability
move sideways as well as up or down. The pre
division of specialist practice into two levels, regis
and consultant, takes no notice of the constant prog
in experience and skill that every man should make
of the great differences in the rate of that progress
are apparent to his fellows. A division that correspo
more nearly to reality, in surgery at any rate, is that of
Services into five grades—trainee, graded surgeon, surg
specialist, officer in charge of a division, and consult
All these are honourable ranks that would be accep
in civil life without the resentment engendered by te
such as "senior hospital medical officer," and al
them correspond to a definite step on the ladder
maturity.

GETTING AND GIVING

We have in our life-time been privileged to take
in the greatest advance in the history of the healing
an advance so great that we are in danger of losing
sense of direction in the exhilaration of the forward r
A forward rush is an advance only when it is consolida
a discovery is an advance only when it is integrated in
body of knowledge, an airborne landing is an adva
only when the parachutists have made contact with
troops on either side and re-established their line
supply. The advances in which we have all participa
and in which we may be engrossed to the exclusion of
else, will help the whole course of medicine only if
keep touch with the great profession in which we

enrolled, remembering that its main purpose is to heal the sick, to preach good tidings to the meek, to bind up the broken-hearted, to give unto them beauty for ashes, the oil of joy for mourning, the garment of praise for the spirit of heaviness.

If we are to integrate our own discoveries and our own skill into this idea, we must never lose sight of the fact that the science of medicine is the instrument whereby the art of medicine is made effective, that the keynote of that art is the spirit of service, and that in our common enterprise the importance of each subdivision must be measured by what it can give, not by what it can get.

Medicine and the Law

"Should a Doctor Tell?"

WHERE it is a question of a member of the medical profession giving evidence in court of matters which have become known to him in the course of treating a patient, the profession claims to observe a standard higher than that of the law. Perhaps these cases would be more frequent were it not that judges are sufficiently sympathetic not to insist upon disclosure. The public does not always appreciate that the doctor who claims privilege does so in the interests of the patient and not in those of the profession. It follows that the patient can, if he wishes, release the doctor from the obligation of secrecy.

In a recent case at Wolverhampton,[1] where a man was charged with having attempted suicide, a hospital doctor quite rightly expressed his reluctance to give evidence against his patient. The police superintendent who was prosecuting, unaware perhaps of the implications of the Hippocratic oath, complained that the doctor had not given the police a statement on the condition of the accused; "this is the first time in my 25 years' police experience where we have failed to get a statement from a doctor at the Royal Hospital; it is most important that we should get it." Well, the importance of a piece of evidence to the prosecution is not the final test of its admissibility. The clerk to the magistrates intervened to comment that in many other courts doctors give evidence almost daily; "do you," he asked, "intend to give this evidence or not?" When the doctor replied "if you direct it," the chairman observed somewhat less insistently: "we do not direct it; we request it." To which the doctor rejoined: "if the patient gives his permission." The accused, who pleaded guilty, assented; the witness thereupon stated that, when he examined the patient on his admission to hospital, he found his condition to be consistent with his having taken an overdose of phenobarbitone. Thus honour was satisfied on all sides.

There is no need now to repeat that the only form of absolute professional privilege recognised by the law is the obligation of secrecy between members of the legal profession and their clients. A learned judge long ago expressed the view that to peer into the private communications passing between barristers or solicitors and their clients would be to purchase the truth at too high a price. For only one profession, however, is the bargain deemed unconscionable. There is no principle, said Lord Jessel in Wheeler *v.* le Marchant (1881), that every confidential communication necessarily made for the purpose of carrying on the ordinary business of life is protected. "The communications made to a medical man whose advice is sought by a patient with respect to the probable origin of the disease as to which he is consulted, and which must necessarily be made in order to enable the medical man to advise or to prescribe for the patient, are not protected. Communications made to a priest in the confessional on matters perhaps considered by the penitent to be more important even than his life or his fortune are not protected." It is nevertheless on record that in Broad *v.* Pitt (1828) Chief Justice Best had declared that he, for one, would never compel a clergyman to disclose communications made to him by a prisoner, although, if the clergyman chose to disclose them, he would receive them in evidence. The textbooks show, too, that Baron Alderson observed in R. *v.* Griffin (1853) that communications made by an accused person to a priest ought not to be divulged. Evidently there are learned judges who, no matter how grave the dilemma of the prosecution, shrink from exposing a witness to this severe ordeal.

The doctor in the witness-box can at least hope to be lucky in his tribunal. On the other hand, if courts are directly faced with the issue they are obliged to enforce the rigour of the law. In the divorce case of Garner *v.* Garner (1920) it was ruled that a doctor might be compelled to give evidence that his patient was suffering from venereal disease, even though the patient was being treated under a scheme governed by statutory regulations which enjoined absolute secrecy upon the doctor—a decision exhibiting a conflict of principle which should never have been allowed to arise.

Public Health

Notification of Infectious Disease

DR. G. A. W. NEILL, medical officer of health for Barnsley, in his report for 1951 describes defects in the notification of infectious diseases.

"In the latter part of the year," he says, "a number of incidents occurred which indicated that there is considerable laxity amongst general practitioners regarding the notification of infectious diseases. Cases have occurred where practitioners have notified persons as suffering from infectious disease without actually having examined them. Practitioners have failed to notify cases under their care or have even notified persons who do not exist at all as suffering from an infectious disease. There are also some practitioners whose patients must be immune from infectious disease as no notifications are ever received from them. But perhaps the most serious default in relation to notification is the delay that has occurred in some cases. This delay is particularly dangerous when it occurs in cases of food poisoning. Members of the medical profession do not seem to be aware that there is an absolute statutory duty imposed upon them by the Public Health Act, 1936, S.144, under pain of a penalty of 40*s.* in default, to notify infectious diseases to the Medical Officer of Health *forthwith.* It is not, of course, the desire of the Health and Sanitary Authority or its officials to add to the proper work of the already over-burdened practitioner. At the same time the Authority has a duty to discharge its statutory obligations and to exercise its powers to preserve the health of the community."

Dr. Neill goes on to suggest that the law relating to notification might with advantage be critically reviewed. "For example, it might be considered advisable to delete some of the diseases which are now notifiable and to add others which at present are not. Furthermore, there is the question of the notification fee which has remained at 2*s.* 6*d.* per case since the Act became law in 1936."

Eire in the Second Quarter

In Eire during the June quarter of this year[1] the birth-rate was 23·8 per 1000 population; this was 1·3 above the rate for the second quarter of 1951. The death-rate was 11·8 per 1000 population (1·8 below that for the second quarter of 1951). The death-rate from tuberculosis was 0·6 per 1000 population (respiratory 0·5, other forms 0·1), compared with 0·8 (0·6 and 0·2) in the second quarter of 1951. The maternal mortality rate was 1·3 per 1000 births registered, compared with 1·7 for the second quarter last year; and the infant-mortality rate was 35 per 1000, compared with 46 for the second quarter last year.

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[1] *Manchester Daily Dispatch*, Oct. 8.

[1] Quarterly Return of the Marriages, Births and Deaths registered during the June Quarter, 1952. Obtainable from the Government Publications Sale Office, G.P.O. Arcade, Dublin. Pp. 31. 6*d.*

In England Now

A Running Commentary by Peripatetic Correspondents

NOTHING reminds me so strongly that I belong to the fringe of a noble profession as the news, when I telephone at 10 A.M., that Doctor X is in his bath because he has dealt with three confinements (or two road accidents, or a maniac) since midnight. In a lifetime spent in consulting omphaloscopy, the number of times upon which professional duties have called me from my bed between shuteye and the seven o'clock cup of tea is statistically insignificant. When, and if, I rise earlier it is—I was going to say for pleasure, but that is a lie—it is for recreation. I wish that I could boast that it is the ascetic joys of wild-fowling that drag me from my warm and downy in the dead hours: I do not carry the pursuit of pleasure to such extremes. But to join my friends in hounding a few fox cubs to a premature end on a dewy morning in the apple season is—against my moral judgment—a delightful self-indulgence. Never does Nimrod's third-best coat look so fine a scarlet as in the early sun; never does his horn send such sensuous frissons down my spine as in the quiet air of dawn; never are neighbours so neighbourly and foes so far away. But, as the alarm-clock goes off deep in the silent pool of night, my only instinct is to write a cheque, a large one, for the League against Cruel Sports, and then to turn over quickly. I resist and, having stifled the din, in quick review I see the unanswered letters, the unpaid bills, the unspoken retort—and I feel sick. Shaving, that primæval curse, makes me feel worse, nor will cocoa from the 'Thermos' or porridge from the hob remove the nausea, though they help to banish recollections of my sins of omission. But—and this is my discovery—one tablet of amphetamine (or any of the related drugs which come by sample post) banishes my nausea in a trice (whatever that may be) and I can face the morning with bloodthirsty cheerfulness. I recommend it to all who rise early from necessity or choice.

* * *

On Sunday, feeling that "Prolongation of Action of Hypotensive Drugs" "and Venous Velocity in Bedridden Patients" were not exactly my choice of reading for a wet afternoon, I turned to the last column of the last page of *The Lancet*. There, under the heading "Miscellaneous," I found more than enough to keep me happy. For instance, the Cameroons Corporation want an M.O. There are opportunities for surgery and free light and fuel. That sounds better than England, though a children's allowance to a maximum of two seems a bit hard. However, in the next paragraph an R.M.O. is required for a Tin Mine and the basic salary is £1800. This is certainly better than our basic £300. The third paragraph, which offers a beautifully furnished maisonette in Harley Street, with someone to answer the phone and open the door, sounds even more in my line. If I take the flat I'll certainly buy the Cambridge Electrocardiograph in perfect condition in its leather case. While sitting in my Harley Street drawing-room I will surely have time to read the *Works of Ambrose Parey* published in 1649 and may even study the genuine 17th-century maps. Now I'm getting into the spirit of the thing I decide without hesitation to send my Rolls and Bentley to be serviced at Croydon 7464. With so many good things in prospect it's about time I started to count my blessings; and to what better place could I go to do this than to Friends Meeting House, which in the next paragraph offers information on Quakerism? I'm nearing the bottom of the page, and my spell of daydreaming is almost over, but there are still two paragraphs left. So I'll get my old testimonials copied and duplicated by Victoria 0141. It will cheer me up to read ten times over that twenty years ago I was a keen and conscientious house-surgeon and that it gave an eminent gynæcologist great pleasure to announce this fact. Alas, time does not stand still, and today I have difficulty in diagnosing a fœtus and a fibroid. But "Miscellaneous," helpful to the last, offers to do it for me in 24 hours.

* * *

Clever chaps, some of my fellow correspondents; but I'm not sure that they're wise in boosting all this statistical stuff. I know it's right up to date and that degrees of freedom and randomised replicates are jolly good things to have knocking about an article. A sprinkling of Greek letters, too, does make a thesis look pretty hot, if you see what I mean. But it isn't always quite so easy to handle them as people make out. Put in a χ^2 where there ought to be a σ and some examiners get quite mad. Can't see that it matters myself, but there it is; can be dangerous. There is a good deal to be said for having a piece of straightforward clear English—like the Great Masters of Medicine have always used. You can't go wrong on that and it goes down well with the simple chaps—chaps in the clinical units and the editors of the weekly journals. Anyway that's how I am going to write up my Observations on Three Cases of Generalised Osteitis Fibrosa Cystica.

The first case was quite clear. On account of its social class (member of the Athenæum), occupation (bishop, rtd.), age (approx. 92), and so on, there was no doubt that the accepted treatment of choice was contra-indicated—in fact, I can say, markedly contra-indicated. On the other hand with the second case the administration of diamidine-diphenoxypentane t.d.s. led to an immediate rise in the Hb, B.P., E.S.R., W.B.C., O.U.T.C. and All, and an equally dramatic fall in the cost of living (for pathological report on P.M. vide appendix). The third case revealed remarkable features, for no-one[1 17 29 42 117] has yet reported a case of Generalised Osteitis Fibrosa Cystica *complicated by odontalgia and a mother-fixation in an oncologist*. An uneventful recovery from all three complaints followed the exhibition of forceps.

Good stuff that. Not only is there a lot to be said for clear and sparkling English but you can say quite a lot in it; and some of the words go a long way to fill up the lines. To my mind they have $\pm 1{\cdot}23$ and $P > {\cdot}05$ beat to a frazzle.

* * *

Our two obstetric registrars have become engaged to each other. It has been decided that unless two locums can be obtained before their wedding at the end of this month they will have to spend their honeymoon *independently*.

* * *

I wonder if all travellers by air to the Continent suffer from the same after-effects as I do. Not the reactions after unaccustomed French cooking—not an over-emphasis of reminiscence of that *Poulet de Bresse* in Montmartre; not the *Quenelles* at Auxerre (and who could possibly imagine that a muddy river fish could be reincarnated by the French art into such morsels of fairy-like consistence and ethereal flavour?); not the noble *Chateaubriand* in the restaurant near Les Invalides. No, what I am thinking of is the new world in which I am living owing to the rejuvenescence of my eustachian tubes. It is twenty-five years since my ear-drums have had to acclimatise themselves with such rapidity to an altitude of 5000–6000 feet. Persistent swallowing on the way up and blowing of the nose on the way down, have not achieved the elasticity necessary to the hardened air-traveller. So now I live in a world of clatters and bangs. That crack of thunder? Merely a yawn. That drumming of heavy rain on a corrugated roof? The sound of chewing rather tough French beans. That rocket anti-aircraft battery opening up? I blew my nose over-enthusiastically.

I suppose that I ought to be able to prescribe a cure for myself; but there is no doubt that the logical one is the attractive one. My tubes clearly need acclimatisation to modern conditions. How can that be better achieved than by a fairly frequent, say once a week, transcontinental air-trip? A medical certificate to that effect—and who knows better how to write that kind of thing? But I wonder whether the foreign exchange department of the Bank of England would be prepared to play.

* * *

Dear Messrs. Guinness,—In case your Kinkajou falls ill or looks pale, I thought you ought to know that its normal red-cell count is 6·52 million per c.mm. and its differential count usually shows about 15% of eosinophils (Wintrobe, M. M. *Clinical Hematology*, p. 819). The view that its blood-cells are upside-down is mere folklore.—WELL-WISHER.

Letters to the Editor

SELECTION OF MEDICAL STUDENTS

Sir,—In his letter of Sept. 13 Prof. Samson Wright has posed an interesting problem: how many applicants are there each year for the 2700 places in our medical schools? Owing to the large number of multiple applications this question cannot be easily answered for the whole country, but it may be of interest to report the preliminary result of a survey of the applications made in 1951 to the twelve London medical schools. The accompanying table expresses the salient facts.

APPLICATIONS FOR PRECLINICAL ENTRY IN 1951 TO THE TWELVE LONDON MEDICAL SCHOOLS

—	(1) No. of applications	(2) No. of candidates	(3) No. of candidates accepted by at least one school expressed as a percentage of col. (2)
Men :			
Applying at one school only	999	999	*29*
Applying at 2–4 schools ..	1983	704	*31*
Applying at 5 or more schools	2960	464*	*38*
Total	5942 (av. 2·74 per candidate)	2167	*32*
Women :			
Applying at one school only	325	325	*27*
Applying at 2–4 schools ..	804	289	*39*
Applying at 5 or more schools	882	138	*53*
Total	2011 (av. 2·67 per candidate)	752	*37*

* Including one (unsuccessful) candidate who applied at all twelve schools.

The figures show that on the average each candidate applied to between two and three schools (there being little difference between men and women in this respect), and that the proportion who were finally successful was just under 30% for those who applied once and increased with a greater number of applications. The precise significance of this increase is not apparent; for no distinction is made between the candidates who (either through zeal or caution) applied simultaneously to a number of schools, and those who made successive applications after successive failures. The other limitation of the first year's results is that we do not yet know how many of the unsuccessful candidates of one year try again (and are possibly accepted) in the next. Not until the scheme has been running for at least three years will it be possible to give a complete picture of what is happening.

This survey was initiated by the Conference of Deans of the Metropolitan Undergraduate Medical Schools, who have authorised me to publish this account. As the first year's work was largely experimental it is not proposed to publish a full report, but I have a few copies left of a stencilled summary.

Department of Medical Statistics,
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London, E.C.1.

M. P. CURWEN.

THE TRENDELENBURG POSITION

Sir,—I should like to comment on some aspects of Mr. Howkins's article last week.

In the first place, the gynæcologist's view of the Trendelenburg position is well expressed by his summary that "it should be safe for the patient and comfortable for the surgeon and his assistants." I would venture to suggest that the anæsthetist's view differs slightly from this, since he regards it as a physiologically bad position which should be used as little as possible. It is recognised that in a conscious patient a 90° head-down tilt is fatal within a few hours, death being preceded by most intense agony—a fact well known to the Inquisition in the 13th century. The usual 30° Trendelenburg slope applied to the anæsthetised patient causes a rise in blood-pressure, œdema of the head and neck, chemosis, and congestion of the cervical veins. It also reduces the vital capacity by 15%, mainly by upward displacement of the diaphragm, quite apart from the additional effects of abdominal packs and retractors. The photographic department of St. Bartholomew's Hospital has provided me with an excellent set of photographs showing clearly the alteration of contour of the abdomen and thorax with the progressive rise of the diaphragm in increasing slopes. The moral of this is that at the end of operation the tilt must be reduced in at least two stages, and the inevitable collection of secretions in the nasopharynx removed by suction before the tracheal tube is withdrawn.

The question of maintenance of the Trendelenburg position has occupied me for a considerable time; shoulder-rests alone are most unsatisfactory and have produced brachial plexus palsy, even if the arms are not abducted. Ogier Ward's pelvic rests avert this but cause bunching up of the anterior abdominal wall and must not be used alone, as heavy patients tend to slip. Even experienced orderlies cannot always make certain that these rests are secure, as there is insufficient leverage on the spanners provided to make the nuts really tight. I have twice seen patients slip with this device; and shoulder-rests, just clear of the shoulders, should always be used as an additional precaution. It is possible that the Hans modification may prove safer in practice.

It has long appeared to me desirable to employ friction as a retaining force, and I have been well pleased by a prototype 'Sorbo' mattress covered with a corrugated rubber sheet (sewn on by the senior resident anæsthetist!). This mattress is strapped to the horizontal bar under the operating-table supporting the hinge of the leg-rests, and consequently cannot itself slip on the table-top. If the patient's bare skin rests on the corrugations, the considerable area of the buttocks and scapula region in contact with them will hold the average patient to a tilt of about 30° without slip. Shoulder-rests must be in position as a secondary precaution, and it must also be realised that if the patient's skin becomes wet, from perspiration or fluid from a ruptured ovarian cyst, the coefficient of friction will be much diminished. I do feel most strongly that the legs must be kept straight, and the usual thick sorbo strip placed under the tendo Achillis (not the heels) to avoid compression of the calf veins.

I think I have said enough to indicate that a high Trendelenburg tilt is not the innocuous position sometimes supposed, and I have personal knowledge of a patient who woke up blind from a retinal detachment after a hysterectomy performed with an exceptionally steep tilt.

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C. LANGTON HEWER.

A "NEW" BLOOD-GROUP CHARACTER RELATED TO THE ABO SYSTEM

Sir,—I have read with great interest the paper by Drs. Bhende, Deshpande, Bhatia, Sanger, Race, Morgan, and Watkins in your issue of May 3, a reprint of which I have just received from Dr. Race.

For several years before the war I searched for the type of blood described by these authors, being certain that it must exist. Despite several thousand tests the result was negative. During the war, when I was obliged to live in the Warsaw ghetto, chance helped where planned investigations had failed. Having difficulties in determining the blood-group in a case of

Hodgkin's disease (in a Jewish woman, who died two weeks later), a bacteriologist asked me to resolve them. The tests, performed in the kitchen of my provisional home with my assistant Róża Amsel, revealed the coexistence of unagglutinable (by any test serums) erythrocytes and strong anti-O agglutinins in the serum of the patient. The titre of the agglutinins was 1/32, the thermal amplitude reached 30°C. With this serum it was possible to demonstrate differences in the O-substance of different O-erythrocytes. It could not be proved whether there was an inherited character of the blood or whether the unusual finding was due to the loss of the O-agglutinogen. In our paper, which could be published only when the Nazi occupation of Poland ended in 1946, the existence of pleiades was discussed.[1] This paper ends with the following words:

> "It is necessary to take into consideration such types of blood in seroanthropological work, because they can eventually indicate the first occurrence of blood factors which are associated with genetic factors."

These observations were made in 1941 with my assistant, the late Róża Amsel. Unfortunately she was unable to live to see the published paper: she was murdered in 1943, during the extermination of all Jews in Warsaw.

LUDWIK HIRSZFELD
Director of the
Institute of Microbiology.

Wroclaw Medical School,
Wroclaw, Poland.

FUTURE OF THE OCCUPATIONAL HEALTH SERVICES

SIR,—The leading article in your issue of Oct. 11 contains much interesting matter. I should like to select one or two points for comment.

1. Referring to the paper by Prof. I. G. Davies it is suggested that a preventive health service for work-places could be provided by "fusing" the duties of the medical inspector of factories, the appointed-factory doctor, and the medical officer of health. Each of these three has a very full job. What is meant by "fusing," and to whom is the "fused" control to be handed?

2. It is suggested that at local level the medical officer of health and his staff, assisted by the A.F.D. and local factory inspectorate, should be made responsible for detailed enforcement and maintenance of health standards. What will then be the position of the medical inspector of factories in relation to the medical officer of health? The local authorities are busy people and not many have extensive experience of factories: their staff would have to be augmented. Why not augment the staff of the medical inspectorate of factories where the experience now lies? The main handicap at present would appear to be shortage of staff to enforce standards and give advice. A large part of the work is educational.

3. Dr. Nash is credited with the suggestion that the precedent of the Public Health Laboratory Service might be followed in setting up an Occupational Laboratory Service. It is true that fewer laboratories would be needed, but it is hard to see how public-health laboratories could be used or adapted. The training, the technique, and not least the apparatus required are very specialised: staff and laboratory space would have to be separate.

Perhaps one laboratory in each region might suffice. Is it not worth considering attachment to a university department of public health or occupational health where experience and apparatus could be made available for postgraduate training? This is in fact what has been done by the London School of Hygiene in conjunction with the Slough Industrial Health Service, and it appears to be a useful example.

Community Centre,
Farnham Road,
Slough, Bucks.

M. E. M. HERFORD.

*** We think that the service provided, as Professor Davies puts it, by "fusing" the duties of the medical inspector of factories, the appointed factory doctor, and the medical officer of health should be controlled by a central Government department. The medical inspector of factories would advise, coöperate with, and if necessary direct the medical officer of health in his duties connected with occupational health. The medical inspectorate of factories should certainly be augmented, as Dr. Herford implies; but it could not carry out the day-to-day work in the factories. Regarding the laboratories, it might be more economical to use existing buildings; but, as we said, it would be necessary to "adapt" them, thus satisfying the conditions mentioned by Dr. Herford. All laboratory work is specialised; that relating to occupational health is not unusual in this respect.—ED. L.

OTITIS EXTERNA

SIR,—Your annotation of Oct. 11 gives the impression that you regard this condition as an infection with, perhaps, an "active underlying dermatosis." In the majority of cases seen in this country otitis externa is an eczema of the external auditory meatus, and it is often accompanied by eczema in other parts.

The concept of "eczema" has by no means been clarified by the introduction of more modern terms like seborrhœic dermatitis, atopic eczema, and exudative neurodermatitis. But it is worth while to remember the words of Sir Archibald Gray[1] in his Harveian Oration, that

> "The relation of pyogenic infection to skin eruptions has presented great difficulties, especially in eczematous conditions. A moist lesion on the skin is, in fact, a living culture tube and it follows that any of the organisms grown from such lesions may be only saprophytic. It is extremely difficult under such conditions to determine the ætiological significance of pyococci."

In the treatment of external otitis it seems reasonable to employ a suitable antibiotic systemically where there are manifestations of secondary infection, such as lymphangitis, lymphadenitis, cellulitis, furunculosis, and erysipelas, and topically for a limited period with the defined objective of reducing a heavy secondary contamination.

On the other hand, the routine prescription of antibiotic ear-drops or ointment, directed with the best intentions against the sensitive organism, will often excite another type of sensitivity—an allergic hypersensitiveness of the epidermal cells—and a dermatitis medicamentosa will result. The wise physician, therefore, will continue to rely on preparations, such as weak aluminium acetate or silver nitrate solution, which have stood the test of time, along with other measures directed at the relief of eczema, such as physical and mental rest.

London, S.W.2.

MICHAEL FEIWEL.

THE NOTIFICATION OF DISEASE

SIR,—I read with considerable interest and pleasure the article by Dr. E. D. Irvine (Oct. 11). I wish to offer no more than some stray reflections on scarlet fever.

Scarlet fever is still classed as a disease in its own right—partly as the result of tradition and history, and the fact that in "the old days" it was a serious disease. Now we know that scarlet fever is simply a streptococcal sore throat in which the bacterial exotoxin happens to include an erythrogenic factor. But hæmolytic streptococci can be equally virulent and infectious whether or not a rash occurs.

One wonders whether there should be any difference in the preventive measures taken in connection with the two conditions. I appreciate that there are practical difficulties relating to streptococcal sore throat which do not apply to scarlet fever. Yet the diagnosis of scarlet fever *may* mean isolation in a hospital, whereas a streptococcal sore throat is perhaps treated by means of chemotherapy until the temperature is normal and the throat clean. I would not go so far as to say that scarlet fever is today a medical anachronism; but there would appear to be a prima-facie case for reconsidering, and possibly reorientating, our measures in respect of these two types of streptococcal infection.

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[1] Hirszfeld, L., Amsel, R. *Pol. med. Wkly.* 1946, no. 51.

[1] *Lancet*, 1951, ii, 795.

I agree that the notification of acute primary pneumonia should be abandoned. It serves no useful preventive purpose.

Halifax. G. C. F. ROE
Medical Officer of Health.

CAROTENÆMIA

SIR,—The interesting article by Dr. McConaghey (Oct. 11) contains statements which should not pass without comment.

Up to the present time, in this country we have expressed the carotene and vitamin-A levels in international units (I.U.), though abroad there is a growing tendency to use the decimal system for this purpose. Both the carotene and the vitamin-A levels are somewhat dependent on the standard of nutrition and are subject to slight seasonal influences. But the normal levels cited by Dr. McConaghey for serum-carotene (240 mg. per 100 ml.) and for serum-vitamin-A (70–160 mg. per 100 ml.) are certainly based on considerable misunderstanding. Our latest published normal figures for the London area were total carotenoids 153 I.U. (91·8 µg.) and vitamin A 121 I.U. (36 µg.) per 100 ml.; and these figures are closely comparable with figures found by others and quoted by us.[1]

London, W.1. Z. A. LEITNER.

WITHDRAWAL OF TEACHING

SIR,—Your admirable article (Oct. 11), on the damage done by the withdrawal of the C.O.I. mobile units and the Crown Film Unit, deserves the full support of all those using films in medical education.

Cinematograph equipment is costly, and the time and labour involved in film production much greater than is generally realised. All this, however, is justified because the results can be shown to audiences all over the country—not only today, but for as long as the subject remains of interest. Thus, any step which tends to restrict the showing of films will increase the cost relative to each individual viewer. The acquisition of a projector by an organisation which is not constantly showing films is an expensive business; and as in most cases a trained projectionist is not available, not only is it costly but the results are crude and amateurish.

It is even more in the field of film production that a trend against centralisation needs to be resisted. Many hospitals possess expensive cameras which are little used. Finance boards which have spent £500 on a ciné camera consider that they have treated their photographer lavishly. In fact they have merely provided him with an instrument that will consume raw film at an appalling rate. Without the rest of the paraphernalia of film-making, the expenditure of much labour, and the exercise of considerable experience, the photographer can only produce some very crude material for a proper teaching film. The use of this unfinished material, and the belief that it fulfils the possibilities of the film in education, is doing more than any other factor to discredit this valuable teaching aid.

The position, then, is that much capital equipment is uselessly scattered among hospitals and institutions while money is frittered away on poorly produced films, whose quality debars them from being shown outside their own home circle. If money is to be spent economically it must be at a higher level than in individual hospitals or medical schools. Only then will there be sufficient capital resources to produce films of a technical standard that will command a wide distribution.

This does not imply that hospitals should be discouraged from making films. On the contrary, they would be able to draw on any items of specialised equipment that they required, with the help of experienced film technicians to guide them where necessary.

Medical films are in some ways more difficult to make than any others. It is thus all the more important that we should husband our resources and use them to the best advantage, instead of scattering them to the four winds.

[illegible] Department,
[illegible] School, PETER N. CARDEW.

PULMONARY COMPLICATIONS OF INFLUENZA

SIR,—I have found, as a matter of experience, that whenever I encounter the word "entity" in medical literature, I have to stop and read the sentence in which it occurs, together with its immediate context, several times in an attempt to find out what information the author was trying to convey to his readers. Sometimes, I confess, I am baffled in this attempt, for the word is a favourite with those who have not succeeded in clarifying their thoughts but are nevertheless determined to put them into print. Scarcely ever does the sentence make sense if for "entity" is substituted its dictionary meaning.

Now, as far as I can recall, I have never used this metaphysical smoke-screen of a word in print, and certainly it does not occur in my paper mentioned in your annotation last week on pulmonary complications of influenza. Yet in that annotation I am represented as having thought that "influenzal pneumonia is a distinct entity, differing clinically from other forms of pneumonia." I am so puzzled by this that I should like to use a little of your space (and, I hope, of the time of some of your readers) to set out clearly what in fact I did in the investigation mentioned, and what were the conclusions reached.

In the first considerable epidemic of influenza in London after the discovery of the influenza virus, I studied all patients admitted to Hammersmith Hospital with good evidence of a recent or present influenza infection. Having defined the group to be studied on the basis of an association with epidemic influenza, I studied especially those patients who showed evidence of lung changes, enlisting the generous aid of my colleagues in the departments of bacteriology, hæmatology, and morbid anatomy. The data so obtained were finally analysed to determine in what respects, if any, the lung changes observed differed from those found in acute lung infections not associated with influenza; and, especially if such a difference were observed, what part the virus was taking in the causation of the lung changes.

The chief feature of the clinical picture was its variability from case to case; and the general conclusion reached about the causation of the lung changes was that "the influenza virus can produce severe changes in the lung in man which facilitate invasion by bacteria. The course of the disease depends upon the extent and virulence both of the virus and of the bacterial infection; the extraordinary variability of the clinical picture is due to the numerous possible combinations of these factors." Thus the cases studied were found to be an ætiologically defined group only in a very limited sense, that of being related temporally to an influenzal infection. Microbiologically, their ætiology was found to be mixed, both the virus and a variety of bacterial types being concerned in the production of the lung changes, so that it is only in a sense so modified as to be trivial that they could be called from this viewpoint "a distinct entity."

Clinically, it is true, I noted that, viewing the cases with consolidation as a group, certain differences could be detected from the features usually associated with simple pneumococcal pneumonia; but the degree of this difference varied greatly even among the cases with lobar consolidation, and the whole group differed from case to case so greatly that it was necessary to divide it for description into no fewer than five subgroups. I should certainly hesitate to suggest that in an isolated case (with the possible exception of the acute fulminating variety) it would be possible to deduce a relation to influenza on the characteristics of the pneumonic stage alone. I do not see how that statement "influenzal pneumonia is a distinct entity" can be construed, even with the greatest ingenuity, so as to convey the modest but clearly expressible conclusions of my clinical study. All it conveys to me is that you are aware that I once wrote a paper relevant to the subject of your annotation.

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[1] Moore, T., Leitner, Z. A. *In* Vitamin A Requirements of Human Adults. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 264. H.M. Stationery Office, 1949; p. 65.

Institute of Diseases of the Chest,
Brompton, London, S.W.3. J. G. SCADDING.

EFFECTS OF LEUCOTOMY

SIR,—Your annotation last week says of me, in reference to a book that I wrote on this subject: "He provided a mass of interesting clinical data, but . . . did not even add up the number of patients in each diagnostic group."

Of course I added these up (many times, since I am bad at arithmetic). The numbers of cases in the largest diagnostic group and its main subgroups are given in a table facing p. 352, while those in its further subgroups are on pp. 230–231. The numbers in all the other groups are given in the text of the appropriate chapters, and are repeated in the summaries that conclude them.

As many more people will read the annotation than will be familiar with the book, perhaps you will be good enough to publish this gentle reproach in correction of your mis-statement.

London, W.1. MAURICE PARTRIDGE.

BUTAZOLIDINE

SIR,—The early reports on butazolidine [1–3] were so favourable that it immediately began to be widely used; and in the British Isles alone about 100,000 patients are said to have received this drug.[4] The first warnings that butazolidine is not so free from serious toxic effects as was at first supposed have already appeared.[5–7] In the small series of cases that we have treated we have been impressed by the frequency of toxic reactions; and we report here a case of jaundice and agranulocytosis in a patient, to whom butazolidine was administered.

The patient, a housewife, aged 66, was admitted to this hospital on July 25, having had generalised muscular pain for the previous 6 weeks; her earlier medical history was uneventful. She was somewhat obese, with tenderness of muscles, especially round the elbows, knees, and shoulders, limiting all movements. There was no evidence of joint involvement. The blood-pressure was 185/120 mm. Hg. Initial investigations showed hæmoglobin 76% (11·25 g. per 100 ml.); white blood-cells 8350 per c.mm. (polymorphs 55%, lymphocytes 39%, eosinophils 2%, monocytes 4%); erythrocyte-sedimentation rate (E.S.R.) 93 mm. in first hour (Westergren). Radiographs of knee-joints showed mild arthritic changes. The urine was normal. Generalised fibrositis was provisionally diagnosed.

Heat treatment was started, but after a week the patient's condition was unchanged. In view of this, and the persistently raised E.S.R. (now 115 mm.) it was thought that the disorder might be early rheumatoid arthritis. The possibility of an infective arthritis was also considered, since radiographs showed apical abscesses in two teeth in the lower jaw. On Aug. 12 eight teeth were extracted under nitrous oxide anæsthesia with penicillin cover. For the next 2 days the temperature was somewhat lower, and the patient's condition rather better.

On Aug. 22 administration of butazolidine was begun in a dosage of 1·2 g. per day by mouth, and the patient was put on a low-salt diet. Within 36 hours her condition had improved notably, and during the next 10 days movements were almost painless. At the end of this time a maculopapular rash appeared on the face, and shortly afterwards slight œdema of the ankles was noticed. On Sept. 2, therefore, the dosage of butazolidine was reduced to 0·6 g. per day. After 2 days the rash, though fading, was still present and the skin of the legs was desquamating. During the next 4 days the patient complained of feeling ill and depressed; her temperature was about 101°F and she had developed mild bronchitis. On Sept. 8 jaundice was evident, and butazolidine was immediately discontinued, a total of 16 g. having been given.

Within 2 days the temperature had fallen to 99°F; but the patient now felt drowsy and had anorexia and nausea, and the jaundice had deepened (serum-bilirubin 6·4 mg. per 100 ml.). The liver was tender but not enlarged; the urine contained bile, but the fæces were normal.

Drowsiness persisted, and on Sept. 15 the hæmoglobin was 66% (9·77 g. per 100 ml.); white blood-cells 2450 per c.mm. (lymphocytes 88%, monocytes 12%, polymorphs nil). Her temperature had now risen to 102°F with two rigors. She was therefore given aureomycin 0·5 g. 6-hourly by mouth; there was no further rigor, but the temperature did not fall. There was no purpura or stomatitis.

On Sept. 18 the jaundice was more pronounced, and the patient was extremely ill. A blood-count showed hæmoglobin 56% (8·29 g. per 100 ml.); white cells 2050 per c.mm. (lymphocytes 94%, monocytes 6%, polymorphs nil); platelets 105,000 per c.mm. The sternal marrow was found to be very poorly cellular, and the few polymorphs present showed pronounced toxic changes; the appearances supported a diagnosis of agranulocytosis (see table).

One pint of fresh blood was transfused; and on Sept. 19, on Dr. A. Piney's advice, the sternum was opened under general anæsthesia and packed with marrow obtained earlier that day from a rib during a thoracotomy on another patient. Two further pints of stored blood were transfused immediately after the operation. A biopsy specimen of marrow obtained at the operation showed some improvement; the marrow was moderately cellular, but segmented neutrophils were extremely scanty.

After operation the patient recovered rapidly. On Sept. 24 the jaundice had disappeared; and apart from a sacral bedsore the patient was well on the road to recovery. Marrow from the iliac crest was found to be moderately cellular; the granular series had reverted to normal, but erythropoiesis seemed still to be somewhat depressed; the myeloid-erythroid ratio was 17 : 1 (see table). Since then in periodic films of peripheral blood the white-cell series has been normally differentiated. The patient has remained well.

This case is of special interest since the patient was in hospital without treatment, apart from heat and tab. codein. co., for 4 weeks before treatment with butazolidine was started. We also confirmed from the patient's general practitioner that he had administered no drugs that are known to produce agranulocytosis; and the patient herself denied taking any drug unbeknown to her doctor. We therefore feel that the agranulocytosis can only be ascribed to the butazolidine. It is noteworthy that the granulocyte-count improved rapidly after the drug was discontinued; and we do not feel that the small amount of marrow implanted at operation contributed materially to this change.

We informed Messrs. Geigy Ltd. the manufacturers; and they kindly arranged for Prof. R. Domenjoz, of

DIFFERENTIAL MARROW-COUNTS

Cells	Proportion (%)	
	Sept. 18, 1952	Sept. 24, 1952
Blast cells	4	Nil
Pro-erythroblasts	4	0·5
Normoblasts	2	3
Myeloblasts	Nil	0·5
Neutrophil myelocytes	4	7·5
Neutrophil metamyelocytes	Nil	19
Polymorphs	4	31·5
Lymphocytes	76	35·5
Monocytes	2	2·5
Unclassified	4	Nil

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1. Bach, F. *Lancet*, July 12, 1952, p. 92.
2. Slot, G. *Ibid*, July 19, 1952, p. 148.
3. Brown, R. A. P., Currie, J. P. *Ibid*, Oct. 4, 1952, p. 682.
4. Geigy Limited, personal communication.
5. Hart, F. D., Johnson, A. M. *Lancet*, July 26, 1952, p. 197.
6. Hart, F. D., Johnson, A. M. *Ibid*, Sept. 20, 1952, p. 587.
7. Loxton, G. E., Le Vay, D., Wilson, P. *Ibid*, Oct. 4, 1952, p. 682.

Basle, to examine the case. He, like the manufacturers, had heard of no similar case.

We suggest that butazolidine should be regarded as a dangerous drug, and that 1·2 g. per day is probably a dangerously high dosage. Before treatment with butazolidine a white blood-cell count should, we suggest, be made; and further counts should be made at least weekly while this treatment is continued. Any definite fall in the number of polymorph cells is, in our opinion, a contra-indication to further butazolidine therapy.

When the case of agranulocytosis reported here was discovered a routine white blood-cell count was made on all our patients receiving butazolidine. One patient had a relative granulopenia (44%) with a total white blood-cell count of 6200 per c.mm. When butazolidine was discontinued the count rose rapidly to its previous level of 74% granulocytes in a total of 12,400 white blood-cells per c.mm.

We wish to thank Dr. Kenneth Playfair, under whose care the patient was admitted, for permission to report the case described here; Dr. A. Piney and Dr. M. S. Ross, who made the sternal punctures and marrow-counts; and Mr. Roy Parkinson, who implanted the marrow.

Queen Mary's Hospital,
Stratford, London, E.15.

D. L. CROWTHER
F. R. M. ELGOOD.

SIR,—With reference to the recent correspondence on the toxic effects of butazolidine, I would like to report the following case.

An unmarried woman, aged 59, had had rheumatoid arthritis for 20 years. She had never had gold injections or any treatment other than spa therapy. She had not been taking any analgesics or "antirheumatic" compounds.

On Sept. 15 her general practitioner started her on a course of butazolidine, 1·2 g. daily by mouth. As soon as she began to take these tablets she got quite severe indigestion, and on the 3rd day she began to get breathless. After 7 days she gave up taking the tablets because abdominal pain and nausea were severe.

On Sept. 23 a maculopapular eruption appeared on her face and lower abdomen; some septic spots appeared all over her body a few days later. On Sept. 25 her left breast became inflamed, and cellulitis developed with enlarged axillary lymph-nodes. This area became extremely painful.

On Sept. 30 her throat became dry and sore. This got progressively worse, and on Oct. 7 it was so bad that she was unable to swallow anything at all.

When admitted to hospital, on Oct. 7, she was very ill with a temperature of 103°F. She had very severe stomatitis and pharyngitis; her mouth and tongue were covered with a thick growth of yeasts. She had moderately severe bronchopneumonia, and her lips were slightly cyanosed. There were several peculiar tender red swellings on her left arm, resembling erythema nodosum. The cellulitis of her breast was quite extensive, and she had several septic spots scattered over her body. Her rheumatoid arthritis was moderately severe, but she had been able to walk satisfactorily before her illness.

Investigation of the blood gave the following results: white cells 4000 per c.mm. (neutrophils 4%, eosinophils 0%, basophils 1%, lymphocytes 40%, monocytes 11%, myelocytes 3%, metamyelocytes 41%); platelets 250,000 per c.mm.; hæmoglobin 72%; red cells 3,630,000 per c.mm.; erythrocyte-sedimentation rate 112 mm. in first hour (Westergren). Sputum grew a mixed culture of *Staphylococcus aureus*, yeasts, *Streptococcus viridans*, and a few hæmolytic streptococci of Lancefield's group A. All organisms except the yeasts were sensitive to all antibiotics in common usage.

The patient was treated with aureomycin, penicillin, pentose nucleotide, and pyridoxine. Within 18 hours her temperature had fallen to 99°F, and it has remained in this region ever since.

A further white blood-cell count on Oct. 9 showed a total of 20,000 per c.mm. with 44% mature polymorphs, 22% lymphocytes, and 28% metamyelocytes. Her general condition has improved remarkably and she is now taking solid as well as liquid foods. The yeasts have been eliminated by painting the mouth with gentian-violet.

There can be no doubt that this patient's symptoms have all been due to butazolidine therapy; and it would therefore seem that routine blood-counts should be done on all patients receiving this drug.

I am grateful to Dr. Geoffrey McComas for permission to publish this case.

Croydon General Hospital. D. J. A. JARVIS.

SIR,—A patient with rheumatoid arthritis whom I was treating with butazolidine developed a temperature of 104°F with a widespread maculopapular rash and severe neutropenia. This occurred after the second injection of the drug.

Dewsbury. GODFREY B. TAIT.

TREATMENT OF BRONCHIAL CARCINOMA

SIR,—Your excellent leading article of Sept. 27 makes no mention of wheezing as an early symptom of bronchial carcinoma. In our experience wheezing is a symptom of the greatest importance, the significance of which is very commonly overlooked. It results from partial bronchial obstruction, and often disappears when the obstruction becomes complete.

A wheeze, or "bronchitis," occurring *for the first time* in a patient over 35 years of age is sufficient ground for a full clinical and radiological examination, supplemented by bronchoscopy. The finding of a *persistent* localised rhonchus on auscultation is of the utmost significance.

Surgery,
ospital

CONSTANCE M. HESLING
GORDON CRUICKSHANK.

THE HERXHEIMER REACTION

SIR,—Your annotation last week is inaccurate in stating that "it fell to Herxheimer to describe the untoward effects of the drugs invented by his fellow-countryman, Ehrlich."

The reaction was first described by Prof. O. Jarisch (1850–1902) in 1895 and was observed during treatment with mercurial inunctions. An exacerbation of a syphilitic roseola eruption was noted during the first few days of a course of mercury.[1] Dr. Karl Herxheimer and his assistant, Dr. Krause, reported in 1902 similar reactions in sixty patients "twenty-four hours after an initial inunction of 40 g. of grey mercurial ointment."[2]

London, W.1. A. H. HARKNESS.

DEVELOPMENT OF TUBERCULOSIS IN CONTACTS

SIR,—Dr. Aspin's interesting paper[3] raises a question often left unanswered. How does the time taken for the infection to develop fit in with our ideas about the pathogenesis of the disease?

A positive tuberculin reaction in early childhood remains positive until puberty and for many years after. Such people do not become contact cases of tuberculosis after puberty unless they are further infected. Negroes are susceptible at an earlier age because of their earlier development.

Has physiological puberty anything to do with this phenomenon? The superinfection necessary to produce active tuberculosis occurs only in certain circumstances of stress unpredictable in adult life.

Dr. Aspin found that the first year after contact yielded 22 times as many infections as the average incidence in the general population would suggest. Thus the usual case of tuberculosis discovered among contacts and in the general population had been in contact with a newly notified case of tuberculosis for one year or less. This original contact case was almost certainly *clinically* negative before contact, and yet developed pulmonary tuberculosis of adult type within a year.

It would be possible to find out how long the newly notified case had had symptoms suggesting infectivity before being

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1. *Wien. med. Wschr.* 1895, 45, 721.
2. *Dtsch. med. Wschr.* 1902, 28, 895.
3. Aspin, J. *Lancet*, 1952, i, 502.

iagnosed and *notified.* This *time would then have to be* dded to give the probable interval between primary infection nd established adult disease.

Will this time suffice for the primary complex to levelop through the secondary stage into the adult ype? It is difficult to understand how this theoretical ourse can be run in so short a time unless the three hases overlap very considerably.

An answer to this question would help to solve the roblem defined by Dr. Aspin—"the periodic review of ertain groups of originally healthy contacts, in the iope of picking out for treatment persons on the point f falling ill."

Léopoldville, Belgian Congo. G. P. LAMBRICHTS.

PNEUMA, PSYCHE, AND SOMA

SIR,—In his thoughtful paper of Oct. 11 Dr. George ay quotes Plato's famous parable of the driver and his air of horses. May I point out, for those who would efer to the context, that the passage is to be found; iot in the *Phaedo*, but in the no less profound and eautiful dialogue *Phaedrus* (pp. 246–254, Stephanos).

Cambridge. G. CYRIL ARMSTRONG.

CLINICAL TESTS OF TRICHLORETHYLENE INHALERS

SIR,—In response to a recommendation of the Working Party on the Recruitment and Training of Midwives, the Medical Research Council appointed a Committee on Analgesia in Midwifery to satisfy itself that a trichlorethylene inhaler could be designed which was safe for use by midwives in domiciliary practice.

Preliminary trials suggest that trichorethylene, when administered in new inhalers designed to a performance specification drawn up by the committee, is both safe and effective in normal labour.

A sufficient number of the inhalers is now available for more extensive trials, which are being organised, in coöperation with the Central Midwives Board, by a joint subcommittee of the Committee on Analgesia in Midwifery and of the Anæsthetics Committee of the Royal College of Obstetricians and Gynæcologists. The trials have been planned to include the use of the inhalers in domiciliary practice, by midwives, for selected patients who are expected to have an uncomplicated labour. Certain local health authorities have agreed to take part in these trials, which are being carried out also in hospitals.

General practitioners whose patients would be suitable for inclusion in the trial are being asked, in each case, for their permission. The Medical Research Council will be most grateful for the coöperation of the profession in carrying out these trials.

GEOFFREY ORGANE
Secretary, Medical Research Council
Committee on Analgesia in Midwifery.

ACUTE AGRANULOCYTOSIS AND THIOSEMICARBAZONE

SIR,—In my article (March 1) on *p*-acetamidobenzaldehyde thiosemicarbazone in the treatment of leprosy, I recorded that in 126 cases treated for periods of up to seventeen months, 1 case of acute agranulocytosis attributable to this substance had been seen. In this group of patients, now numbering 150, I have had 2 more cases of acute agranulocytosis.

A young African man in good physical condition, with mild leprosy, started T.B.1 treatment on Feb. 9, 1952; the dosage was 50 mg. a day for one week, 100 mg. a day for the second week, and 150 mg. a day for the third week. On the twenty-second day of treatment he felt unwell and feverish in the evening, and next morning he reported with a temperature of 101°F. Malaria was suspected, but a blood-film revealed acute agranulocytosis. T.B.1 was stopped, and 1 million units of penicillin was given and was repeated daily until recovery. 'Pentnucleotide' was not available.

That afternoon the temperature rose to 105°F. There was no serious inflammation of the mouth or throat; there was a small septic focus on one foot at the site of a cut, and later a similar focus appeared on one hand.

High remittent fever continued for seven days, reaching its maximum 106·2°F—on the second day and then slowly subsiding. No serious local inflammation developed anywhere, and the general condition of the patient remained excellent. The spleen became palpable on the fourth day. Apart from the high fever no serious symptoms developed. Blood-culture was not possible here.

The white-cell count began to rise greatly within eight days, with signs of intense bone-marrow activity; from the seventh day many myelocytes and metamyelocytes were seen in the blood-films. The number of white cells per c.mm. before treatment and on the first ten days of the illness were as follows (granulocytes in parentheses): before treatment, 6500 (3185); day 1, 1800 (180); day 2, 1300 (106); day 3, 1900 (143); day 4, 2300 (115); day 5, 2000 (40); day 6, 4200 (428); day 7, 8500 (2550); day 8, 10,000 (5230); day 9, 10,400 (6184); day 10, 17,900 (12,942).

Of the clinical features, the very high fever in the absence of any local signs of infection was striking. The prompt diagnosis and penicillin treatment almost certainly prevented serious local inflammation in the mouth, throat, and elsewhere.

The second case was similar, but was complicated by an acute suppurative lymphadenitis in both groins.

Both these cases and the case previously recorded occurred during the first month of treatment; but many of our patients have received two years' treatment without trouble. It appears possible that agranulocytosis occurs early or not at all. Some workers have suggested that it is an allergic rather than a toxic phenomenon.

These further cases confirm the view previously expressed that T.B.1 treatment should be given only under close medical supervision. If any fever develops, particularly during the first few weeks of treatment, agranulocytosis should be suspected and the blood examined. With prompt diagnosis and energetic penicillin treatment, recovery may take place in about a week; for it appears that if serious infection can be prevented or controlled, the agranulocytosis will look after itself.

Uzuakoli, East Nigeria. JOHN LOWE.

Parliament

Experiments on Animals

IN the House of Lords on Oct. 14, Lord DOWDING, speaking on surgical and medical experiments on animals, declared that the law designed for the protection of animals against cruelty was gravely defective. There was neither adequate inspection nor proper enforcement. The experiments were excessive in number, repetitive, and often unpractical when it came to applying them to human maladies. Laymen had no access to the laboratories and the evidence was incomplete and restricted to accounts given by the experimenters themselves in medical and scientific journals. It was not unreasonable, he thought, to assume that the actual situation might be a good deal worse than was shown by the available evidence. The number of experiments had increased from 300 in 1876, when the Cruelty to Animals Act was passed, to over 1,750,000 in 1950. Yet the number of inspectors had only been increased from 2 to 5. He was greatly perturbed by a new form of animal *exploitation* which had caused vivisection to take a secondary place. He referred to the use of animals in the manufacture and testing of many modern drugs. Apart from the use of calves for the production of smallpox vaccine, animals were also used in testing insulin, suprarenal hormone, thyroid, and pain-killing drugs. Surely, Lord Dowding said, it should be possible to substitute chemical and mechanical tests for this traffic in flesh and blood. He asked the Government to make an official inquiry into this question, which had not been touched by earlier legislation. He also asked for a stricter enforcement of the Act of 1876.

Lord HAILEY did not believe that the scientific world would object to an inquiry if necessary, and it was admitted that in some respects the Act was out of date and might need amendment. But he feared that an inquiry might once more stimulate the energies of the anti-vivisection societies to advocate the total abolition of all forms of animal experiments, with the result that science would be deprived, not merely of the means of achieving advance in physiological science, but also of the means of testing and standardising new drugs. That was a danger which the scientific world would deprecate.

Lord WEBB-JOHNSON said he was in complete sympathy with Lord Dowding in his anxiety that proper precautions should be taken in the issue of certificates for experiments on animals, and for eight years as president of the Royal College of Surgeons he had refused to sign many applications for licences, either because the experimenter was not working under satisfactory conditions, or because the experiment had been repeated a sufficient number of times to prove that the results obtained were established as facts. His visits to other countries had satisfied him that the precautions taken here were stricter than those in any other country of the world. He himself believed that the British safeguards were sufficient.

The EARL OF SELKIRK pointed out that the Act of 1876 was unique in the sense that no other country in the world had an Act of that character. It provided that no experiments on living vertebrates might be carried out except under stringent conditions. Such experiments might be carried out only for definite purposes—i.e., for the acquisition of knowledge useful in the saving of life or the alleviation of suffering—and not for training or practice. Before anyone obtained a licence he required two signatures, one from the president of a learned society, and the other from a professor of a branch of medical science. Under the licence given the animal must be anæsthetised during the whole operation; and if the pain was likely to continue after the anæsthetic ceased, the animal must be killed before recovery. Experiments could be carried out only in registered places, and full records must be kept and annual reports submitted stating the number and nature of the experiments performed. These places were, of course, open for inspection at all times. The duties of inspectors were to visit regularly all the places licensed, and this meant a visit nearly once a quarter. Visits were nearly always unannounced. The chief inspector received 1200 reports a year from his subinspectors and submitted an annual report to the Secretary of State, which was presented to Parliament. The chief inspector had assured Lord Selkirk that he was fully satisfied that he knew what was going on in every place on his register.

It was true, Lord Selkirk continued, that there had been no prosecutions under the Act, but that was not a wholly satisfactory way of judging the success of the Statute because, besides noting the irregularities each year in the annual report, certificates and licences had been refused, and warnings had been issued. He agreed that the production of sera was not covered by the 1876 Act, but this work was covered by the Protection of Animals Act, 1911. Inspectors were appointed under the Therapeutic Substances Act, 1925, to ensure that the places where the work was carried on were suitable and that the animals were maintained in a healthy condition. If any sera were tested the process came under the 1876 Act. In 1948 the then Home Secretary had received a delegation who presented a number of specific cases. All these had been carefully investigated, and Mr. Ede came to the conclusion that no sufficient grounds existed, either in respect of the law or of its administration, to justify the appointment of a Royal Commission; and nothing had arisen recently to cause the present Home Secretary to take a different view.

QUESTION TIME

N.H.S. Charges

In answer to a question Mr. IAIN MACLEOD gave the following particulars, comparing the demand for drugs, dental treatment, and appliances under the National Health Service during the four months June to September, 1952, following the introduction of charges on June 1, 1952, under the National Health Service Amending Act, 1952, with the demand in the corresponding period of 1951 (see table).

Replying to a further question Mr. Macleod said the charges had led to some fall in the demand for drugs and to other savings in costs, but it was too early as yet to make an estimate of the financial saving likely to be effected.

B.C.G. Vaccine

Mr. P. F. REMNANT asked the Minister whether B.C.G. vaccine was now being manufactured in this country.—Mr. MACLEOD replied: Manufacture in this country will be considered as soon as the level of requirements justifies this course. Mr. REMNANT: Is the Minister aware that a considerable amount is being imported by air and that at present its manufacture here is illegal under the Therapeutic Substances Act? Will he at least give permission, by law if necessary, for it to be manufactured here?—Mr. MACLEOD: We import from Copenhagen and Paris but the amount involved at present totals only £1600 a year, and until the use of B.C.G. becomes more widely approved I do not think that there is any point in changing the present position.

Food-poisoning

Mr. J. K. VAUGHAN-MORGAN asked the Minister what steps he was taking, particularly in conjunction with the Minister of Food, to offset the continued increase in outbreaks of [illegible] LEOD replied: A major factor in [illegible] the recognition by both industry an [illegible] re and cleanliness in all aspects of food-handling, and much publicity work has already been done on this by the departments concerned, local authorities, and other bodies. At the same time, in conjunction with my department the Ministry of Food is considering what further measures can usefully be taken in the light of recent reports as regards meat and meat products, and is also looking into the subject of synthetic cream. I have also under consideration a revision of the Public Health (Infectious Diseases) Regulations so as to give wider powers in relation to food-poisoning.

Mr. VAUGHAN-MORGAN: Is the Minister aware that according to his Ministry's report 83 of the 539 outbreaks last year were in hospitals and institutions? Will he take whatever disciplinary action is necessary to stop this?—Mr. MACLEOD: Certainly.

Experiments on Living Animals

In answer to a question Sir DAVID MAXWELL FYFE stated that the total number of experiments performed in 1951 on living animals under the Cruelty to Animals Act, 1876, was 1,919,424. Of these, 1,665,120 experiments not involving any procedure more severe than simple inoculation or superficial venesection were performed without anæsthetics. Cats, dogs, horses, asses, or mules were used in 10,262 experiments.

	1951				1952			
	June	*July*	*Aug.*	*Sept.*	*June*	*July*	*Aug.*	*Sept.*
Prescriptions								
Prescriptions presented for dispensing by chemists (to nearest 1/4 million)*	17m	16 1/4m	15m	—	14 1/4m	15 1/4m	14m	—
Dental Treatment								
Completed courses of treatment, other than the provision of dentures to which 1952 charges do not apply	354,000	332,000	380,000	378,000	372,000	361,000	406,000	366,000
Courses for limited treatment†	209,000	228,000	302,000	242,000	151,000	121,000	144,000	117,000
Appliances (including replacements)								
Surgical boots (number of pairs)	4003	3533	3398	3594	2569	2479	5537	
Abdominal supports	8874	9636	7311	7315	5311	4221	8865	
Wigs	715	729	604	698	434	420	918	
Elastic hosiery ordered through hospital service	2954	2901	2736	2951	2450	2354	5107	

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*Includes elastic hosiery prescribed by general practitioners. There are no separate statistics for prescriptions issued by hospital outpatient departments.

†The courses for limited treatment usually cost under £1 and, since patients would have to pay the whole cost under the National Health Service, many may be assumed to have had the treatment privately.

Obituary

PHILIP HENRY MITCHINER

., C.B.E., M.D., M.S. Lond., D.Ch. Durh., F.R.C.S.

men have had more influence on the surgery of
than Philip Mitchiner, and he had won an almost
ry reputation as a clinical teacher. Though it
own that he had latterly been obliged to restrict
berant activities, the news of his death on Oct. 15
s a shock.

[Elliott & Fry

on June 17, 1888, he was the eldest son of
M. Mitchiner, and was educated at Reigate
ar School. At St. Thomas's Hospital, which he
in 1906, he was awarded many prizes and distinctions, including the Mead and Bristowe medals and Beaney scholarship. As a student he was one of the original members of the the combined Guy's and Thomas's contingent on the foundation of the medical unit of London University O.T.C., and this remained one of his outstanding interests. When he qualified in 1912, he obtained the gold medal in the M.B. examination, and his house-appointments at St. Thomas's included that of house-surgeon to Sir George Makins. In 1913 he obtained the F.R.C.S. and the following year the M.S. degree.

the outbreak of the 1914–18 war Mitchiner was
in and adjutant of the medical unit of London
rsity O.T.C., and he was retained in this appoint-
because of his administrative ability and against
ishes. At the beginning of 1915 he was appointed
al registrar at St. Thomas's, but in 1916 he managed
entangle himself and he proceeded on active service
Balkan front, where he was employed as a surgical
alist, first to a Serbian hospital and later, in 1917,
e 49th General Hospital. For his services he was
ated with the Serbian Gold Medal, the Order of
ava, and the Russian Order of St. Stanislas. Return-
o St. Thomas's in 1919, he served for a time as
ent assistant surgeon, but he gave up this appoint-
to join the Serbian Relief Fund. In 1920 and 1921
gain worked as a surgical specialist in Serbia, where,
g to war and typhus the normal medical services
almost entirely broken down. His work was of
imable value because of his knowledge of the
age and high surgical standing. On his return to
and he was appointed to the surgical staff of the
l Northern Hospital, and also completed his tenure
esident assistant surgeon at St. Thomas's, where
ecame assistant surgeon in 1922. His interest in the
C. continued, and he succeeded Colonel A. M. H. Gray
ommanding officer of the medical unit.

etween the two wars Mitchiner was intensely busy
teacher, consulting surgeon, examiner, and author.
Science and Practice of Surgery, written with Mr.
anis and first published in 1926, is possibly his
-known work. For many years he was an examiner
ondon University, and in 1936 he was appointed to
court of examiners of the College of Surgeons. In
Hunterian lecture to the college in 1933, he dealt
the problem of burns. In 1932, as a senior Territorial
er, he was appointed honorary surgeon to the King,
two years later he became full surgeon at St.
mas's. He was appointed C.B.E. in 1938. As a member
he senate he was also active in the affairs of the
versity.

t the outbreak of war in 1939 Mitchiner was first
loyed in the Northern Command and later as D.D.M.S.
the Anti-Aircraft Command of the whole country.
he latter part of the war he proceeded as consulting
geon to the Middle East. At the end of hostilities
was appointed C.B., and he held the rank of major-
eral in the Territorial Army.

During the war St. Thomas's had suffered considerably, and the dispersion of the hospital activities and buildings increased the work of the honorary staff. Mitchiner's administrative experience on his return to civilian life was of notable value to the hospital at this time, particularly in view of the coming of the National Health Service. Paradoxically he had to retire in March, 1948, because the retiring age at St. Thomas's had always been 60: within three months, the retiring age was advanced to 65, to conform with the general practice of the health service. He remained, however, an extremely busy man though he was no longer a member of the active surgical staff. He was chairman of the court of examiners of the Royal College of Surgeons from 1946 to 1948, having become a member of the council in 1943, and he only completed his term of office as vice-president shortly before his death. As member of the South West Metropolitan Regional Hospital Board, he served on a number of committees, and he was also a deputy-lieutenant of the County of London and deputy vice-chancellor of the University of London. He had a prominent part in shaping the destinies of the Association of Surgeons of Great Britain and Ireland over the past twenty years, and he was president at its last meeting in London.

His characteristics as surgeon, soldier, and teacher are reflected in tributes from friends. R. H. O. B., to whom we are indebted for biographical details, adds the following personal words:

"Mitchiner will always be remembered as a man who did many kind acts for many people and without any ulterior motive. He was a great champion of the under-dog against the powers of vested authority. An iconoclast, he had at the same time great constructive ability in administration. As an undergraduate teacher of surgery he was magnificent. A profound knowledge of facts and a droll and sometimes Rabelaisian power of expression impressed his students, and by amusing them he imprinted knowledge in their minds. As a surgeon he was original in many of his ideas and he was a rapid operator. As an examiner he was extremely shrewd and scrupulously fair, not suffering fools gladly although sometimes leaving them under the impression that they had done better than was in fact the case. As a member of any committee he could be counted on to have a firm grip of the facts under discussion, and to instil common sense into its deliberations. His work for the O.T.C. and Territorial Army was unique, and it is doubtful whether any non-professional soldier will ever equal him. For his friends the world will be a sadder place without him and many will miss being able to turn to him for helpful advice."

R. J. V. P. knew Mitchiner as his student, as his junior in the O.T.C., as a fellow officer in the Middle East, and finally as a fellow member of committees. He writes:

"Philip Mitchiner had a zest for life, a sincere sense of duty which lasted the course, an infallible gift for recognising the arrogant, the pompous, and the bully, and the most devastating wit in exposing these qualities. It was the last of these gifts which made him a legend, and which will lead, as with Abernethy, to every pointed medical story of his time claiming his fatherhood. There is one infallible test of authentic record. If in a tale his rapier pierced field-marshal, general, consulting physician, or matron, the record has the ring of truth. But never in his life did Mitchiner score a point over a student, a house-officer, or a private soldier.

"These tales will carry Mitchiner's name to posterity as one who abhorred insincerity, unfairness, and oppression. But in many hundreds of Thomas's men's memories there lives the kindly quaint figure with shorn head and thin-rimmed glasses, to whom they went with their scrapes, and their worries, and from whom they sought advice when starting on their career. As a teacher he scorned to sit on the fence or to qualify; he was dogmatic and emphatic, and none ever forgot what Mitchiner taught, though men sometimes met examiners whom he had not.

"Of my own memories of him two stand out; of a kindly, busy, amateur archæologist, exploring Palestine and Syria with a camera in one hand and a Bible in the other, and my final meeting when, a sick man, he spoke with all his old zest of the soldiers in Korea and their right to the best doctors.

"The Army, or perhaps, the uniform, was Mitchiner's enduring delight. No-one had less use for discipline, and he trod on more corns than anyone I have ever met; but he loved the little glories of military life, the bright ribbons, the hint of adventure that went with the uniform. He did more than most to reconcile the amateur R.A.M.C. officer to the inevitable constraint of Army life; they laughed with him at the insincerities, the stuffed pigeons, the façades. But they were often pulled up short by the simple phrases of a just and serious man, whose sense of duty crowned him with a dignity he feigned to despise."

His last house-surgeon before his retirement describes Mitchiner's impact on a younger generation:

"I took up my appointment as house-surgeon to Mr. Mitchiner with mixed feelings, for a wealth of anecdote had created a formidable figure. The container certainly looked harmless enough, but I was apprehensive of igniting the gunpowder said to be within. A characteristic response to my attempt to use a 'no touch' technique when doing a 'cut down' for transfusion soon reminded me that the Mitchiner legend was built round his detestation of pretentiousness. This quality could also be embarrassing, and my ears still burn at the memory of being told I looked hungry during a formal dinner at the Royal College of Surgeons, and at having to accept Mitchiner's own helping passed under the noses of the eminent, and the disapproving frowns of the liveried waiters.

"He was a loyal and considerate chief. Wrong-doing was corrected by a gentle 'Naughty boy, you shouldn't have done that'—though a repetition of the misdeed might well elicit something more in accordance with the legend. Most of the fireworks were reserved for the graphic illustration of his teaching, and as a teacher of undergraduates he had few equals in the expression of fundamental principles in a fundamental way. He had a wonderful way with patients, and the change in attitude of a difficult patient after his ward rounds was dramatic.

"I am one of many who have reason to remember his unobtrusive kindness. Those of us who worked under him in the immediate post-war years will remember Mitch with affection."

C. M. P. recalls his work for the students at St. Thomas's.

"Philip Mitchiner established a reputation as a witty and effective teacher of undergraduates and he was always a popular supporter of many student activities. By bent and education he was essentially a general surgeon and in that capacity he extended his interests considerably outside the purely professional arena. His services to the senate of London University and his devotion to the Territorial medical unit of that organisation are examples of that tendency. He possessed a clear head and a critical ability which made him a useful member of any committee, albeit his approach was at times brusque and lacking in the traditional courtesies. But his obvious sincerity and sound common sense robbed this attitude of any offence. His capacity for direct speech and clear judgment will be especially missed at the meetings of the council of the College of Surgeons.

"Mitchiner had character and also that element of it which inspires a strong sense of public duty. This possession, I think, enabled him to carry on much valuable work in council and committee despite the recurrent illnesses which harassed him in his latter years."

A. L. C. writes with nostalgic pride as one who received his "military baptism by serving in Mitchiner's Army."

"The R.A.M.C., and particularly that part of it associated with the Territorial Army, has suffered an irreparable loss in the death of Philip Mitchiner. No more shall we see that slightly bizarre but ever popular figure with close-cropped head, kindly eyes, and impetuous tongue. There was a touch of Grimaldi about him that endeared him to his juniors. His devotion to the Territorial Army never flagged. Long years of service included many important appointments. The two in which, perhaps, he wielded most influence were those of commanding officer of the medical branch of the University of London O.T.C. and of D.D.M.S. of Anti-Aircraft Command. In the former there passed through his hands many generations of students who were to win honour and distinction in the recent war, and in the latter he created the medical services of General Pile's famous command. No-one contributed more towards the welding together of the Regular and Territorial elements of the Corps into their present close and happy relationship. Kindly and generous-hearted, he was quick to pounce on inefficiency and pomposity, exploding them with a robust phraseology, a little suggestive perhaps of the 'rude and licentious soldiery' whom he loved so well."

W. H. O. leaves St. Thomas's men to recount the Mitchineriania, true and apocryphal, but "as a contemporary, a comrade in uniform in three wars, a friend and admirer of many years' standing, a fellow member of the Surgical Travellers and the council of the College of Surgeons, I should wish to pay my tribute to a very great man."

"Mitchiner's courage, honesty, and loyalty," he writes, "are the qualities that come at once to mind. He had courage—physical and moral—above most men. If he believed in a cause he would fight for it, if he believed in a man he would support him. There was no fencing with Philip. He came to the point at once, and further he left no possible doubt as to what the point was. His language was direct, forcible, almost Chaucerian in its imagery, but phrases that, coming from others might have given offence, were detoxicated by his glowing sincerity. Soft soap and compromise were alien to his nature. He was a remarkably efficient committee man, better able than most to see the essential point of a problem, more ready than most to state it clearly and forcibly. He had, in debate, the natural eloquence of a man of action.

"His personal appearance went well with his colourful and forceful character. He had the clear-cut features and piercing eyes of a medieval pope. He wore his hair clipped short. He dressed simply and travelled about London, bareheaded and on foot. In his general appearance, his erect stance, and his direct look, he recalled the portrait of Anthony Carlisle by Shee, the most striking painting in the council room of the College of Surgeons. Most of his friends will think of him in uniform, for Mitchiner spent many years on active service. He was decorated more than any civilian, and in full dress uniform on ceremonial parades, his soldierly bearing and bemedalled chest picked him out at once for attention. Off duty in a theatre of war, his disregard of display and even of the prescribed details of Service dress were sometimes an embarrassment to his fellows and his superior officers.

"A very great surgeon, and a loved member of our profession, has gone. He was unselfish, he was loyal, he was an indefatigable worker. Of few men could it be said with equal sincerity that British surgery will never be the same without him."

Mitchiner married in 1928 Miss Margaret Philpott, who survives him.

WILLIAM EWART GYE

M.D. Edin., F.R.C.P., F.R.S.

W. E. Gye, who died in Australia on Oct. 13, was an outstanding figure in British cancer research. He was the son of a railway signalman, Charles Bullock, being born on Aug. 11, 1884. In his early days he worked as a "knocker-up" and had experience on the railways and in a factory. But his mind was on higher things, and a fortunate set of circumstances enabled him to continue his education and, with the aid of a scholarship, to graduate as M.D. at Edinburgh (with gold medal) in 1913. On his marriage he changed his name to Gye, his wife's maiden name. After a short period in general practice, he turned to cancer research, obtaining a position on the staff of the Imperial Cancer Research Fund under Bashford and, later, Murray. He became familiar with the fundamental work on mouse tumours in progress there, and published a number of papers on pathology, including some on the fringes of biochemistry.

He served during the 1914–18 war in France and Italy as a captain in the R.A.M.C. As a result of his war experiences he became interested in anaerobic infections of wounds and "defence rupture" through the agency of chemical substances, particularly calcium salts. Five papers were published with W. Cramer on this subject, the first bearing the title On a New Factor in the Mechanism of Bacterial Infection. One of the substances causing "defence rupture" was colloidal silica, and it was not surprising that he turned next to silicosis, collaborating with E. H. Kettle. It is believed that he had encountered the industrial hazards of silicosis in his very early days.

After the 1914–18 war the programme of the National Institute for Medical Research, then in its beginnings, included an attack on virus infections. Gye joined the staff in order to study dog distemper. While waiting for tock of virus-free dogs to be bred, he gained experience viruses by working with that of Rous's fowl-sarcoma, ving been intrigued with this remarkable agent since earlier cancer research days. When the dogs were ally ready, Gye was so deeply engaged in the problem fowl tumours that H. H. Dale, the director, allowed m to carry on with it; and Laidlaw joined the staff r the distemper work.

In 1925 a considerable sensation was caused by Gye's per, published in THE LANCET, with J. E. Barnard, the Ætiology of Malignant New Growths. It was aimed that fowl tumours, and cancers in general, ere due to viruses which were cultivable in a cell-free edium and could be portrayed by ultraviolet photoaphy. The specificity of various growths was deterined not by the properties of this virus but by a specific factor" derived from the host. This was an genious attempt to reconcile the idea of a ubiquitous tential cancer virus with the extreme individuality cancers as met with in Nature, and the thesis was eveloped in following years, especially in a book with W. Purdy, *The Cause of Cancer*. Unfortunately, her workers were not able to reproduce the fundaental experiments on which Gye's thesis rested. One portant fact, however, was established—that the ous virus was inactivated in the presence of complement by anti-fowl sera. Subsequent work with Purdy tumours which grew both in fowls and in ducks further tended knowledge of this matter.

In 1936 Gye succeeded Murray as director of the mperial Cancer Research Fund and he played the leading art in planning its laboratories now existing at Mill ill. In 1949 he reported the propagation of mouse mours by means of dried tissue and drew the conclusion hat a virus must be their cause, even though filtration ad not been achieved. It appears, however, that this as a premature conclusion, for James Craigie later emonstrated that a particular kind of cell, present many cancers, was unexpectedly resistant to freezing, rying, and other insults. The presence of such cells ccounted for the positive results with dried tumours.

Gye's contribution to cancer research is much more mportant than the above account would suggest. he filtrable fowl tumours described by Rous in 1911 ad, in the '20s, been forgotten, or were ignored or dismissed as something sui generis with no bearing on the ancer problem. Peyton Rous had lost heart at the lack f recognition of their significance. Gye brought them o life again, compelled their acceptance as true tumours, nd made the virus theory of cancer once more a living ssue. It is true that his two claims to have proved this hesis have failed to carry conviction. Nevertheless, t is largely due to Gye that the virus theory is today one heory of cancer ætiology which has to be reckoned with. He had a masterly lucidity in expounding his ideas oth in writing, in lectures, and in talking to visitors.

Gye was a man of much charm and many interests. Through an interest in politics he had many friends n public life, and he was also a keen cricketer. Unfortunately he never fully recovered from the effects f a renal infection contracted while he was still a fairly oung man, and in the last few years of his life his health was poor.

He was elected F.R.S. in 1938. In 1943 he was appointed professor of experimental pathology at the Royal College of Surgeons, and on his retirement in 1949, he became emeritus professor. His first wife, by whom he had three sons, died in 1943, and he later married Dr. Ida Mann, professor of ophthalmology at Oxford. On medical advice he retired in 1949 to the more equable climate of Western Australia.

HUGH TUKE ASHBY

B.A., M.D. Camb., F.R.C.P.

Dr. Ashby carried a name which for two generations has meant much to the Royal Manchester Children's Hospital, where he and his father had together served for a span of over seventy years.

He was born in 1880, the son of Henry Ashby, F.R.C.P., and he was educated at Clifton College and the Universities of Cambridge and Manchester. After qualifying in 1907 he held resident appointments at Manchester Royal Infirmary and at Manchester Children's Hospital, then known as Pendlebury Hospital. After postgraduate visits to pædiatric centres at Marburg, New York, Boston, and Philadelphia he returned to Manchester where he became senior medical officer to the outpatient department of the Children's Hospital, and in 1912 he was elected to the staff as assistant visiting physician. About this time he was also appointed to the staff of the Salford Royal Hospital, and later he joined the staff at Booth Hall Infirmary for Children and became visiting physician for children to the Manchester public-health committee. He also lectured on diseases of children at the university.

His experience in the crowded outpatient clinics and wards of the Manchester hospitals in the early years of the century soon drew his attention to the urgent problem of infant mortality, and his book *Infant Mortality*, published in 1915 and revised in 1922, emphasised the difficulties that mothers had to contend with in those days, and paved the way for the improvement of midwifery and the provision of antenatal and infant-welfare services and of cleaner milk. In 1922, with the help of the late Charles Roberts, he completed the not inconsiderable labour of revising his father's textbook written with G. A. Wright, on the *Medical and Surgical Diseases of Children*.

His own papers were largely concerned with the dietetic disorders of infancy, and the anæmias and secondary results of malnutrition, that were so common at that time. "Ashby's writings," T. N. F. recalls, "always emphasised the practical aspects of this subject, an attitude of mind that was an essential feature of his approach to clinical medicine.

"He had pre-eminently that love for, and understanding of, children and wide experience of their demeanour in health and disease that are a first requisite in the good children's physician, and which gave him an almost uncanny insight into the problems of diagnosis and prognosis. Not uncommonly in his outpatient notes would appear some such unorthodox diagnosis as 'mal de la mère,' written in a hand that might need some experience of his writing to elucidate, that went straight to the heart of a difficult clinical problem.

"On a ward round, after examining a sick child and prescribing or approving the treatment, he would lean over the end of the cot. There would be a pause, while he and the distressed acutely ill child seemingly gazed thoughtfully at each other, as though some mystic communion passed between them; and then with a laconic 'He'll do,' Ashby would pass to the next child, and his worried house-physician would feel assured that all would be well. Or (at a discreet distance from the older more comprehending child), 'It's a bad do there,' and the outlook was correspondingly gloomy. He was indeed a master of the homely phrase that immediately put nervous and worried parents at ease; and he would, as effectively, bring a committee meeting that was not getting anywhere down to the point at issue, or, most disarmingly, prick the bubble of unnecessary verbosity or pomposity."

Ashby was one of the founder members of the British Pædiatric Association and his colleagues elected him their president in 1949. Later he exchanged this well-deserved national honour for the presidency of the Manchester Pædiatric Club. He was also a vice-president of the Medical Defence Union. After his retirement from the staff he continued to take a close interest in the affairs of the Manchester Children's Hospital and particularly in the health and welfare of the nurses, who owe more than many realise to his constant efforts on their behalf. He died on Oct. 9 at his home at Didsbury.

Of Ashby's life outside the ward and the consulting-room his friend T. M. B. writes:

"Hugh was a stoic. All his life he suffered a progressive crippling disablement to which he never referred. In spite of this he determined to, and did, enjoy a full round of sports. Fond of tennis, he confined himself to clever placing of the ball to dismay his opponents. As a golfer, his short game, on his day, was masterly. For 25 years, he was a co-secretary to the Manchester and District Medical Golfers' Association, serving a year as captain, and finally being elected an honorary life-member. From his youth he was accustomed to sailing on the Norfolk Broads, and he was always skipper of the yacht on which he, the late Daniel Dougal, the late Lawrence Kilroe, and I enjoyed many happy weeks before and after the first world war.

"He was a man of simple tastes, with a dislike of any ostentation. Essentially kind and considerate, the trite saying 'He never had an enemy' indeed applied to him. But he was tenacious in holding positive opinions regarding right or wrong, and expressing them forcibly. At home he was a keen amateur gardener, raising an abundance of flowers, especially roses, and he loved to potter in his greenhouse.

"His strong, clear voice, his blue eyes, his laugh with its curious chuckle, and above all his kindly ways will remain a lasting memory for his friends."

Dr. Ashby leaves his widow with a son and two daughters.

Appointments

Richards, Myrtle, M.B. Edin., D.C.H.: asst. M.O., Warwickshire.
Rigby, W. E., M.B. Manc., C.P.H.: asst. county M.O., Warwickshire.

The Hospital for Sick Children, Great Ormond Street, London:

Forsyth, Constance, M.D. Edin., M.R.C.P.: asst. medical registrar.
Halfhide, A. W., M.R.C.S., D.L.O.: senior E.N.T. registrar.
Holt, K. S., M.D. Rochester, N.Y., M.R.C.P.: house-physician.
Horton, Jean, M.B. Lond.: junior resident anæsthetist.
Hugh-Jones, Kenneth, M.D. Lond., M.R.C.P.: asst. medical registrar.
McGreal, D. A., M.B. St. And., M.R.C.P., D.C.H.: house-physician.
Rooms, Margaret, M.B. Lond.: junior resident anæsthetist.
Smyth, B. T., M.B. Belf., F.R.C.S.: house-surgeon.
Stephens, D. J., M.B. Leeds: house-surgeon, orthopædic and plastic department.
Wilson, J. A. C., M.B. Edin., M.R.C.P.: house-physician.

Liverpool Regional Hospital Board:

Gifford, J. H., M.B. Manc.: tuberculosis M.O., North Liverpool area.
Mosscrop, L. E., L.R.C.P.E., D.A.: part-time consultant anæsthetist, Southport and Ormskirk groups.
O'Beirn, Nicholas, M.B. N.U.I.: medical director and asst. chest physician, no. 2 mass-radiography unit.
O'Malley, A. G., M.B. Edin., M.CH.ORTH. Lpool, F.R.C.S.E.: part-time consultant radiologist, hospitals in the Warrington area.
Shatwell, G. L., M.CH.ORTH. Lpool, F.R.C.S.: part-time consultant orthopædic surgeon, hospitals in the St. Helens area.
Snell, Emanuel, L.R.C.P.E., D.P.H.: tuberculosis M.O., East Liverpool area.
Weldon, H. J., M.B. N.U.I., D.A.: part-time consultant anæsthetist, Southport and Ormskirk groups.
Whitehead, A. S., M.D. Lpool, M.RAD., D.M.R.D.: part-time consultant radiologist, Mill Road, Newsham General, and Bootle Hospitals.
Wri Lpool, D.M.R.D.: part-time consultant in the St. Helens and Warrington groups.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

Brown.—On Oct. 1, at Colac, Victoria, Australia, to Joan (née Frecheville), wife of Dr. A. Graham Brown—a daughter.

Dick.—On Oct. 4, to Gurna (née Isles), wife of Dr. T. H. Graham Dick, 39, Malone Park, Belfast—a daughter.

Fisher.—On Oct. 12, at 125, Castle Lane, Bournemouth, to Rosemary (née Sterling-Hill), wife of Dr. James Fisher—a daughter.

Fryer.—On Oct. 10, at Farnborough, Hants, to June (née Bradley), wife of Flying-Officer D. I. Fryer, M.B.—a son (Timothy Peter).

Groundes-Peace.—On Oct. 18, to Zara (née Yeoman), wife of Dr. John Groundes-Peace, M.B.E., of 6, Belford Mews, Edinburgh—a son.

Happel.—On Oct. 12, to Margaret, wife of Dr. John Happel, of Ropley, Hants—a daughter.

Towers.—On Oct. 14, to Beryl Margaret Helen (née Davies), wife of Dr. Bernard Towers, of 74, Colchester Avenue, Cardiff—a daughter.

MARRIAGES

Wilson—Smith.—On Oct. 11, Edric Frank Wilson, F.R.C.S., of Plymouth, to Dorothy Smith, of Chipping Campden.

DEATHS

Andrew.—On Oct. 14, at 15, Howell Road, Exeter, Henry Andrew, M.R.C.S., aged 86.

Carew Hunt.—On Oct. 17, at The Barn House, Church Handborough, Oxon, Mary Helen Carew Hunt, M.D. Brussels.

Hay.—On Oct. 17, at 555, Lincoln Road, Peterborough, William Peach Hay, M.B. Edin., aged 82.

Mitchiner.—On Oct. 15, Philip Henry Mitchiner, C.B., C.B.E., M.D., M.S. Lond., F.R.C.S., of 6, Morpeth Mansions, London, S.W.1, aged 64.

Morris.—On Oct. 14, at 27, Okehampton Close, London, N.12, John Mudie Morris, M.A., M.B. Edin., D.P.H., formerly of Neath, Glamorgan, aged 86.

Perram.—On Oct. 16, at Overstowey, Teignmouth, Devon, Edward Arthur Perram, M.D. Lond., aged 88.

Notes and News

GENERAL PRACTICE IN NORTHERN IRELAND

In its report[1] for the year 1951–52, the Northern Ireland General Health Services Board observes that during the year the proportion of the population included in doctors' lists increased slightly from 98·43 to 98·94%. The average number of patients on a doctor's list increased by 43 from 1864 to 1907. This was due to a fall in the number of doctors (including assistants) on the list from 772 to 744—a decrease occasioned by the operation of the Health Services (Temporary Provisions) Act (Northern Ireland), under which the board limited additions to the list to 4, although 32 doctors died, retired, or resigned. The board remarks that its attempts to encourage the public to exercise discretion in its calls on the medical services had met with a substantial response. "There remained, however, a considerable body of persons who, despite numerous public statements to the contrary, continued to hold the erroneous view that the Health Services are paid for wholly from their insurance contributions and that they must, therefore, try to obtain full value regardless of the increased burden in the form of taxation which must arise from their heavy demands for medicines and appliances."

INTEGRATION OF CHILD HEALTH SERVICES

One of the most important lessons from the first four years of the National Health Service has been the need for better integration of its three branches and for some redistribution of responsibilities between them. This lesson is nowhere more evident than in the child health services, where all three branches play an important part. Thus at a conference held at Whittington Hospital, London, on Oct. 11, Dr. L. J. Stoll argued that the general practitioner should resume his rightful position at the centre of the medical services. The general practitioner alone, said Dr. Stoll, was chosen by the patient, was always at hand, and saw the patient throughout his life. If the family doctor were to undertake the periodic examination of infants and children which were now made by the assistant medical officer of health, he would have a complete record of physical development and illness. The health visitor should be in much closer contact with the family doctor, whose knowledge of the family and its background would be invaluable to her in her work. Furthermore, to hasten the turnover of inpatients, staff nurses from the local hospital should do six months "on the district," nursing the children at home under the supervision of the family doctor and the consultant from the local hospital.

Dr. Catherine Mackie also urged the need for closer understanding between the various parts of the child health services; but she suggested that this might be achieved by giving experienced assistant medical officers greater responsibility in a limited area of their borough, where they would guide the team of medical officers, health visitors, and clinic nurses, know the schools and their teachers, and discuss common problems with doctors practising in the neighbourhood. She added, however, that ideally preventive and curative medicine should not remain separated; eventually both should be practised by the family doctor working from a health centre.

As a social worker, Miss I. M. Neil was disconcerted by the tendency to transfer sessions from local clinics to hospitals. Though administratively convenient, this lost to the patient the personal atmosphere of the local clinic; wherever possible, the specialist should be brought to the child, and not the child to the specialist. Coöperation with general practitioners might be improved by their getting to know and to use the resources at the command of the local authority.

Dr. S. Yudkin deplored the almost total absence of integration between the hospital on the one hand and general practitioners and the local health authority on the other. The result of this was long lists of chronic outpatients and lack of information among family doctors about their patients. At the Whittington Hospital patients were always referred back to their doctor; and letters were sent to the doctor on the day of discharge. Dr. Yudkin agreed that in the future the care of the child should be mainly the task of the general practitioner; but the hospitals must help by keeping him informed of recent developments.

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[1] Northern Ireland General Health Services Board: Fourth Annual Report, 1951–52. Pp. 47. 1s.

Other speakers also expressed uneasiness about the division responsibilities. Dr. Lindsey Batten, for example, marked that the local authorities and hospitals could, by xpanding their services, eliminate the general practitioner; ut he himself was convinced that the family doctor's authority ust be restored. Dr. E. Hinden admitted that the hospital nd local authority were doing more and more work; but e suggested that this was the outcome of reluctance of amily doctors to participate in an integrated scheme. Dr. . M. Clayden evidently felt no such reluctance; for he alled on medical officers of health to convene regular meetings t which practitioners could exchange information with ther workers in the child health services. Dr. D. G. Berry, owever, held that health centres and increased participation y the family doctor in the work of hospitals were essential reliminaries to integration of the services.

Summing up, Prof. A. A. Moncrieff, the chairman, eminded the meeting that the present period is one of transiion and experiment. Clearly the status of the family doctor nust be restored; and the health visitor and family doctor hould work together. Clearly, too, it would be better if ospitals were local centres with local connections. The public hould be better informed of the services provided for the are and welfare of children.

DISTRICT NURSING IN LONDON

The London County Council pays for 90% of the cost of unning the home nursing service in London: but the emaining 10% (which this year is likely to amount to some 30,000) has to be found by the voluntary committees. Many nembers of the public mistakenly believe that the whole cost s borne by the authorities; and the Central Council for District Nursing in London has appealed to practitioners to correct his impression. Sir Harold Kenyon, the chairman, remarks hat "many who use the service would be only too pleased o make a donation if they were aware of the facts." It would, he adds, be most unfortunate if the home nursing service, the demands on which are constantly increasing, were to lose its voluntary status through lack of necessary funds. Donations may be sent to the central council, 25, Cockspur Street, London, S.W.1.

ANIMAL WELFARE

A well-developed conscience is always a better custodian of good behaviour than the law and its penalties. In this country conscientious concern for the welfare of laboratory animals is now so general that most laboratory workers do more to ensure it than the law requires of them. Hence it is not always easy, as the Universities Federation for Animal Welfare[1] (UFAW) knows, to offer guidance to members of other countries who wish to forward legal protection for laboratory animals. During the past year such a request came from scientists in Israel, and UFAW had to explain that our Cruelty to Animals Act, 1878, is too complicated to be readily understood abroad, and that its value depends largely on the way it is administered. The scientific subcommittee of the federation, however, with the help of other British scientists, is preparing draft suggestions to submit to Israel, in which the British law is made as clear as possible, and those points which deserve to be included in any new legislation overseas are emphasised. Interest in the subject is certainly growing, as sales of the federation's handbook on *The Care and Management of Laboratory Animals* indicate: copies have now gone to all parts of the world.

Our own standards, of course, are still capable of improvement. The annual report mentions two changes made for humanitarian reasons last year at the Lister Institute. Sheep used to produce vaccine lymph are now given pentobarbitone before scarification; and before the lymph is collected they are killed with a captive-bolt humane-killer. UFAW points out that no Order has yet been made to control the preparation of veterinary therapeutic substances, such as would bring inspection into line with the inspection carried out by the Ministry of Health, under the Therapeutic Substances Act, 1925, in the case of therapeutic substances for human use. Such an Order could be made by the Minister of Agriculture, under the Diseases of Animals Act, 1935; and indeed it was promised by the Chief Veterinary Officer of the Ministry of Agriculture in January, 1949, to a deputation which included UFAW representatives. It is surely time this promise was kept.

University of Cambridge

On Oct. 11 the following degrees were conferred:

M.B., B.Chir.—P. G. Allen, *M. A. Baddoo, R. J. H. Harris, *L. B. P. Hartley, J. H. Kerr, *D. N. H. Owen, *J. D. H. Slater.

* By proxy.

University of London

At a recent examination the following were successful:

Academic diploma in [illegible] Akram, J. A. Campbell, Jean E. [illegible] an, C. E. Marshall, G. A. K. Misse [illegible] Watson, K. H. White, Mary I. Wright, Saiyid Sibte Hasan Zaidi.

External diploma in clinical pathology.—Gyawni Aung, R. M. Cross, David Hewspear, James Ward.

At a recent examination for the academic postgraduate diploma in public health Valaydon Poonoosamy and William Dharmarajah Ratnavale were successful.

On Friday, Nov. 21, Prof. J. Gough is to give a lecture on Pneumoconiosis the World Over. On Monday, Dec. 8, Dr. P. Gyorgy, professor of nutrition in pædiatrics in the University of Pennsylvania, will deliver a lecture on Blood Group and Related Polysaccharides in Growth and in Resistance to Disease with special reference to Human Milk. Both lectures are to be given at the London School of Hygiene, Keppel Street, W.C.1.

University of Sheffield

Dr. S. Oleesky has been appointed lecturer in therapeutics, Dr. R. S. Weetch, temporary lecturer in therapeutics, Dr. D. Beasley, temporary lecturer in child health, and Dr. E. K. Blackburn, honorary lecturer in pathology.

Royal College of Physicians of London

Dr. Richard R. Bomford will deliver the Bradshaw lecture on Thursday, Nov. 6, at 5 P.M., at the college, Pall Mall East, S.W.1. He will speak on Changing Concepts of Health and Disease, with Particular Reference to "Psychosomatic Medicine."

British Medical Association

Sir James Learmonth will deliver the Victor Horsley lecture at B.M.A. House, Tavistock Square, London, W.C.1, on Thursday, Dec. 11, at 5 P.M. He will speak on Ischæmia in Surgery.

Royal Institute of Public Health and Hygiene

On Nov. 10, at 4.30 P.M., Major-General H. C. D. Rankin, M.B., will deliver the Blackham lecture at the institute, 28, Portland Place, London, W.1. His subject is to be a Review of Army Health.

Institute of Laryngology and Otology, London

On Saturday, Nov. 8, at 11.30 A.M., at the institute, 330, Gray's Inn Road, W.C.1, Dr. Arthur W. Proetz (St. Louis, Mo.) will deliver a lecture on Olfaction.

On Friday, Nov. 21, at 4.30 P.M., Mr. I. Simson Hall will deliver the annual address. He will speak on Conservative Treatment of Cancer of the Larynx.

Postgraduate Course in Rheumatism

The Empire Rheumatism Council is to hold a postgraduate course on Nov. 21 and 22, at the Arthur Stanley Institute, Peto Place, Marylebone Road, London, N.W.1. Prof. R. E. Tunbridge will give the opening lecture on Diagnosis of the Rheumatic Disorders at 4.30 P.M. on Friday, 21st. Further particulars may be had from the general secretary of the council, Tavistock House North, Tavistock Square, W.C.1.

Royal Society

At a meeting on Thursday, Nov. 6, at 4.30 P.M., at Burlington House, London, W.1, Mr. A. S. Parkes, F.R.S., and Dr. Audrey U. Smith will read a paper on Regeneration of Rat Ovarian Tissue Grafted after Exposure to Low Temperatures. On Thursday, Nov. 20, Prof. A. J. Kluyver, who holds the chair of microbiology at the University of Delft, will deliver the Leeuwenhoek lecture. He will speak on the Changing Appraisal of the Microbe.

Institute of Biology

The Biological Council, which is composed of representatives of some 15 biological societies, has resolved to become an advisory body to the institute. At a meeting of the council on Sept. 29, the following officers were elected: chairman, Mr. W. P. K. Findlay, D.SC.; hon. treasurer, Prof. F. L. Warren, D.SC.; hon. secretary, Mr. J. L. Cloudsley-Thompson, who may be addressed c/o the institute, Tavistock House South, Tavistock Square, London, W.C.2.

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[1] Twenty-sixth Annual Report, 1951–52. Published by UFAW, 284, Regent's Park Road, Finchley, London, N.3. Pp. 28.

West Midlands Physicians Association

The general meeting of this association will be held at Dudley Road Hospital, Birmingham, on Saturday, Nov. 1, at 11 A.M.

Stephen Paget Lecture

Sir Howard Florey, F.R.S., will deliver the Stephen Paget lecture at a meeting of the Research Defence Society to be held at University College, Gower Street, London, W.C.1, on Thursday, Nov. 20, at 5.30 P.M. He will speak on the Advance of Chemotherapy by Animal Experiment.

National Insurance Advisory Committee

The Minister of National Insurance has appointed Dr. Benjamin Hutchison to be a member of this committee in succession to Dr. John Ritchie, who has resigned. Dr. Hutchison is vice-chairman of the executive council and chairman of the local medical committee in Lanarkshire.

School for Spastic Children

On Oct. 14 Lord Horder opened a school for spastic children at Swindon. The school has been sponsored by the Swindon and District Hospital Management Committee and the Wiltshire County Council and Swindon Borough Council education committees.

British Standards

The British Standards Institution has issued standards for rubber ice-bags for hospital use (B.S. 1898 : 1952), and for metal-framed wheeled screens for use in hospitals (B.S. 1895 : 1952). Copies (price 2*s.*) are obtainable from the sales branch of the institution, 24, Victoria Street, London, S.W.1.

The institution has also issued a draft standard for sedimentation tubes for red blood corpuscles (CO [LBC] 4936), comments on which should be submitted before Nov. 27.

Midland Tuberculosis Society

The following officers have been elected for the 1952-53 session : President, Dr. J. E. Geddes ; secretary, Dr. G. W. N. Luntz ; treasurer, Dr. H. J. T. Ross ; members of committee, Dr. P. G. Arblaster, Dr. A. Gordon Evans, Dr. T. W. Lloyd, and Mr. S. J. McHale.

Medical Honour

Captain Robert Barnes, M.B. Adelaide, R.A.A.M.C., has been appointed M.B.E. in recognition of gallant and distinguished services in Korea.

Kathleen Schlesinger Fellowship

The Medical Research Council invite applications for the fellowship which is tenable at the National Hospital for Diseases of the Nervous System, Queen Square, London, for one year in the first instance, renewable annually up to a maximum of three years in all. The annual stipend will be within the range £700–1000. Preference will be given to *candidates who elect to work on the mechanisms* underlying degenerative processes affecting the brain. Applications, including an outline of the proposed research and the names of two referees, should be sent to the secretary of the council, 38, Old Queen Street, S.W.1, not later than Nov. 15.

CORRIGENDUM : *Education by Travel.*—At the end of his article in our issue of Aug. 30 (p. 396) Dr. Raymond Whiteh mentioned the List of Whole-time Awards for Scientific Research, other than Professorships, offered by Public and Private Bodies in Great Britain and Northern Ireland. This list is issued, not by Messrs. Gale & Polden who printed it but by the Royal Commission for the Exhibition of 1851, 1, Lowther Gardens, London, S.W.7. Copies may be obtained from the Secretary at this address.

Diary of the Week

OCT. 26 TO NOV. 1

Monday, 27th

NSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Mr. J. T. Abrams, PH.D. : Deficiency Diseases of Young Animals.
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
4.30 P.M. Dr. E. Stengel : lecture-demonstration.
MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Dr. H. F. Brewer, and Dr. A. E. Mourant : Perils of Blood-transfusion.
UNIVERSITY OF OXFORD
2.30 P.M. (Radcliffe Infirmary). Dr. Wesley Spink (Minnesota) : Intracellular Parasitism in Brucellosis.
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *Section of General Practice.* Prof. R. Platt : Opportunities for Research in General Practice.

Tuesday, 28th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Mr. R. M. Haines : Tumours of the Uterus. (Erasmus Wilson demonstration.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of Surgery.* Dr. L. S. Fallis (Detroit) : Acute Pancreatitis.
8 P.M. *Section of Medicine.* Dr. C. Dukes, Dr. W. Trevor Cooke, Mr. E. C. B. Butler : Intestinal Granulomata and Reticuloses.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. E. J. Moynahan : Collagen.
ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5 P.M. Mr. T. M. Tyrrell : Epiphora.
WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, W.1
5.30 P.M. Mr. G. C. Knight : Subarachnoid Hæmorrhage.
PADDINGTON MEDICAL SOCIETY
8.45 P.M. (St. Mary's Hospital, W.2.) Dr. L. Zeitline : Genius and Madness. (Presidential address.)
MANCHESTER MEDICAL SOCIETY
4.30 P.M. Mr. D. Lloyd Griffiths : Fractures and Fracture-Surgeons. (University lecture.)

Wednesday, 29th

ROYAL SOCIETY OF MEDICINE
8.30 P.M. Mr. Bernard Darwin : Dickens's Doctors. (Lloyd Roberts lecture.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. *Dr. R. W. Riddell : Tinea Infections.*
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Mr. Victor Bonney : Conservatism in Gynæcology.
INSTITUTE OF UROLOGY
5 P.M. (St. Paul's Hospital, Endell Street, W.C.2.) Mr. A. C. Morson : *Non-tuberculous Infections of Renal Tract.*
ROYAL EYE HOSPITAL
8 P.M. Dr. Norman Ashton : Cortisone Therapy in Ocular Disease
UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary.) Prof. Dorothy Russell : Disturbance of Hypothalamic Function in Man. (Litchfield lecture.)
BIRMINGHAM MEDICAL INSTITUTE, 154, Great Charles Street, Birmingham, 3
8 P.M. *Section of Psychiatry.* Dr. W. Ross Ashby : Cybernetic and Psychiatry.

Thursday, 30th

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. V. Zachary Cope : William Cheselden—and th Separation of the Barbers from the Surgeons. (Thoma Vicary lecture.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1 Prof. J. T. Randall, F.R.S. : Biophysical Studies of Con nective Tissue.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Riddell : Tinea Infections.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Major J. M. Adam : Korean Experiences.
ROYAL EYE HOSPITAL
5.30 P.M. Miss M. Savory : Diagnosis of Proptosis.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.
5 P.M. Sir Paul Mallinson : Psychiatry lecture-demonstration.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8.30 P.M. (South Kensington Hotel, 41, Queen's Gate Terrace S.W.7.) Dr. Geoffrey Konstam : Some Cardiological Mis conceptions. (Presidential address.)
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh. Dr. R. F. Robertson : Clinical and Cytological Investiga tion of Pleural Effusion.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. W. I. Card Problems of Gastric Secretion of Hydrochloric Acid.

Friday, 31st

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Moynahan : Scleroderma and Dermatomyositis.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road W.C.1
4.30 P.M. Mr. G. H. Howells : Nasopharyngeal Tumours.
INSTITUTE OF NEUR [illegible] National Hospital, Queen Square, W.C. [illegible]) : Physiology of th
5 P.M. Prof. G. [illegible] Cerebrospi
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Dr Russell Fraser : Thyroid in Pregnancy.
ROYAL EYE HOSPITAL
5.30 P.M. Prof. C. A. Keele : Physiology of Lacrimal Secretion.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 1 Chandos Street, W.1
7.30 P.M. Dr. G. W. Czonka : Bejel.

Saturday, 1st

MIDLAND TUBERCULOSIS S [illegible]
3 P.M. (Chest Clinic, 15 [illegible]
Dr. Peter Kerley : [illegible]
disease.

THE INDIVIDUAL AND THE GROUP IN MODERN MEDICINE*

R. J. V. PULVERTAFT
O.B.E., M.D. Camb., F.R.C.P.
ROFESSOR OF CLINICAL PATHOLOGY IN THE UNIVERSITY OF
LONDON, AT WESTMINSTER MEDICAL SCHOOL

LEAVING on one side the technicalities of clinical athology, I propose to consider what influences are moulding our professional behaviour, and in what way we, as doctors, reflect the contemporary climate of hought. For no-one today can be a hermit; perhaps in no age has man been so assaulted by persuasion. Indeed, I might be excused were I to spend all the time at my disposal in deploring the wholly excessive amount of information and opinion that now inspissates the ether and reduces whole forests to wood-pulp and dismay. For the greater part of recorded time man has deplored disaster when it has occurred; it was left to this generation, in daily prodigality, to bewail in addition disaster to come.

But I shall resist the temptation and instead ask the question, "what is it that differentiates the age we live in from others before it?" The question answers itself; it is surely the search for an acceptable compromise between the individual—always essentially remote, unique, and rebellious—and the herd into which a contracting, overpopulated, and overelaborated world seeks to constrain him. This is, of course, the oldest problem of civilisation; but it has been posed in stark crudity today both by the division of the world into Russianism and Americanism, and by the often frenzied efforts of every country to contrive the maximum degree of order within its own confines while permitting, at least in some countries, the maximum degree of privacy and licence to the individual. The pendulum has swung far towards the development of impersonal and group values at the expense of private and individual ones; and both in medicine as a whole and in clinical pathology we are involved in this tendency. We can no more stand outside it as scientists than can the artist; just as the incoherent nausea of the '20s expressed itself in the fœtid poetry of those years, so we doctors of today sail, without even realising it, as the tempests of our time drive us.

It really is important, I think, for each of us to consider his attitude towards tendencies in our profession, and to express that attitude. The obligation to orientate or reorientate our activities is ours, and can be delegated to none.

In facing the world's troubles I note two popular evasions. The first is to find a simple paranoid explanation—such as that all evil is due to an international Jew-Banker conspiracy or an international antisemitic trust. The other is an equally fallacious confidence in the existence somewhere of a committee of first-class brains who, in spite of all appearances, are looking after things. I must admit that until quite recently I believed in that committee: until, in fact, advancing years forced committees upon me—when I found, to my horror, that committees, however egregious, were composed of puzzled asses like myself. Committees are necessary evils; but they are staffed largely by men too lazy, too old, or too inefficient to manage their own affairs, seeking in extenuation to manage those of others. Unlike an army, whose pace is that of the slowest man, a committee's intelligence is well *below* that of its stupidest member, who is often oneself. Occasional gleams of light flatter to deceive. I remember a committee man whose contributions were always startlingly different; but soon, alas, I realised that it was because he never, by any chance, was referring to the matter on the agenda.

Our world is not run by an international conspiracy or by a divinely wise committee: it is run by you and by me. And unless we pause now and again to see how we are running it, we may well find ourselves outrageously trimming our sails to inauspicious breezes.

SELECTION OF DOCTORS

In considering how far we have moved from private enterprise to impersonal patronage it is well to remember that a revolution has taken place in the method whereby our profession is recruited. In Eire today 95% of the medical students are supported by their parents or by themselves, and in my youth a similar condition obtained here. But in Great Britain at least 80% of medical students are supported by grants of some kind. I should be the last to deplore this, for I fancy that the tendency began after the 1914 war, when, with my contemporaries, I gratefully, if with some bewilderment, accepted my fellow citizens' benevolence. It is not surprising, however, that the opportunity of belonging without expense to the most lucrative profession outside the black market has attracted a flood of applications, far exceeding the vacancies in schools or the requirements of medicine. In one medical school male applicants for 30 vacancies numbered 540 last year; 120 women applied for 5 vacancies. (A great many, of course, applied to more than one school, and about 1 in 3 were eventually admitted somewhere.) This thirst to succour suffering humanity must make all but the cynic blush with pride; but even the most unsuspicious mind must wonder whether a method of medical recruitment which involves no personal sacrifice, still less hardship, for anyone attracts the right men and women. Moreover, it is well to remember that the dispensation of national patronage is vested in remarkably few hands. All these candidates come forward with very similar educational qualifications and the eulogies of pedagogues; a handful of deans, with or often without committees, bestows largesse and selects the doctors of tomorrow. For selection it is, and this selection is new. Twenty-five years ago, medical students could gain admittance at will to a medical school, almost always the first they chose. The very fabric of our profession is changed; it no longer selects itself; it has become to that extent anonymous.

ANONYMOUS SERVICE AND MASS MEDICINE

Anonymity, however, is not always, not necessarily vicious. If I seek an expression today of all that is best in the development of group interests, if I seek encouragement in this Freud-bespattered age for confidence in human decency, if I seek assurance that charity is not always imposed by the Welfare State on donor and recipient alike, I find it in fullest measure in the miracle of the blood-transfusion service. Was there ever so exquisitely anonymous, so touchingly charitable a manifestation of man's consciousness of his common interest and indebtedness? For all his conquests, frail man lies in his sickbed a mendicant; shall we not be proud that, in this country, and first and foremost in this country, he may beg of his brother's life-blood, and has never yet been refused? And that blood is given to king or criminal anonymously; none asks whence it came or whither it goes. It is through our hands, as clinical pathologists, that this kindliness finds its channel; last year over 500,000 calls were made on donors, and over 500,000 issues of blood were made; no thanks were sought, and none were given.

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* Presidential address to the Association of Clinical Pathologists, delivered on Oct. 3, 1952.

If I select this service as the prime example of group consciousness and anonymity in medicine, it is only because it is so widespread and so peculiarly personal. I know well that in the vast sphere of medical research, for example, the same unambitious devotion is manifest; and indeed that in all medicine, in nursing, and in all ancillary branches, the lesson is to be learned that technique is kindliness, and kindliness a technique. We, the doctors, supported now largely by the State, are our fellow-man's expression of his kinsmanship with the Good Samaritan. We are the agents: the bequest was another's.

Indeed, the greatest services, viewed by results, are those which medicine gives broadcast—such services as control of the purity of water-supplies. To a very remarkable degree the health of every member of the community is protected by technique over which the individual has no control, and concerning which the majority are quite ignorant. The most rabid opponent of the bacterial theory of infectious disease is still forced to drink chlorinated water; pasteurisation of milk is imposed even on Christian Scientists. No-one but a crank would seek to restrict the control of infection in this way, or to oppose the hundred-and-one safety measures of the M.O.H. There are limits, however, to the extent to which men may properly be doctored in spite of themselves. A diet deficient in iodine might properly be adjusted by its addition; but can we extend this indefinitely to include, for example, fluorine? If, to push the question to absurdity, authorities supposed that we were becoming effeminate, could we approve the addition of testosterone to margarine as we already approve the addition of vitamins? Health authorities may rightly keep undesirable things out of food and water; how much may we legitimately put in?

We must never forget that opinions tend to change with regard to the harmlessness of materials. When I was working with resorcinol in connection with air sterilisation, I was assured that it might safely be used to sterilise the air of cinemas without the consent or even knowledge of the public; but we have since learnt that it is far from inactive in the human body. Insecticides are used more and more in control of insect life, yet they are not always without action on man. I would hazard a guess that sooner or later—so complex is the allergic state—some person will be found to react unfavourably to almost any substance, organic or inorganic. I am sure that health authorities are fully alive to these considerations; I merely restate an obvious truism that men should only be doctored at their own consent and that nothing should be administered universally until it is overwhelmingly and universally approved.

THE DOCTOR'S CONTRIBUTION

For the greater part of medical history doctors had little or no effect on vital statistics; it would have made no difference to the average survival of the people if there had been no doctors at all. That is, not to say that the doctor had no function; in the relief of anxiety and pain, in prognosis and the ordering of men's lives, and above all as a support, however frail, in times of stress, he has had the same functions at all times as he has now. Moreover, it is by the study of disease through centuries barren of therapeutic discoveries that we today have so largely conquered acute and infectious disorders. But until the time of Pasteur and the triumphs of the laboratory the doctor was fortunate in not being paid by results: it was Pasteur who paved the surgeon's road from tradesmen's entrance to the House of Lords. If some lives were saved by the arrest of hæmorrhage and relief of asphyxia, how many others were lost by infection conveyed by surgeon and midwife?

Indeed, though medicine is often blamed for the over-[illegible]tion of the world, the enormous spurt in population began before doctors had any effective remedies, and was the direct result of the Industrial Revolution. The most overpopulated areas, such as Egypt, are the least doctored. On the other hand, in Western countries it does undoubtedly make a difference to the individual today whether or not he visits a doctor. The doctor now has more to offer than a bedside manner—which probably accounts for his modern sartorial insignificance. It is therefore inevitable that there should be an element of conflict between the doctor's sense of his duty to the community, in acquiring new knowledge, and to the individual, in facing that individual's personal and immediate emergency.

EXPERIMENT AND VOLUNTEERS

New knowledge in medicine must come by the scientific method of trial and error, by experiment. Much of that experiment can be carried out in test-tubes, with no victim more highly developed than bacteria, in whose interests no societies appeal. Much is carried out on animals, and this does pose an ethical problem which not all men answer alike. However, rightly or wrongly, we pathologists accept animal experiments as a necessary evil, realising that far too much of human choice is the selection of the lesser of two evils, and believing, selfishly enough, that relief of human pain is properly purchased at the expense of the animal.

But, sooner or later, knowledge must be applied to man, and need arises for experiment on man. I imply by the word "experiment" that the result of the doctor's intervention is not and cannot be assured, and that it may not be beneficial to the particular patient. Quite often it must be carried out on healthy men; we must ask for volunteers. When we do, let us be quite sure what we mean by volunteers. Obviously an infant or a child cannot be a volunteer, and this places a responsibility on the pædiatrician. In law, certain lunatics may be volunteers; for the law recognises the power of choice in certain aberrations of mind. In other classes of mental ailments all power of choice lapses and no question of volunteering remains. In other ages and countries experiments on persons of unsound mind have been performed, and published without reserve, but in this country and in this age such an approach would be intolerable. We must remember how recently, and not far away, the grossest excesses were perpetrated on sections of the community because an inebriated generation had conceived that that section was deprived of human privilege. We and they have awakened from that nightmare; but there is only one safe rule—no action of a doctor must have any other objective save the individual's personal welfare, without that individual's entire and competent approval. I have the most complete confidence, based on intimate and personal knowledge, in the integrity of the medical services of the Armed Forces in such matters; but, particularly now that service is compulsory for all, they must be prepared to resist any tendency to find a useful reservoir of clinical experiments in this group of healthy young men—especially since, in a disciplined force, the "volunteer" can easily be encouraged by sanctions or privileges. Similar considerations should influence us in approaches to undergraduates or medical students. No scientific doctor should ask another to "volunteer" for measures in which he does not share; and I must admit to the curiosity with which I always seek, in publications, for evidence that the writer satisfied his curiosity, in the first instance, on himself.

An extreme example of pharmacological assay may be offered as displaying methods today obsolete. Curare is now titrated by observing its power to destroy the tone of neck muscles in the rabbit; but its original discoverers were ignorant of this physiological action, and were forced to alternatives. Elderly women were therefore collected and put in prison in a hut with the boiling drug; if they died the curare was accepted as being of optimal strength. This experiment has much in common with contemporary methods except that nowhere on earth would it be done in exactly that way.

Again, an experiment may be entirely legitimate at one stage in our knowledge, and as certainly unethical at another. In the early days of vaccination for smallpox, vaccinated patients were challenged by inoculating smallpox virus. This was, however, entirely proper since the experiment was performed at an institution founded to inoculate smallpox prophylactically; contemporary criticism would have been directed at the vaccination. The experiment failed in matters of detail and as scientists we should much like to repeat it today; but as doctors, indeed as civilised men, we are prevented. Indeed there are many routines in medicine, such as the use of rabies virus in prophylaxis, which are of very doubtful value; yet we can never test their validity since there is evidence (of a kind) of their efficiency.

As an example of an outmoded technique, we may recall that Alfred Donné attempted to establish the significance of vibrios in syphilitic ulcers by human experiment, injecting pus into one leg and pus treated with vinegar into the other. It is in fact remarkable how irresponsibly attempts were made at the end of the last century to produce venereal disease experimentally. Urethritis was produced with pure cultures of the gonococcus in both men and women by at least five separate workers. It is hard to believe that they were not aware of the implications both to the human beings infected and to their children. Human experiments with the cholera vibrio have been, so far as I know, in the best tradition of medical ethics; for von Pettenkofer and Emmerich used themselves for the test, and Emmerich contracted a severe attack of cholera. It is only fair to doctors as a whole to say that as a general rule they have submitted themselves to experiments which they have performed on others. I recall a distinguished laboratory chief who put not only himself but the whole laboratory staff out of action for a fortnight through an unfounded confidence in the nature of his test reagent.

It is right that we should cease to dwell on the horrors of the last war. War is a kind of intoxication, and nations, like men, must be evaluated when sober. I once met a lawyer who held office during the prosecution of Germans for war crimes, and asked him how a nation so renowned for its humanitarian services could have perpetrated such horrors. "There is only one step to take," he answered. "You may not think it possible to take it; but I assure you that men I thought decent men did take it. You have only to decide that one group of human beings have lost human rights."

How far medical experiments were performed on human beings in the late war will probably never be known, for many of the records are said to have been destroyed. Some evidence appears to be fully authenticated—for example, experiments at Buchenwald on typhus inoculations.

> Ninety beds were set aside for experiments; and in the midst of extreme squalor and starvation these were maintained at the ordinarily high level of hospital amenity. Diet was liberal and nursing attentive.
>
> A proportion of the patients volunteered for admission either as a deliberate method of suicide or as a desperate gamble which would at least ensure good food and comfort for a short time. Others were forcibly admitted as criminals or political prisoners. In all, just under one thousand persons were accepted as a study in experimental typhus fever contracted by intravenous inoculation with blood taken on the fifth day of the disease from other patients.

Germans are pedantically careful people. I have read the account of this experiment and as one who has seen this type of epidemic I have no idea why it was carried out, for it seems to have proved nothing not previously known about typhus. But it does prove that under quite extreme, and it may be hoped, unique conditions, human beings may treat each other as animals. We should not forget that he who condemns his brother condemns himself. There but for the Grace of God go we. That ghastly experiment will have had one good result if we only remember that it was in fact carried out.

CONTROL PATIENTS

In test-tube or animal experiments the control test presents no ethical problem. In fact we rack our brains in an attempt to ensure that every possible variant is kept constant save one; I remember a biologist at Cambridge who always recorded barometric pressure, although his experiments were usually on staining methods. But when we come to the human being, the dilemma of the control test is very real. If, for example, we study the cerebrospinal fluid in disease how are we to establish its state in health? If we remove a portion of liver—a procedure not without risk—in order to study hepatitis, with what norm shall it be contrasted? If we think we have discovered a useful treatment, are we justified in withholding it in selected cases and thereby perhaps risking life?

Many will remember that this is the central problem of the novel *Martin Arrowsmith*—perhaps the best fictional study of laboratory life ever written.

Actually, in the early stages of great discoveries the scarcity of the new agent supplies only too many controls. When penicillin reached us in the Middle East we had less than a million units to dispense, and the question was quite literally which of hundreds of dying men were to be selected for survival. A similar problem was treated dramatically by that talented bore Bernard Shaw in *The Doctor's Dilemma*; it is in very truth a fact that the choice between life and death is today in a pathologist's hand every time a new therapeutic agent emerges. The choice is not in practice difficult: for the least likely to survive are selected, thus satisfying both ethical and scientific requirements. One must admit to some concern at the fact that in Britain new discoveries from the dollar countries are often limited at first to those who can pay for them. But there is always a chance that they may be less harmless than is imagined, and in this case it is the rich who are the guineapigs.

I recall an occasion in the late war when a very limited amount of typhus vaccine was made available by the American manufacturers for civilian distribution during a typhus epidemic. My own view was that it should be given to armament-workers and other men of importance in the prosecution of the war; my American colleague insisted that it should be distributed without regard to age, sex, race, or occupation. He won; but as a result we were left in complete ignorance of its protective value; and I myself remain uncertain of its efficacy.

The use of antitoxic serum is still considered imperative in dangerous infections, such as diphtheria and tetanus, where antibiotics are of little value. Indeed to omit their use in a diagnosed case would evoke full medicolegal sanctions. No-one today, therefore, would dare to treat alternate cases with and without antitoxin; but when diphtheria antitoxin was first introduced, and none could surely predict its value, such an experiment was done. This was in my opinion quite legitimate and probably inevitable owing to shortage of supplies. In "Topley and Wilson" the results of this experiment rightly rank as some of the most important evidence for the value of antitoxin. Personally I should much like to repeat it for I am far from satisfied of its validity. But this would be quite impossible; antitoxin does little harm, if any; and to withhold it might be fatal.

The case of rabies is even more remarkable. Many persons bitten by rabid dogs do not get rabies; many who get antirabic treatment die of rabies none the less. But who dare refuse prophylaxis in a disease always fatal?

We are really faced with this problem every day. Medicine can never become fully scientific unless it becomes completely inhuman.

As clinical pathologists all our work, without exception, is a research. Slowly—often, I must admit, with exquisite boredom; often, I proudly claim, with the keenest intellectual pleasure—we collect accurate data from human sources. One objective must inspire our every action—that the interest of the patient must in some way be served by our intervention, unless it is explained to him, without possibility of misunderstanding, that we are seeking not his own welfare but the long-term welfare of humanity. I repeat that all research involves controls: by definition the test on the control cannot possibly be in that individual's immediate interest. It is true that in the ordinary man and woman there is a lordliness which will nearly always give generously of discomfort or even pain when asked to share with us the privilege of our voyage into the silent sea of knowledge. Our proud and angry dust has always found in self-sacrifice its challenge to a hostile universe. But what we may humbly ask we may not arrogantly demand; and I think that it is here that the conflict between our duty to the individual patient and to the whole sad host of human misery presents itself most clearly to the pathologist.

The possibility of transgressing this rule has been made more plausible not only by the increasing application of scientific methods to medicine but by two other factors—the independence of the doctor from private practice and the increase in academic appointments. So long as a doctor's pocket suffered by undue attention to herd interests, his scientific aspirations were held on a tight rein. As for academic appointments, it is difficult to wear any uniform without sooner or later feeling that one must live up to it. The Salvation Army lass reaches for her tambourine, the general for his sword (or perhaps in these days for his telephone), and the professor of medicine, surgery, or pathology for his fountain-pen. But let us not delude ourselves; the more we emphasise the academic aspects of medicine the more closely we must watch the interests of the individual patient.

EXTENSION OF LIFE

I have spoken of the doctor as the agent of his countrymen in the fulfilment of their philanthropic instincts. In these activities he is not given complete freedom. However much the pædiatrician may be tempted to practise infanticide it is forbidden; euthanasia may be advised, but it may not be instituted. In other cases what the law permits individual religions do not; contraception and sterilisation are examples.

There are some problems of great complexity on which neither State nor Church ventures to rule, but which the doctor must none the less face. At what price may extension of life legitimately be inflicted on a patient? Life is an incurable disease, as Oliver Wendell Holmes said, and always ends fatally; but is mere length of days, however dread the burden, to be sought? I have said that doctors are unfairly blamed for the over-population of the world; but the doctor must bear his share of blame for longevity, that second curse of mankind today. It is science as a whole which pleads guilty to overpopulating the world while underfeeding it; but medicine stands accused of making old age possible before making it endurable. In part I think a valetudinarian age must share the blame; the citizens of the second Elizabeth contrast strangely with those of the first, and life is a journey which nowadays many people finish with too much petrol in their tanks.

In no period has length of days been considered in itself a proper aspiration, and indeed the time when desire shall fail and the grasshopper be a burden is as much a reality as ever. I have often wondered what specialty Shakespeare would have chosen had he been a doctor of today. But certainly the author of *King Lear* would never have taken up geriatrics; and when I see what modern medicine does for the aged, I recall his words "O! let him pass; he hates him that would upon the rack of this tough world stretch him out longer."

The patient meets his doctor with a very wide mandate. He is anxious, and seeks peace of mind; he is in pain, and seeks relief; with the prospect of death, he asks reprieve. But the mandate goes further, and always there is in his mind the unspoken request: "Some time I must die. As a layman, I cannot tell the choice, if choice there be, of my path; but I trust your greater knowledge to see me through in the kindest way."

It is in the management of malignant disease that, to my mind, surgeons and radiotherapists of today are at times wrongly orientated. There is too much emphasis on the remote chance of "cure," too little on the mitigation of the reasonably certain course of the disease. There is some modern surgery which merely ensures that the patient's remaining days will be spent in convalescence from the operation. And there remains always the distressing fact that a patient or his relatives, faced on the one hand by an honest and correct statement that recovery is impossible and on the other by a statement that it may be ensured in certain especially skilled and expensive hands, will sometimes choose a road that is sadly against his interest. The final degradation of medicine is to become the blackmail of the dying with the fear of death.

THE ONLY SIGNIFICANT PROBLEM

During the last twenty-five years the laboratory has dominated medicine in the service of man. But this is only a temporary phase; at one time or another it has been given to physician, anæsthetist, or surgeon, or to the specialist in public health, to hold pride of place; and already the physicist is knocking at the door. (I refer, of course, not to the physicist as radiotherapist; it is the physicist in his exploration of the structure of living matter to whom the future belongs.)

Years ago I met in Jerusalem a very old and learned Jew, and complimented his race on its high proportion of great artists. "You are wrong to congratulate us," he replied. "The artist is always, in each age and race, an honoured guest. Our pride is in our welcome." It is in that spirit, I know, that we rejoice that our branch of medicine has in these last years had such high privilege.

But medicine, and above all scientific medicine, must never forget that in the ultimate analysis the only significant problem is the interest, both immediate and remote, of one frightened patient. Our vague but insistent feeling that humanity's problems are so vast that only vast generalisations can deal with them may lead us to forget that frightened unit. We have inherited a degree of trust more entire than that given to any other group of men—in these days we are trusted more than the priest. If we forfeit that trust by allowing the anonymity of our age to hide the unique personality of the patient, we may learn much and more quickly of the nature of disease, but we shall have lost a friend.

ISONIAZID IN PULMONARY TUBERCULOSIS

ITS USE WITH AND WITHOUT STREPTOMYCIN

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After the synthesis of certain thiosemicarbazones and the demonstration of their antituberculous activity by Domagk et al. (1946) a number of similar compounds were made (Fox 1951) and tested against artificially induced tuberculosis in animals. Of these, isonicotinic acid hydrazide (isoniazid) was found to be effective against tuberculosis in mice (Grunberg and Schnitzer 1952) and subsequently in man (Robitzek et al. 1952). These workers wrote enthusiastically of its effects, and the echoes of their remarks reached the lay press in America and this country. A more cautious attitude was adopted by Elmendorf et al. (1952); but they, like the American Trudeau Society, recommended further clinical trials.

A large-scale trial has been conducted by the Medical Research Council which has recently published findings and conclusions after three months' observation (Medical Research Council 1952). The conclusion in this report is that "isoniazid is a very effective drug in pulmonary tuberculosis, but given alone it is not more effective than streptomycin plus P.A.S."

The investigations carried out at Guy's Hospital have fallen into three groups: (1) microbiological studies of the action of isoniazid in vitro (Knox et al. 1952); (2) studies of its efficiency in experimental tuberculosis (Goulding and Robson 1952); and (3) a clinical trial of its effectiveness alone and in combination with streptomycin in a small series of patients with pulmonary tuberculosis. The present paper gives the results of the clinical trial.

METHODS

Clinical trials with isonicotinic acid hydrazide both alone and in combination with other substances were started in March, 1952, and are still in progress. The investigation was made on outpatients who had been attending the Bermondsey and Southwark chest clinics. All patients were sputum-positive and had chronic fibrocaseous disease which in almost every case had been present for many years. Some had had chemotherapy at some stage in their illness, but the effects of this were judged to have ceased and only one instance of definite streptomycin resistance was discovered. Clinically the patients varied from the "good chronic" doing a part-time job who appeared to have achieved an unhappy symbiosis with the organism, to the toxæmic invalid in whom the disease was pursuing a slow but relentless downhill course. All patients attended Guy's Hospital once each week for clinical assessment (C. L. J. and K. S. M.). In addition they were weighed and blood was collected for erythrocyte-sedimentation rate (Westergren). Radiographs were taken before treatment and subsequently at intervals of three or six weeks. These were all examined by the same radiologist, who had no knowledge of what treatment was being given. Each patient submitted three early morning sputum samples each week, and kept a daily record of morning and evening temperatures with standard thermometers which were provided. Initially the plasma levels of isoniazid were measured; but when it was found that satisfactory levels were always achieved, this was discontinued. Similarly urine samples were collected before and after six weeks' treatment. No abnormalities were found; and this, too, was subsequently discontinued. A clinical umpire was appointed (E. K. P.) to whom any patient showing signs of deterioration was referred, and his decision about further treatment was accepted as final.

Bacteriological Methods

Sputum samples were sent to the laboratory in screw-top waxed cartons enclosed in stout envelopes bearing the patient's name. The macroscopic appearance of the specimen was recorded and the volume (scanty or copious) was noted. Films were made from the untreated sputum and stained by Ziehl-Neelsen's method, using malachite green as a counter-stain. These films were examined by one observer (P. J. C.) using a $^1/_7$-in. fluorite oil immersion objective. In each instance 100 fields were searched and the count was expressed as number of tubercle bacilli per 100 fields. All negative films were checked by another observer, and neither was aware which patients were receiving treatment. Thus no specimen was reported as negative microscopically unless 200 fields had been examined. Slides and record cards bore serial numbers only, as a further protection against recognition.

Culture.—Digestion of sputum was carried out by Jungmann and Gruschka's (1938) method. Particular attention was paid to the use of 10 vol. hydrogen peroxide as recommended in their original paper. Digesting fluid was run into each carton from a hooded burette and the mixture transferred to a wide-mouthed universal container for shaking and centrifugation. The deposit was neutralised with one 25 ml. wash with normal saline. Material from each container was inoculated on to three Lowenstein-Jensen slopes and incubated at 37°C for six weeks. Specimens from all patients were cultured thrice weekly for the first six weeks and thereafter, as far as possible, at intervals of three weeks. Cultures were examined at weekly intervals and the results entered on individual record cards. Where single colonies appeared, the numbers were noted as was the number of contaminated slopes. Subcultures were made in Dubos liquid medium for estimating the sensitivity of strains to isoniazid and streptomycin.

PRELIMINARY INVESTIGATION

As no controlled investigation had been reported on isoniazid in tuberculosis in man, a preliminary comparison was made between the effects of this substance and identical capsules containing lactose. 24 patients were selected and carefully paired in terms of age and duration, degree, and progression of disease. 1 of each pair received isoniazid (250 mg. daily in five 50 mg. capsules, one after each meal and two last thing at night, for six weeks) and the other the dummy capsules in the same way. The distribution was made in a random fashion and was unknown to the clinicians. 2 patients defaulted, both of whom were subsequently found to have been receiving lactose.

A clear difference was seen in the progress of the two subgroups, so that the clinical assessors made 19 correct predictions of treatment from the 22 remaining patients. Details of the observations made on the treated group are given later, but the weight changes in the two subgroups are compared in fig. 1.

The sputum from the patients in the treated group showed striking naked-eye and microscopic changes

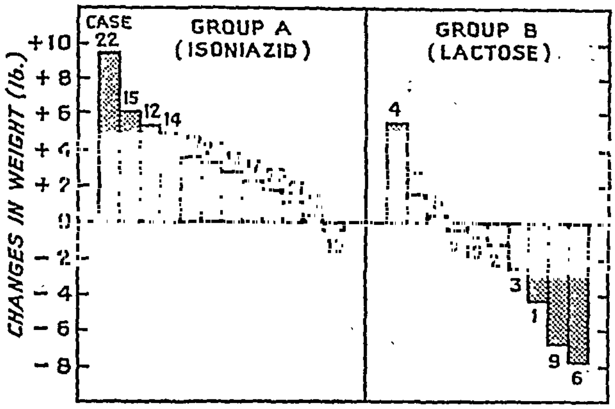

Fig. 1—Preliminary experiment to compare changes in weight in two groups of patients, one receiving isoniazid and the other identical capsules containing lactose for six weeks.

which are described more fully later. No such changes were seen in the control group.

During this period plasma levels of isoniazid were determined by the method of Rubin et al. (1952). Estimations made during the first three weeks of treatment showed levels between 2·0 and 0·79 µg. per ml. in the patients receiving the drug. As therapeutic concentrations were clearly being achieved on the dosage administered, further estimations were considered unnecessary.

THE MAIN TRIAL

This preliminary investigation showed clearly the effectiveness of isoniazid over a short period. It seemed important to investigate next whether this effect continued during longer periods of treatment and whether the drug was most effective alone or in combination with streptomycin. Accordingly, after the preliminary six weeks the patients who had so far served as controls, together with 1 newcomer, were given isoniazid in the same way, and also streptomycin 1 g. six days a week intramuscularly. The trial was conducted as before, and the results obtained during the first eighteen weeks of treatment in each group have been compared.

The Groups

Group A comprised 12 patients (3 women and 9 men), aged 25–49 years, who received 250 mg. isoniazid by mouth daily.

Group B comprised 11 patients (4 women and 7 men), aged 21–58 years, who received isoniazid in the same way, and also streptomycin sulphate 1 g. intramuscularly on six days of each week.

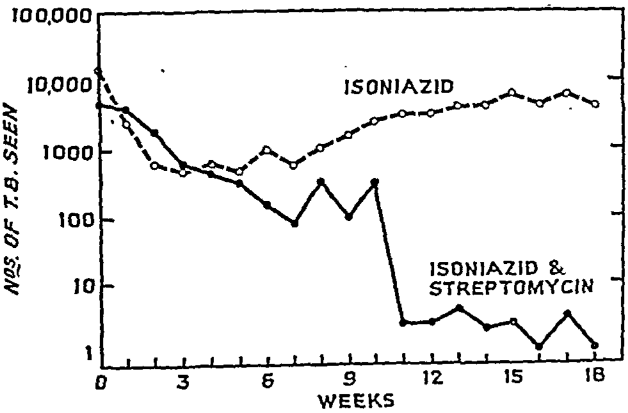

Fig. 2—Changes in excretion of tubercle bacilli in the sputum of patients in group A (isoniazid alone) and group B (isoniazid and streptomycin). (For explanation see text.)

Owing to an administrative difficulty, group B (with the exception of the newcomer) received isoniazid alone for the first of the eighteen weeks during which observations were made. Only on 11 occasions were weekly appointments missed, and when this occurred a mean value was taken from the readings obtained at the prior and subsequent attendances. As this was necessary only once in 40 values, it has been disregarded as a source of error.

Clinical Results

Between the first and the sixth week there was a striking clinical improvement in both groups. Attention is especially directed to the increased sense of well-being and better appetite which almost all patients enjoyed. The cough improved in a uniform way. It first decreased in frequency and severity, and then the sputum became less. Only 2 patients in group A and 4 in group B were pyrexial; and in 5 of these 6 patients the temperature was restored to normal. The remaining patient (in group B) had chronic bronchitis, which was thought to be causal. 2 other patients in group A who had previously had normal temperatures showed mild and transient pyrexial reactions for two and three days immediately after starting on isoniazid. No patient in either group noticed any increased frequency of hæmoptysis.

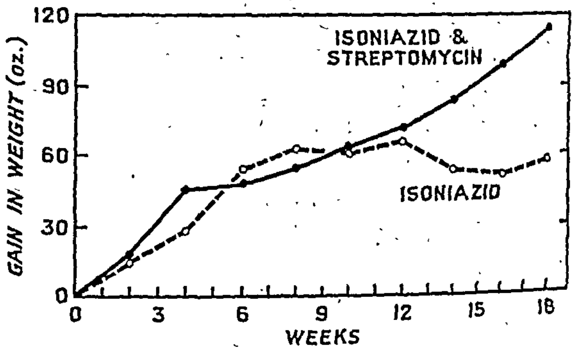

Fig. 3—Mean (cumulative) weight changes, recorded fortnightly, of patients in group A (isoniazid alone) and group B (isoniazid and streptomycin).

This improvement was maintained in group B throughout the eighteen weeks' observation period, and at the end of the course all the patients said that they had felt themselves improving progressively all the time. In group A, however, most of the patients said that they had noticed most improvement in the first half of the course, and 4 felt that they were relapsing during the last part. Another patient (fig. 7, no. 15) improved spectacularly until the eleventh week, and then relapsed so acutely that she had to be withdrawn from the trial at sixteen weeks.

Radiographs

At the end of eighteen weeks in group A 2 patients had improved and 2 were worse; 8 remained unchanged. In group B 4 had improved and 7 remained unchanged.

Sputum

Successive specimens of sputum from the patients in both groups showed at first a progressive change in macroscopic appearance. In addition to a decrease in volume the physical characteristics altered considerably. For example, some specimens changed from purulent to mucoid and finally became salivary, while others decreased strikingly in volume and their tenacious consistency resembled that of the sputum in acute lobar pneumonia. In later weeks, however, in the sputa of group A there was a progressive relapse in physical properties with a return to the original volume and purulent characteristics. In group B, on the other hand, the improvement was maintained.

WEIGHT CHANGES (IN OUNCES) IN GROUPS A AND B OVER EIGHTEEN WEEKS

Group A (isoniazid alone)				Group B (isoniazid plus streptomycin)			
Case no.	Period (weeks)			Case no.	Period (weeks)		
	0–6	6–12	12–18		0–6	6–12	12–18
12	+ 83	− 29	− 75	1	+ 63	+ 101	+ 73
13	+ 48	− 4	− 8	2	+ 37	− 19	+ 1
14	+ 80	+ 34	− 16	3	+ 55	− 23	− 29
15	+ 98	+ 37	− 187*	4	+ 45	+ 5	+ 69
16	− 5	− 18	+ 59	5	− 20	+ 28	+ 42
17	+ 35	− 6	− 35	6	+ 71	+ 88	+ 55
18	+ 3	− 19	+ 36	7	+ 32	+ 15	+ 14
19	+ 55	+ 4	− 18	8	+ 11	− 47	+ 69
20	+ 24	+ 23	+ 21	9	+ 158	+ 50	+ 97
21	+ 5	+ 39	+ 5	10	+ 42	+ 45	+ 46
22	+ 154	+ 111	+ 95	11	+ 17	+ 23	+ 22
23	+ 54	− 17	+ 16				
	Av. + 57	+ 13	− 9		+ 46	+ 23	+ 42

* Twelfth to sixteenth week only (withdrawn).

The bacillary count per 100 fields in three specimens from each patient was totalled to give an estimate of the weekly excretion of *Mycobacterium tuberculosis*, and the mean number per patient was plotted on a convenient scale against time in weeks. Fig. 2 gives the mean number of tubercle bacilli found per patient in the two groups. The transitory fall shown by group A is in striking contrast to the persistent fall shown by group B. Figs. 6 and 7 include the sputum-counts of individual patients. It was already clear by the third week of treatment that most cases in both groups were showing a striking fall in bacillary count. It can be seen, however, that in group A by the sixth week some patients were already showing an upward trend in their graphs. This occurred at the same time as the naked-eye relapse mentioned above and continued in later weeks. In group B, on the other hand, the initial fall in the sputum-count was maintained, apart from an occasional "flare-up," to the end of the eighteen-week period.

Culture of Myco. tuberculosis

All the patients in groups A and B supplied specimens of sputum in the pre-treatment period, except case 11. We do not propose to discuss the cultural results in detail here; but whereas in the pre-treatment period positive cultures were obtained without difficulty, in specimens from patients receiving isoniazid either alone or with streptomycin the proportion of successful isolations became less during the course of the trial.

For this and other reasons our information about the development of resistance in patients receiving chemotherapy is rather scanty. Cultures from 22 patients (12 from group A, 10 from group B) were tested for sensitivity to isoniazid and streptomycin at the start of the trial. All of these were sensitive to 0·1 µg. per ml. of isoniazid or less. Of the 22 cultures 1 was resistant to more than 10 µg. per ml. of streptomycin, 3 were sensitive to 1 µg. per ml., and the remainder were sensitive to 0·4 µg. per ml. or less. During treatment, in group A 2 out of 11 patients in the fourth week and 5 out of 6 patients in the tenth week had produced strains resistant to 0·1 µg. per ml. or more of isoniazid. Their resistance to streptomycin was unchanged. In group B in the fifth week 5 out of 5 patients produced cultures sensitive to 0·1 µg. per ml. of isoniazid and streptomycin.

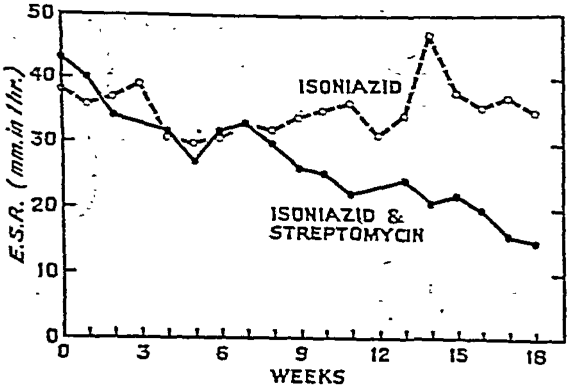

Fig. 4—Mean weekly erythrocyte-sedimentation rate in group A

Weight

The weights were recorded weekly. Fig. 3 shows the average gain and loss in ounces of each group over each fortnightly period of the trial. This graph shows that whereas the isoniazid group failed to gain weight after the eighth week, the group treated with streptomycin in addition showed a steady gain throughout the whole period of the trial. Case 15, a patient who was losing weight rapidly and who was unfit to continue in the trial after the sixteenth week, is not included in the average for the final fortnight.

That the difference between groups A and B is not due to a very large change of weight in one or two cases is well shown by the accompanying table, which gives the weight change of all cases over the first, middle, and final six-weekly period of the trial. In the final period 3 cases in group A gained, and a similar number lost, 2 lb. or more; while in group B 7 gained, while none lost, this amount. This is in strong contrast to the initial period, where the two groups show a striking similarity, 8 patients in each gaining, and none losing, 2 lb. or more.

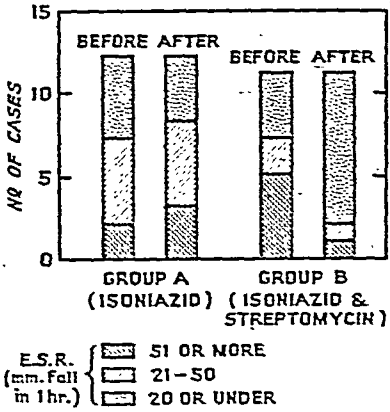

Fig. 5—Distribution of high, moderate, and low erythrocyte-sedimentation rates in the two groups before and after the trial.

The weekly weights of these 23 patients are shown graphically in figs. 6 and 7. In group A, case 22 gained weight rapidly throughout; case 15 gained weight rapidly at first, but in the last six weeks her weight fell precipitously and she was withdrawn from the trial; case 12 behaved similarly, but the fall was not quite so severe. Cultures from both these last 2 patients developed resistance to 10 µg./ml. of isoniazid at about the fifth week of treatment. In group B, the greatest gains in weight were shown by patients 1, 6, 9, and 10, all of whom were losing weight during the seven weeks before treatment started (fig. 1).

Erythrocyte-sedimentation Rate

Mean weekly values are shown in fig. 4. Case 15 was withdrawn at sixteen weeks. This figure shows that the value for the erythrocyte-sedimentation rate (E.S.R.) fell in both groups until the fifth week, after which this tendency ceased in group A. In group B it was maintained throughout the eighteen-week period.

That this difference is not accounted for by one or two cases showing very large changes in the sedimentation-rate is shown in fig. 5. Here the number of patients in each group having high (51 mm. +), moderate (21–50 mm.), and low (under 21 mm.) sedimentation-rates at the beginning and end of treatment is shown graphically. The weekly E.S.R. for each of the 23 patients

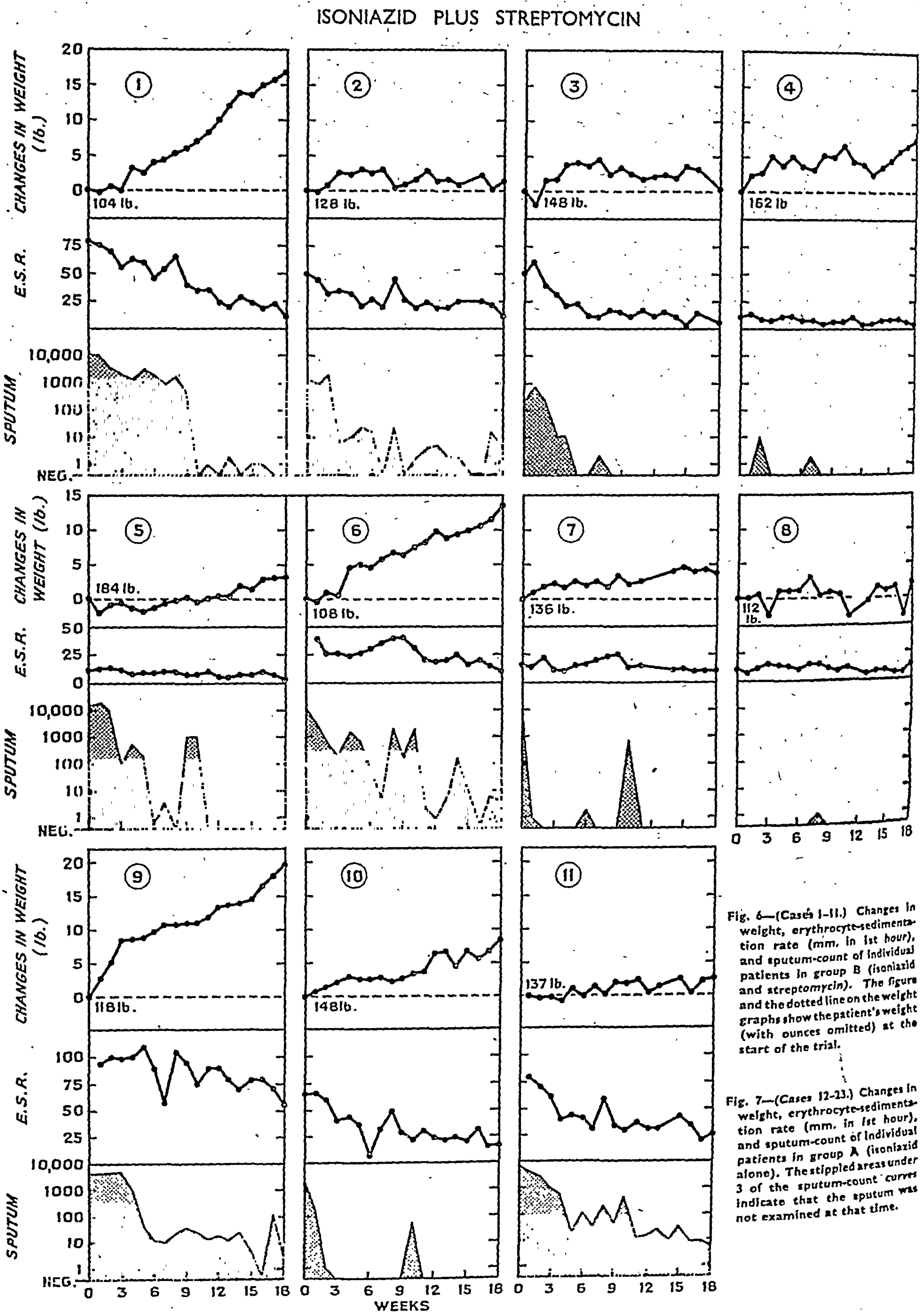

Fig. 6.

Fig. 6—(Cases 1-11.) Changes in weight, erythrocyte-sedimentation rate (mm. in 1st hour), and sputum-count of individual patients in group B (isoniazid and streptomycin). The figure and the dotted line on the weight graphs show the patient's weight (with ounces omitted) at the start of the trial.

Fig. 7—(Cases 12-23.) Changes in weight, erythrocyte-sedimentation rate (mm. in 1st hour), and sputum-count of individual patients in group A (isoniazid alone). The stippled areas under 3 of the sputum-count curves indicate that the sputum was not examined at that time.

ISONIAZID ALONE

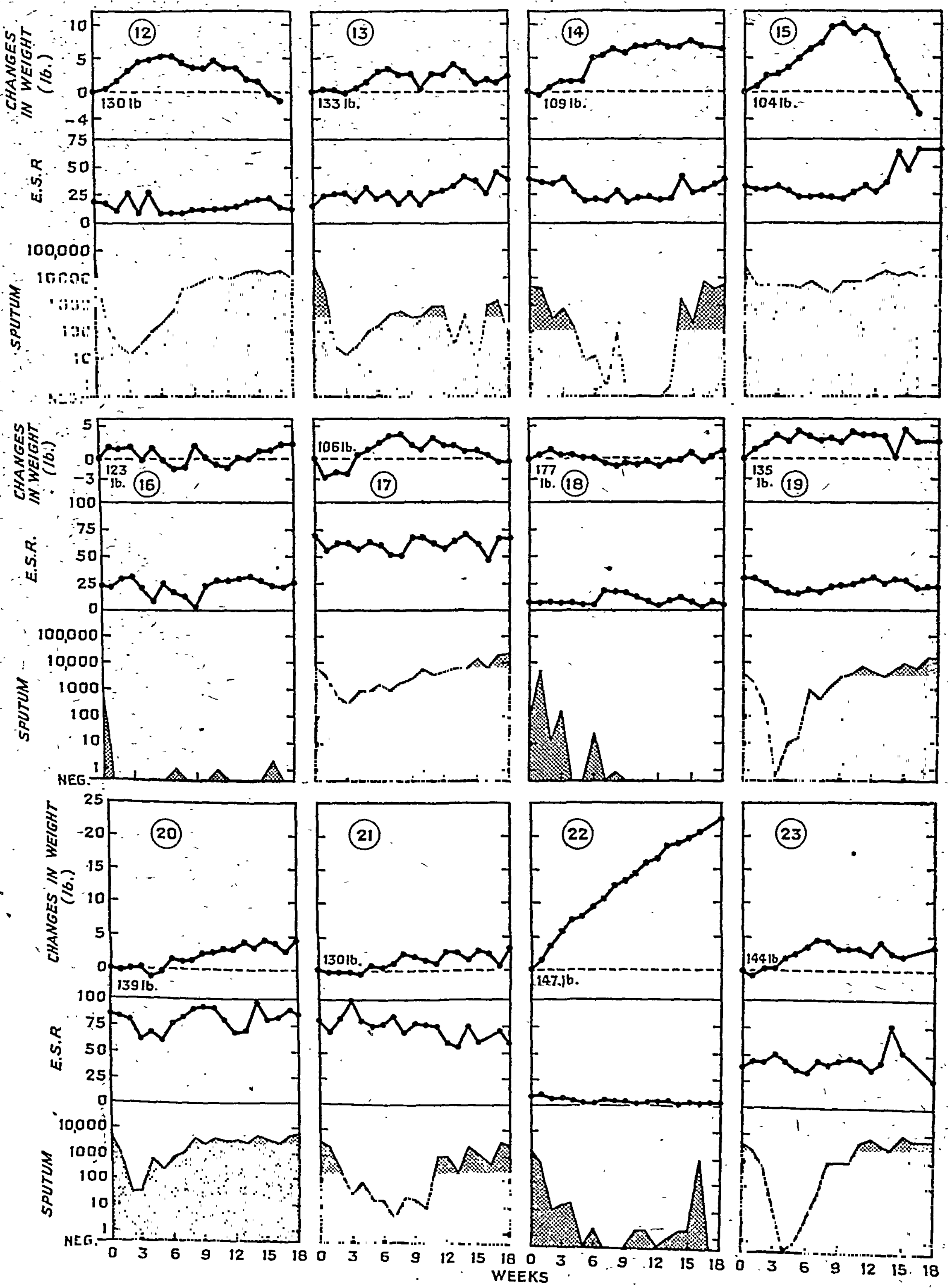

Fig. 7.

Toxicity

No patient noticed any subjective toxic reaction to isoniazid. One observer (K. S. M.) thought that after about six weeks some hyperreflexia was present, and that it persisted throughout the course. In group B 3 patients developed rashes between the thirteenth and eighteenth week. In 1 case this was so severe that the dosage of streptomycin was reduced to 1 g. three times each week in the last two weeks.

COMPARISON WITH STREPTOMYCIN AND P.A.S. THERAPY

It seemed clear that patients on isoniazid plus streptomycin had fared better than those on isoniazid alone. It was now important to ascertain how this form of combined treatment compared with the well-tried combination of streptomycin plus *p*-aminosalicylic acid (P.A.S.). Two groups of paired patients—group C (9 patients given isoniazid and streptomycin) and group D (9 patients given streptomycin plus P.A.S. plus lactose)—were investigated. In group D, of the original 9 patients, 1 defaulted and in 1 treatment was stopped because of a reaction to streptomycin. That trial, and certain others, will be reported fully at a later date, but certain interim results, given below, appear pertinent.

Weight

The mean weight gains in groups C and D were as follows:

Group	*Weeks* 0–6	*Weeks* 6–12
C (9 cases)	4 lb. 9 oz.	3 lb. 10 oz.
D (7 cases)	2 lb. 8 oz.	1 lb. 12 oz.

Sputum

In both groups the sputum-counts fell at about the same rate, and this improvement was maintained.

E.S.R.

The mean E.S.R. values (Westergren, mm. in first hour) were as follows:

Group	*Weeks' treatment* 0	6	12
C (9 cases)	61	28	21
D (7 cases)	75	37	28

The E.S.R. in both groups showed approximately equal improvement.

DISCUSSION

The number of cases reviewed in this report is small, and the results do not therefore lend themselves to detailed statistical analysis. Nevertheless, the data obtained from each case were considerable. Clinical assessment, erythrocyte-sedimentation rate, and body-weight were recorded weekly by the same physician; and specimens of sputum from each patient were examined twelve times each month, so that the criterion for a negative microscopic result was strict. In this way it was possible to compare very accurately the progress of patients receiving different treatment.

The investigation is only concerned with patients with chronic pulmonary tuberculosis corresponding to group 3 in the Medical Research Council (1952) trial. It might be expected that such patients would do worse than those with the more acute early pulmonary lesions, and that the problem of resistance would be at its maximum.

The patients were drawn from working-class homes, and all were treated as outpatients. Thus the conditions of the trial were those under which most patients with this type of disease have to be treated today. Great hopes had been entertained that isoniazid would prove of immense benefit in this type of case, and it was with a view to providing some information on this all-important question that this investigation was planned.

The method of pairing cases and including one of each pair in each group ensured that groups A and B contained very similar clinical material. Owing to the preliminary experiment during which group B received lactose capsules for a total period of seven weeks, we know that most of these patients were losing ground when treatment with isoniazid and streptomycin was started (see fig. 1). The rapid clinical improvement in pulmonary tuberculosis after administration of isoniazid is now well established. This effect was demonstrated conclusively during the initial period when group A received isoniazid and group B lactose-capsules, and will not be discussed further here.

Comparison between the effect of isoniazid alone and isoniazid plus streptomycin over an eighteen-week period is, however, of great interest. While there is little difference in the progress of the two groups during the first half of the course, a great change becomes apparent after the twelfth week. The majority of patients receiving isoniazid alone deteriorated during the last six weeks of the course. This was shown by a return of tubercle bacilli in the sputum, cessation of weight gain, and in several cases weight loss; while the erythrocyte-sedimentation rate, which had in most instances undergone a moderate improvement, returned to the original level. Of 12 patients 5 realised that they were losing ground, but with 1 exception all thought they were better than before treatment. It was our impression that the subjective sense of well-being continued after the disease, as judged by sputum examination, erythrocyte-sedimentation rate, and weight change, had recrudesced to its former level. Mention must be made of case 15. This patient who was initially the most severely ill of the group made a spectacular improvement for eight weeks. Her temperature settled and she had put on over 9 lb. in weight. From the twelfth to the sixteenth week, however, the disease again became extremely active, her weight fell by 12 lb., and her temperature rose to a higher level than before treatment. On the other hand, all patients receiving streptomycin in addition to isoniazid improved steadily throughout the eighteen weeks.

A further series of 9 patients receiving isoniazid and streptomycin have now been followed to fourteen weeks. Again steady improvement has continued. This series (C) was not strictly comparable with group B as it contained a higher proportion of more toxic patients. The weight gain, while following the same steady increase throughout the fourteen weeks, was nearly double that observed in the first fourteen weeks in the group-B cases.

This discrepancy is of interest. Weight gain in tuberculous patients treated with isoniazid must depend upon two factors—namely, the increase in appetite consequent upon the disappearance of *toxæmia*, and the amount of food available for the patient to eat. Our patients had not access to the colossal diets available to the first cases described at the Sea View Hospital, New York, and so the weight increase tended to be more modest. Nevertheless, while it is possible that group C had slightly better home conditions than group B, the difference, if any, was small and cannot be held to explain the very pronounced variation between the two groups. The explanation probably lies in the greater toxicity in group C before treatment was started (E.S.R. average: group C 61 mm., group B 43 mm.). It is likely that patients in group C had suffered greater weight loss in the period immediately before treatment, and so gained weight at a greater speed when the toxæmia was removed. This emphasises the great importance of ensuring that groups to be compared should consist as far as possible of patients whose disease is in a similar state of activity as well as having comparable radiological appearances.

The remaining patients in group D, who have received streptomycin and P.A.S. for fourteen weeks, have shown a steady increase in weight although of very much smaller degree than was seen in group C. Nevertheless they have gained weight at almost as great a rate as group B. We consider that as they were extremely toxic at the beginning of treatment (E.S.R. average 75 mm.) the comparison with their paired group C is valid. Since groups C and D were both receiving the same dose of streptomycin, the results suggest that the greater increase of weight in group C was due to the isoniazid and thus indirectly support the conclusion reached in the Medical Research Council trial that isoniazid does cause an increase in weight not seen in patients treated with streptomycin and P.A.S. The improvement in the sputum and erythrocyte-sedimentation rates was of about the same order in groups C and D. The combination of isoniazid and streptomycin also has the advantage that patients find isoniazid easy to take, and it does not cause the nausea characteristic of P.A.S.; but larger series will have to be treated over a longer period before it can be certainly established that isoniazid plus streptomycin is in all respects the equal of P.A.S. plus streptomycin.

The important feature of this trial at the present time would seem to be the observation that most patients who receive isoniazid alone regress after a period of eight to ten weeks. This regression is associated with the development of isoniazid resistance. It is too early to be certain whether streptomycin prevents this resistance to isoniazid, or whether isoniazid acts like P.A.S. and the beneficial effect seen in the later weeks of an eighteen-week course of isoniazid and streptomycin is due to the fact that the tubercle bacilli remain sensitive to streptomycin.

These results suggest that the haphazard use of isoniazid alone in treatment of chronic pulmonary tuberculosis must be strongly condemned. There is a grave risk that the last state of patients treated with isoniazid alone may be worse than their first and that they will transmit isoniazid-resistant organisms to others. On the other hand there is no doubt at all that isoniazid, initially at least, hits the tubercle bacillus both in vitro and in vivo in a particularly vulnerable spot. It may be possible to find some modification of the molecule which will overcome its gravest disadvantage—the ease with which resistant strains develop. At present there is no doubt that this disadvantage can be greatly lessened by at least one form of combined therapy. While it may be that in time patients receiving streptomycin and isoniazid may become resistant to both before the sputum can be rendered permanently negative, this combination is apparently very effective and deserves much further trial.

CONCLUSIONS

Certain definite conclusions can be drawn from these results:

1. Isoniazid alone has a beneficial effect on certain cases of pulmonary tuberculosis in the first three to six weeks of treatment. In the next few weeks the initial improvement is no longer maintained; and soon deterioration ensues, especially at first in the sputum-counts. This deterioration is associated with the excretion of resistant strains of tubercle bacilli in the sputum.

2. Combined therapy with isoniazid and streptomycin, on the other hand, gives a completely different picture when continued for a long enough period. There is the same initial improvement as in the patients treated with isoniazid alone; but the improvement is maintained until at the end of eighteen weeks there is a great difference between the two groups. The initial rapid improvement in the sputum-counts, the gain in weight, and the fall in the erythrocyte-sedimentation rate all continue and there is paralleled improvement in the clinical condition.

We are indebted to Dr. B. J. Malley, chest physician, Bermondsey chest clinic, who allowed us to include some of the patients under his care, and Dr. E. V. Medill, who independently assessed the radiological changes. We should also like to thank Mr. D. E. Seymour, of Herts Pharmaceuticals Ltd., who kindly made available the supplies of isoniazid ('Pycazide') used in the trials. We should also like to thank Miss D. M. Read for her help in organising the clinical aspects of the trial, and Mr. J. A. Hughes and Mr. R. C. Woodroffe for their invaluable help in the laboratory. We should also like to acknowledge the secretarial and other help which we have received from members of the hospital staff and the Medical School of Guy's Hospital.

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ISONIAZID IN THE CONTROL OF EXPERIMENTAL CORNEAL TUBERCULOSIS

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It has been shown that experimental corneal tuberculosis in both mice and rabbits provides the basis of a reliable and rapid in-vivo test by which the antituberculous activity of various chemotherapeutic substances may be assessed (Robson 1944, Gardiner et al. 1949, Rees and Robson 1950, 1951). Following the injection of a standard suspension of tubercle bacilli, the "cornea responds in a regular and prediotable manner." The way in which the natural history of such artificially induced lesions may be modified by treatment of the animals reflects the antituberculous properties of the agents so employed. The results already obtained in this way with streptomycin, *p*-aminosalicylic acid (P.A.S.), and the thiosemicarbazones are, significantly, in accord with clinical observations.

The object of the present investigations has been to ascertain the effectiveness of isoniazid, either alone or in combination with other drugs, in the control of experimental tuberculous infections of the cornea. The opportunity has thus arisen to relate the behaviour in vivo to the properties in vitro as now reported (Knox, King, and Woodroffe 1952) and also possibly to provide experimental evidence in support of the combined drug therapy that has been tested in clinical practice (Joiner et al. 1952).

METHODS AND MATERIALS

The experiments here described fall into two groups. In those with mice the technique followed was that of Rees and Robson (1950) and in those with rabbits the procedure was that of Gardiner et al. (1949).

Mouse Experiments

Albino mice, each weighing approximately 25 g., were subjected to deep anæsthesia by means of bromvaletone and ether. Into one eye of each animal a standard suspension of *Mycobacterium tuberculosis*, comprising about 1000 organisms in a 'Tween 80' medium, was then introduced. Cultures of both human (H37RV) and bovine strains were employed. The latter was supplied originally by Dr. W. M. Levinthal, of the Royal College of Physicians, Edinburgh. It has since been maintained by passage through the mouse, inoculation upon Dorset egg medium, and weekly subculture in Dubos medium containing 'Tween 80' and bovine albumin, up to a maximum of seven subcultures before return to a mouse. Seven-day cultures in the fluid medium formed the basis of the suspensions actually injected.

The developing lesions were subsequently observed at short intervals by the aid of a low-power binocular microscope. In the absence of treatment, the average incubation period is twelve days from inoculation. The corneal tubercles which then appear advance to a maximum at about thirty days, and thereafter undergo spontaneous partial regression until they are ultimately stabilised. In the present series, treatment was always initiated on the first day of the experiment and continued for a definitive period of twenty-eight days. During this time feeding was standardised, M.R.C. mouse diet 41 being offered at the rate of 5 g. per head per day. Initially, also, penicillin was given daily by subcutaneous injection with a view to limiting the secondary infection which occasionally occurred. Isoniazid and P.A.S. (as the sodium salt) were given in the diet, and the streptomycin (as the calcium chloride preparation) was administered daily by subcutaneous injection. The dosages were as follows: isoniazid 0·3 mg. per mouse per day (equivalent to about 12 mg. per kg. body-weight), streptomycin 4 mg. per mouse per day (equivalent to about 0·16 g. per kg. body-weight), and P.A.S. 2% of the sodium salt in the diet (equivalent to about 4 g. per kg. body-weight).

In each instance the course of the disease in the treated animals was compared with that in a control (untreated) group. Note was made of the incubation period, the extent of the lesion (by an arbitrary method of scoring), its rate of advance, and the number of animals involved. Thus a comparison could be made between treated and untreated animals week by week, either according to the percentage in each group protected from the disease or according to the average extent of the lesion in each group. Graphing such figures tended to emphasise any differences.

Rabbit Experiments

With the rabbits, deep anæsthesia was obtained by the use of ether alone and, this time, the standard amount of suspension of *Myco. tuberculosis* injected intracorneally into each eye contained only about 300 organisms. All animals were kept in individual cages and fed on the same diet. The corneæ were examined each week and the extent of the lesion was noted in each case. Again, an arbitrary method of scoring was applied. In the untreated rabbit, such experimental corneal tuberculosis has an incubation period of twelve to fourteen days. From this stage, when minute primary tubercles appear in the needle track, the disease steadily advances, eventually proceeding to panophthalmitis and, in about three months, to generalised tuberculous infection of the animal. The effectiveness of any antituberculous agent can therefore be judged by the degree and rate at which this normal course is modified by treatment.

In one experiment with rabbits treatment was started on the day of inoculation. To one group streptomycin (as the calcium chloride preparation) was given by subcutaneous injection, twice daily, at a dose equivalent to 100 mg. per kg. body-weight per day; and to another group isoniazid similarly at the rate of 10 mg. per kg. body-weight per day. Treatment was maintained for eight weeks in all. In the second experiment with rabbits, treatment was not initiated until moderately advanced lesions had already become established. Then, streptomycin was given to one group, isoniazid to the second, and the two drugs together to the third, in each case at the dosages already stated.

RESULTS

Mouse Experiments

Control of infections of Myco. tuberculosis (bovine strain) with isoniazid.—Two groups, each of 8 mice, were inoculated intracorneally with *Myco. tuberculosis* of bovine strain. One group served as a control and the other was given isoniazid in the diet. In the control animals the disease took its expected course, all but one being ultimately affected. In the treated animals, on the other hand, no lesions at all developed whilst treatment was maintained. Yet, fourteen days after cessation, characteristic lesions arose and followed a course almost identical with that in the controls. Again, most of the animals were eventually involved.

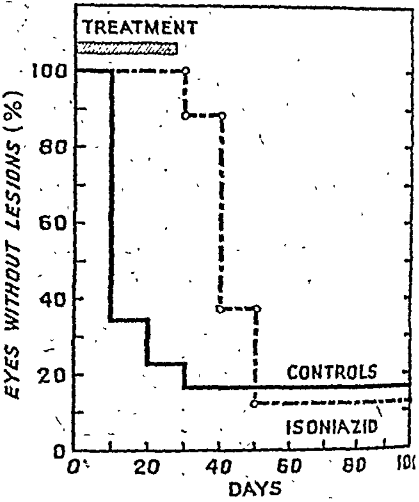

Fig. 1—The effect of isoniazid in protecting mice from experimental corneal tuberculosis (bovine strain); the incidence of the disease in untreated animals is shown for comparison.

Suppression during the course of treatment and recrudescence later are clearly shown in figs. 1 and 2.

Control of infections of Myco. tuberculosis (human strain, H37Rv) with isoniazid.—Repeating the experiment under similar conditions but using a culture of a virulent human strain of organisms there occurred, as expected, the customary lesions in the control group and, once again, a delay in the appearance of lesions in the other group until after treatment had been discontinued. This is demonstrated in figs. 3 and 4.

Significantly, perhaps, the subsequent breakdown was seen in fewer of the animals than in the previous experiment and the actual lesions were more limited.

Control of infections of Myco. tuberculosis (human strain, H37Rv) in which resistance to isoniazid had been developed in vitro.—By the kindness of Prof. Robert Knox, a culture of *Myco. tuberculosis* (H37RV) was provided in

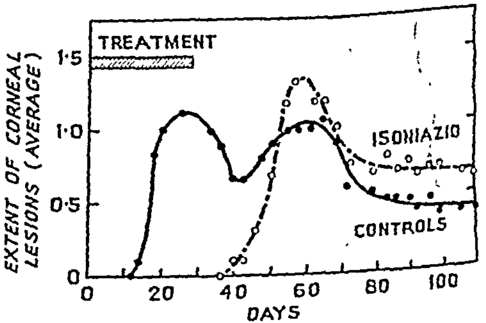

Fig. 2—Comparison of the development of experimental corneal tubercles (bovine strain) in untreated mice and in mice treated with isoniazid. The sizes of the lesions are expressed in arbitrary units, an average figure being given for each group.

which a high resistance to isoniazid had been developed in vitro by serial passage through media containing increasing concentrations of the drug (the inhibitory concentration in the test-tube was then 8–40 µg. per ml. instead of the usual 0·0128 µg. per ml.). A standardised suspension of such organisms was inoculated intracorneally into two groups, each comprising 11 mice. One group was then given isoniazid in the diet at the dosage already demonstrated as effective, while the other remained as controls. The development of lesions was then almost the same in the two groups—in time, extent, and quality (see fig. 5). Indeed, the drug had virtually no effect under these conditions—a result which has already been mentioned in a preliminary communication (Goulding et al 1952).

Control of infections of Myco. tuberculosis (bovine strain) by a combination of isoniazid and streptomycin.—Four groups, each of 15 mice, were given the usual intracorneal inoculation of *Myco. tuberculosis*, the culture being that of the bovine strain with a known sensitivity to both isoniazid and streptomycin. One group was left untreated as a control; the second received streptomycin, as described, by daily subcutaneous injections; the third was given isoniazid in the diet; and the fourth group received both drugs simultaneously. Among the controls, as expected, corneal lesions developed within two weeks of inoculation and pursued a characteristic course; all but 2 of the animals were ultimately involved. In those treated with streptomycin, the effect, as demonstrated by Rees and Robson (1950), was prolongation of the incubation period and some curtailment of the subsequent progress of the disease. With isoniazid alone the response was identical with that reported above—namely, complete suppression of the disease so long as treatment was maintained, and thereafter a relapse in which, apart from 3 animals, all exhibited lesions as seen in the controls. In the last group submitted to the combined therapy, however, not only was there complete absence of any disease during the twenty-eight days' course of treatment but, subsequently, a relapse occurred in only 4 of the animals and even then the lesions were both slow to arise and more limited in extent (see figs. 6 and 7).

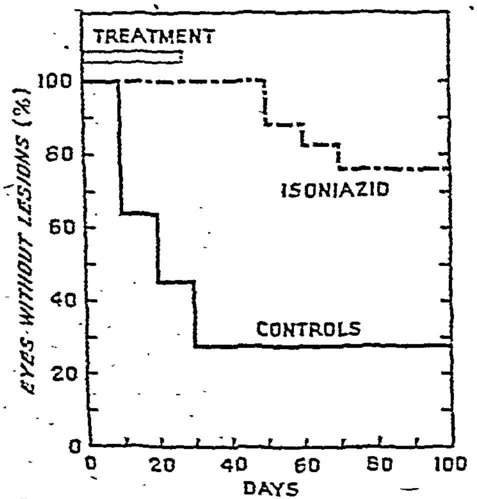

Fig. 3—The effect of isoniazid in protecting mice from experimental corneal tuberculosis (human strain H37Rv).

Control of infections of Myco. tuberculosis (bovine strain) with a combination of isoniazid and P.A.S.—In order to ascertain whether P.A.S. in combination with isoniazid would have a similar effect to streptomycin and isoniazid, yet another test was performed in mice with corneal infections of bovine *Myco. tuberculosis*. Again the controls followed a typical course. Moreover, whilst the combined drugs were administered in the doses quoted, no lesions appeared in the treated animals. Yet within three weeks of treatment being withheld the disease appeared in this group, involving, after altogether eight weeks' observation, 8 out of the 12 mice concerned. What is more, the lesions so arising advanced with that vigour generally seen in untreated animals (see figs. 8 and 9).

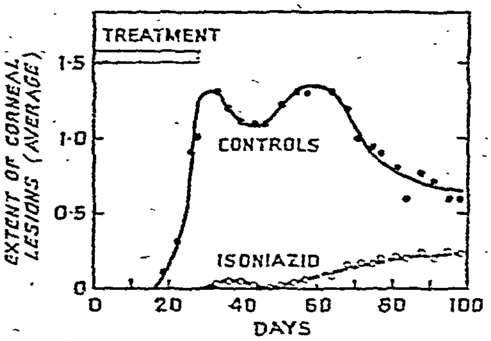

Fig. 4—Comparison of the development of experimental corneal tubercles (H37Rv) in untreated mice and in mice treated with isoniazid.

Rabbit Experiments

Acute lesions.—Of 10 adult rabbits on which bilateral corneal inoculation with *Myco. tuberculosis* (bovine strain) had been performed in accordance with the procedure outlined earlier in this paper, 2 were left untreated, while 4 were given streptomycin and 4 isoniazid in the dosages already specified. Treatment was started in each case on the day of infection. After two weeks, both the control animals bore incipient corneal lesions. These advanced steadily so that, by seventeen weeks, bilateral panophthalmitis was to be seen. The animals were accordingly sacrificed and at post-mortem examination generalised tuberculosis was found. Involvement of the lungs was gross and, indeed, in one of these rabbits radiographic evidence of pulmonary tuberculosis had been obtained five weeks previously. These findings conform to those of Gardiner et al. (1949).

By contrast, in those rabbits receiving streptomycin the onset of the lesions was delayed until almost four weeks had elapsed and, subsequently, the advance of the disease, though steady, was by no means as rapid as in the controls. Withholding treatment after eight weeks was not attended by any dramatic change.

In the rabbits given isoniazid, on the other hand, the disease was completely suppressed throughout, all corneæ remaining clear, not only during the eight weeks of treatment but even afterwards as well. The total period of observation extended over eighteen weeks. (One animal in this group was found dead a week after the experiment began. At necropsy the lungs were collapsed and hæmorrhagic, and there was some sign of hæmorrhagic colitis.)

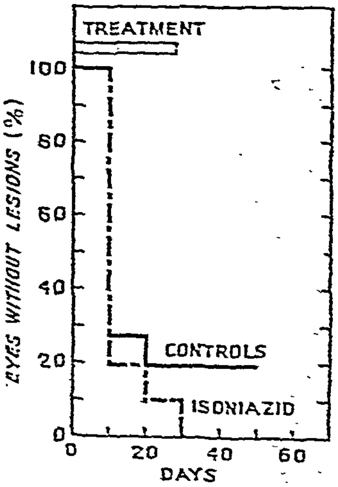

Fig. 5—The effect of using an isoniazid-resistant strain of *Myco. tuberculosis* H37Rv for inoculation of mice: the incidence of experimental corneal tuberculosis was virtually the same in both treated and untreated groups.

The distinct difference in the progress of the infection in the three groups is shown graphically in fig. 10.

Established lesions.—16 rabbits, with established corneal lesions of moderate severity from inoculation with *Myco. tuberculosis* (bovine strain) six weeks previously, were divided into three comparable groups, one being

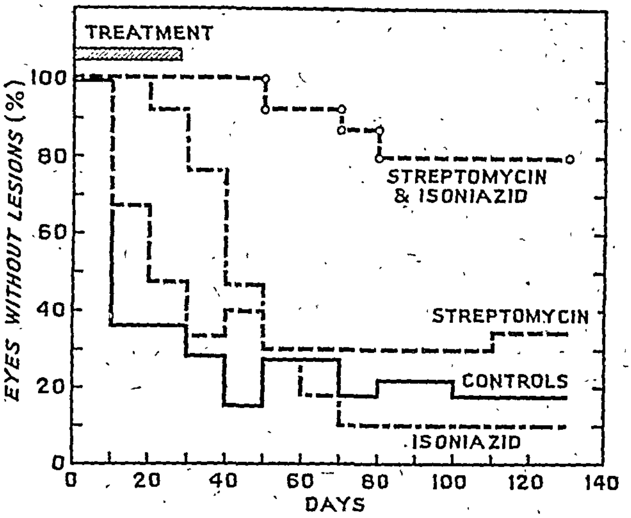

Fig. 6—Comparison of the effects of isoniazid, streptomycin, and a combination of the two in protecting mice from experimental corneal tuberculosis.

treated with streptomycin, the second with isoniazid, and the third with the two drugs together. Almost at once the lesions began to resolve and, after eight weeks of therapy, very little active disease could be seen on inspection. The corneæ were by no means clear, of course, for residual scarring remained prominent. Treatment was therefore stopped and in none of the animals was there any recrudescence in consequence. Moreover, the radiographs of the chests of these rabbits remained apparently clear.

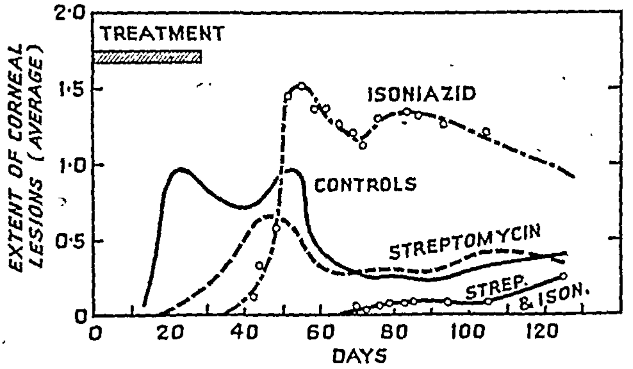

Fig. 7—Comparison of the effects of isoniazid, streptomycin, and a combination of the two on the development of experimental corneal tubercles.

Between the three methods of treatment no significant difference in response could be discerned at any stage (see fig. 11).

DISCUSSION

From these results it appears that, in mice, isoniazid by mouth in doses of the order of 12 mg. per kg. body-weight controls experimentally induced corneal tuberculosis, at least so long as treatment is continued. Once treatment ceases, however, the infection is no longer restrained. The breakdown which ensues in the corneæ is more pronounced with the bovine than with the human strain of *Myco. tuberculosis*—a distinction that is in line with their relative sensitivities to isoniazid in vitro. Such behaviour suggests that this drug is essentially bacteriostatic rather than bactericidal. Furthermore, under the conditions of these experiments, its efficacy, at least during the period of administration, is greater than that of streptomycin, though the eventual restraint imposed on the infection may be rather less. In fact, the pattern of reactions with isoniazid tends to follow that with the thiosemicarbazones tested by the same technique (Rees and Robson 1951).

The fact that resistant strains do exist is once again of sinister import, for it is clear that against these isoniazid can have little success either in vitro or in vivo. Attention has been drawn to this aspect repeatedly since isoniazid was introduced as a chemotherapeutic agent. What then becomes most important in this context is the rapidity and frequency with which such organisms may arise in clinical practice. In the report of the Medical Research Council (1952) trial it is stated that, among a sample of isoniazid-treated patients, " after one month some 10% were resistant; after two months 50%; after three months 70%." Furthermore, " those who developed drug resistance fared, as a group, less well than the others " in the matter of clinical improvement. Again, in the trial by Joiner et al. (1952) those patients receiving isoniazid alone, after benefiting almost dramatically at the start, deteriorated after eight to ten weeks; and this regression, too, was associated with the emergence of isoniazid resistance.

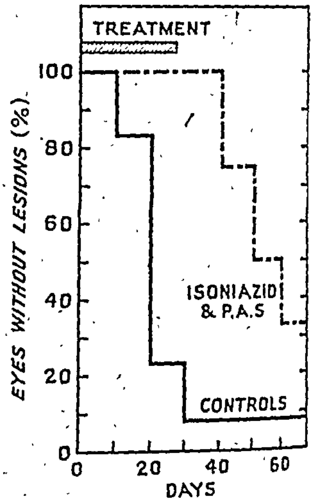

Fig. 8—The effect of isoniazid and P.A.S. in protecting mice from experimental corneal tuberculosis (bovine strain).

Data furnished by Knox et al. (1952) on the stability of the sensitivity end-point for human tubercle organisms grown in media containing isoniazid together with streptomycin or P.A.S. " suggest " that, in such circumstances, the development of resistance may be delayed. Moreover, a leading article in THE LANCET (1952) cited experiments in which a combination of streptomycin with isoniazid had delayed or averted bacterial resistance to both drugs in vitro. The suggestion was then made that " the effect of this combination in vivo should be investigated as quickly as possible," especially as large numbers of patients are already being subjected to such combined therapy. The way in which experimental corneal infections have reacted to combinations of isoniazid with other accepted antituberculous drugs may therefore be specially informative. With a streptomycin-P.A.S. régime there was complete inhibition of corneal tuberculosis in mice during the twenty-eight days of treatment; but within another twelve days all but 3 of 10 animals bore typical lesions (Rees and Robson 1951). When thiosemicarbazone (0·085% in the diet) was given along with streptomycin, the animals were not merely protected

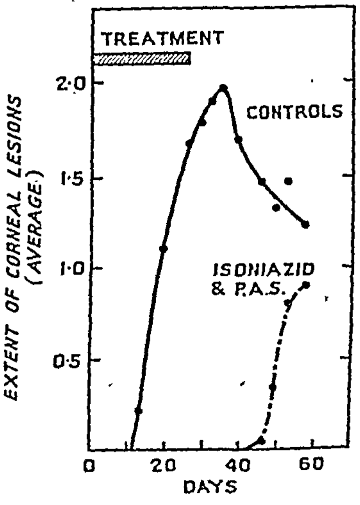

Fig. 9—Comparison of the development of experimental corneal tubercles (H37Rv) in untreated mice and in mice treated with isoniazid and P.A.S.

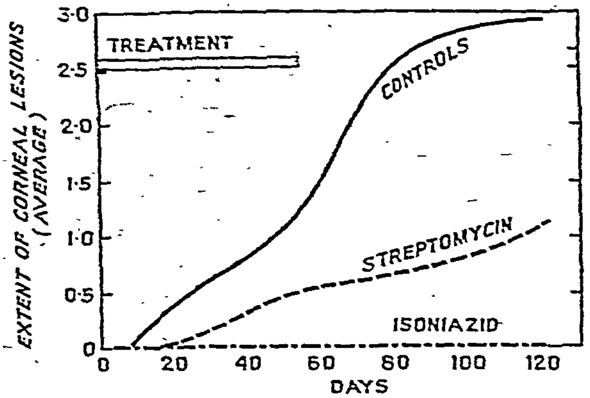

Fig. 10—Comparison of the development of corneal tubercles (bovine strain) in untreated rabbits and in rabbits treated with streptomycin and with isoniazid.

for the twenty-eight days when the two drugs were exhibited, but later, only 3 out of the 10 developed lesions during 128 days' observation. In the present series isoniazid and streptomycin gave results that were somewhat better than those with streptomycin and P.A.S., and more akin to those with streptomycin and thiosemicarbazone. Against this, isoniazid and P.A.S. together proved hardly more effective than the former drug alone.

If this technique does in fact afford some indication of the manner in which the various combinations may behave in the treatment of tuberculous patients, then the use of isoniazid in conjunction with streptomycin should be most promising—a possibility which has been at least provisionally confirmed by the results in the clinical trial now described by Joiner et al. (1952) and also the interim remarks in the report of the Medical Research Council (1952). Whether a similar combination of isoniazid and P.A.S. would prove as satisfactory in practice is, on the showing of our laboratory experiments, somewhat unlikely.

Finally, in rabbits, isoniazid showed itself more strongly antituberculous than streptomycin when used in the "umbrella" type of experiment; perhaps significantly, it so ablated the disease that there was no recrudescence after the drug was withdrawn. In this instance, therefore, it may well have behaved as a bactericide and not just as a bacteriostatic agent as on other occasions. This striking species difference between the rabbit and the mouse is difficult to explain. Normally, with corneal tuberculosis, the mouse exhibits the higher natural resistance. Yet, under the influence of isoniazid the rabbits in these experiments were completely protected. Perhaps the answer lies in the effect of temperature, to which Knox et al. (1952) have drawn particular attention. Though, as yet, corneal temperatures in the two species have not been accurately determined, nevertheless their body-temperatures, recorded rectally, show a striking difference: the average figure in the mouse is 34·3°C, and in the rabbit 38·3°C. It is interesting at this stage to speculate whether the startling responses to isoniazid by pyrexial patients can be attributed to an enhanced action of the drug where the higher temperature prevails.

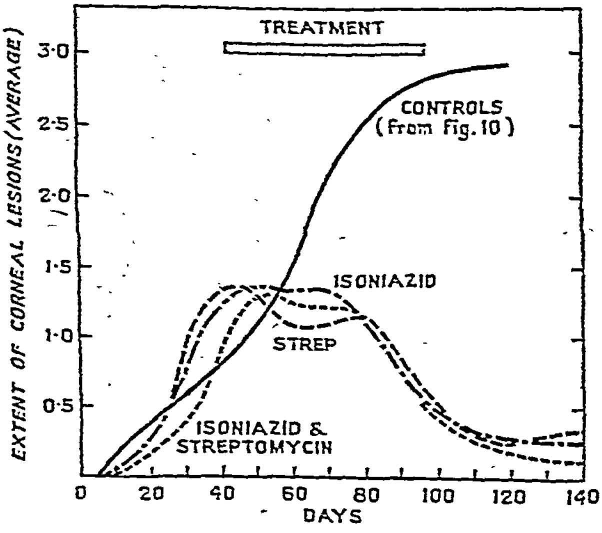

Fig. 11—The response of established corneal lesions to streptomycin, isoniazid, and a combination of the two. The control curve has been taken from fig. 10.

Against established lesions isoniazid alone by injection seemed just as potent as streptomycin or a combination of these two drugs. The prompt, uniform, and persistent response to all three modes of treatment in this experiment is in fact, surprising. That it was no more than a spontaneous regression might have been accepted had not previous and contemporary experience with controls shown that, in rabbits, experimentally induced tuberculosis of the cornea proceeds along a relentless course, so that in the end the animal is systemically afflicted.

SUMMARY

Methods are described for inducing experimental corneal tuberculosis in mice and rabbits and an account is given of the normal course of the disease in the two species.

The way in which such disease is modified by treatment reflects the antituberculous properties of the drugs employed, there being a parallel in this respect between experimental findings and clinical experience.

In mice, isoniazid alone had a suppressive effect on the tuberculous infection only while it was administered. Combined with P.A.S. it was very little more effective. When, however, the isoniazid was given along with streptomycin, the control of the disease, though not quite complete, was much more distinct.

In rabbits, isoniazid alone had a greater suppressive action than streptomycin. The difference between the two species is discussed and a possible explanation offered.

In vivo studies with isoniazid-resistant organisms are also reported.

We are grateful to the W. H. Ross Foundation (Scotland) for the Prevention of Blindness for further help in this research: to Mr. D. E. Seymour, of Herts Pharmaceuticals Ltd., for the supply of isoniazid used in these investigations; to Mr. R. W. Stanford, M.A., and Dr. John Vance, of the physics department, Guy's Hospital Medical School, who generously collaborated in the radiography of the rabbits; to Mr. P. A. Gardiner, who kindly examined the eyes in some of the rabbit experiments; and to Mr. P. Redgrave, who helped in the preparation of the figures reproduced in this article.

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IN-VITRO ACTION OF ISONIAZID ON MYCOBACTERIUM TUBERCULOSIS

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THE first reports about isoniazid and related substances (Fox 1951, Grunberg and Schnitzer 1952, Robitzek et al. 1952) made it clear that, whatever might be the final judgment on the value of these drugs in the treatment of tuberculosis, their highly effective and remarkably specific action on the tubercle bacillus demanded immediate study. Investigations of their in-vitro action were started at once in this laboratory, and this paper gives an outline of the experimental results obtained. Some of these merely confirm work already published, but we wish to emphasise a number of other observations which do not seem to have been recorded so far.

MATERIALS AND METHODS

Media.—For these investigations the fluid medium used was that described by Dubos and Middlebrook (1947) and was supplied by the Southern Group Laboratory, Lewisham. The basic medium containing 'Tween 80' was supplied in 100 ml. amounts, and 5% bovine albumin in 10 ml. amounts. Bovine albumin from several bottles was pooled and resterilised by filtration through a Seitz E.K. filter. For use, 4 ml. of this was added to each 100 ml. of Dubos base. Tube titrations were carried out in racks of 6 × $^5/_8$ in. tubes plugged with cotton-wool and containing 4 ml. of the complete Dubos medium. Serial dilutions of the drugs (tenfold, fivefold, or doubling) were made in these tubes. For experiments that would last several weeks, the medium was stored in screw-capped containers to prevent evaporation.

Cultures.—Cultures of the H37RV strain of the human tubercle bacillus were grown at 37°C, usually for ten days, in screw-capped bottles containing 10 ml. of Dubos medium. One drop from such a culture was added from a Pasteur pipette to each tube of [illegible] um and to a control tube containing [illegible]

Stock solutions of isoniazid and streptomycin.—These drugs were made up in distilled water in a concentration of 1000 µg. per ml. The isoniazid solution was Seitz-filtered, but the streptomycin solution was made up and dispensed under sterile conditions; the two solutions were kept in 10 ml. amounts in screw-capped universal containers at 4°C. The preparation of isoniazid used in the bulk of this work was 'Pycazide,' supplied by Herts Pharmaceuticals Ltd., who report that it is 99·63% pure according to the method Haugas and Mitchell (1952).

EXPERIMENTAL RESULTS

Measurement of In-vitro Activity of Isoniazid

Specificity of action.—Table I shows the effect of isoniazid in liquid media on human and bovine tubercle bacilli, other mycobacteria, and a number of other common micro-organisms. These results confirm the American observation that isoniazid has a highly potent and specific action on mycobacteria and especially on *Mycobacterium tuberculosis* (Pansy et al. 1952). A number of related substances have been tested for their action in vitro against mycobacteria, and they will be dealt with in a later paper.

Length of incubation.—In measuring the action of a drug on a slow-growing organism like *Myco. tuberculosis* obvious difficulties arise from the long incubation necessary before results can be read. Table II shows that at 37°C in Dubos liquid medium the end-point—i.e., the apparent sensitivity of *Myco. tuberculosis* to isoniazid—depended on the period of incubation. After incubation for from five to seven days (when growth could first be reliably recorded) the end-point was 0·01 to 0·002 µg. per ml. After longer periods of incubation the end-point progressively shifted until, after thirty-four days' incubation, growth occurred in the tube originally containing 1·6 µg. per ml. With streptomycin, on the other hand, the end-point was much more stable, and there was nothing like the same shift after prolonged incubation (see table II).

TABLE I—SENSITIVITY OF VARIOUS MICRO-ORGANISMS TO ISONIAZID

Micro-organism	Sensitivity (µg. per ml.)	Micro-organism	Sensitivity (µg. per ml.)
[illegible]	0·0128		
[illegible]	0·064		
[illegible]	1·6		
Myco. phlei	8·0	*Shigella flexneri*	> 1000
		Shigella sonnei	
Salmonella typhi	1000	*Bact. alkaligenes*	
S. typhimurium	1000	*Bact. coli*	
S. paratyphi A	1000	*Proteus vulgaris*	
S. paratyphi B	1000	*Ps. pyocyanea*	
Bact. aerogenes	1000	*Staph. pyogenes*	
Bact. friedländer	1000	*Strep. pyogenes*	
Proteus mirabilis	1000		
Proteus OX 19	1000		
Monilia albicans	1000		

TABLE II—SENSITIVITY OF H37RV TO ISONIAZID AND STREPTOMYCIN

Isoniazid

Days at 37°C	Concentration (µg. per ml.)										Control
	200	40	8	1·6	0·32	0·064	0·0128	0·002	0·0005	0·0001	
5–7	0	0	0	0	0	0	0	+	+	+	+
14	0	0	0	0	0	0	0	+	+	+	+
27	0	0	0	0	0	±	+	+ +	+ +	+ +	+ +
34	0	0	0	+	+	+ +	+ +	+ + +	+ + +	+ + +	+ + +

Streptomycin

Days at 37°C	Concentration (µg. per ml.)										Control
	200	40	8	1·6	0·32	0·064	0·0128	0·002	0·0005	0·0001	
5–7	0	0	0	0	+	+	+	+	+	+	+
14	0	0	0	0	+ +	+ +	+ +	+ +	+ +	+ +	+ +
27	0	0	0	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +
34	0	0	0	+ +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +

0 = absence of growth. + signs indicate approximate amounts of growth.

TABLE III—SENSITIVITY OF H37RV TO ISONIAZID AT DIFFERENT TEMPERATURES

Temperature of incubation °C	Weeks of incubation	Concentration of isoniazid (µg. per ml.)										Control
		200	40	8	1·6	0·32	0·064	0·0128	0·002	0·0005	0·0001	
35	1	0	0	0	0	0	0	0	0	0	0	+
	2	0	0	0	0	0	0	0	0	0	+	++
	3	0	0	0	0	0	0	0	+	+	++	++
	4	0	0	0	0	0	+	++	++	++	++	++
37	1	0	0	0	0	0	0	0	+	+	+	±±
	2	0	0	0	0	0	0	0	++	++	++	++
	3	0	0	0	0	0	++	++	++	++	++	++
	4	0	0	0	0	+	++	++	++	++	++	++
40	1	0	0	0	0	0	0	0	tr.	tr.	tr.	+
	2	0	0	0	0	0	0	0	++	++	++	++
	3	0	0	0	0	0	0	0	++	++	++	++
	4	0	0	0	0	0	0	0	++	++	++	++

This shift in the end-point with isoniazid has been found consistently with cultures of *Myco. tuberculosis* whenever it has been looked for by prolonging the period of incubation. It has occurred not only with H37RV but also with strains freshly isolated from patients. In performing routine sensitivity tests on such strains it is therefore clearly necessary to use standard conditions of incubation, and we have found it most convenient in practice to read our results after an incubation period of fourteen days.

Inoculum size.—We have not investigated the effect of this very closely, but it appears that the sensitivity of *Myco. tuberculosis* to isoniazid is more dependent on inoculum size than is its sensitivity to streptomycin. In one experiment a seven-day-old culture of H37RV was used, both undiluted and diluted 1 in 10 with Dubos medium, to inoculate two rows of tubes containing fivefold dilutions of isoniazid. After fourteen days' incubation at 37°C the dilute inoculum appeared to be 25 times more sensitive than the heavy inoculum. When the same cultures were tested with streptomycin, no such difference was observed between the two inocula.

Temperature of incubation.—The sensitivity to isoniazid was tested in water baths at 35°, 37°, and 40°C, and in the incubator at 37°C. In the incubator and in the water bath at 37°C the sensitivity of *Myco. tuberculosis* was found, as before, to lie between 0·01 and 0·002 *µg.* per ml. At 35°C, however, the organisms seemed to be more sensitive, and after fourteen days' incubation growth was inhibited by as little as 0·0005 µg. per ml. At 40°C the sensitivity after fourteen days' incubation was the same as at 37°C—i.e., growth was inhibited in 0·01 µg. per ml. On further incubation the shift in the end-point described above took place at 35°C and at 37°C, *but not at 40°C* (see table III).

Effect of albumin.—It is known that the activity of many substances against *Myco. tuberculosis* can be affected by the presence or absence of albumin (Youmans and Youmans 1948). Steenken and Wolinsky (1952) found that the addition of serum somewhat increased the sensitivity of cultures of *Myco. tuberculosis* H37RV to isoniazid. In our experiments using fivefold dilutions, we have usually found no significant difference in sensitivity with or without albumin. This is in marked contrast to our results with *p*-aminosalicylic acid (P.A.S.).

Effect of Streptomycin and P.A.S. on Sensitivity to Isoniazid

Streptomycin.—In a number of experiments various combinations of isoniazid and streptomycin were tested for their effect on the growth of H37RV. It was found that the shift in the end-point which was observed with isoniazid alone did not occur to anything like the same extent in the presence of concentrations of streptomycin which by themselves were not inhibitory. Part of one such experiment is illustrated in table IV.

P.A.S.—In the absence of albumin, P.A.S. strongly inhibited the growth of *Myco. tuberculosis,* either alone or in the presence of isoniazid; but, in the presence of albumin, P.A.S. alone was relatively inefficient, for it failed to suppress growth completely even in a concentration as high as 200 µg. per ml. and it gave no sharp end-point. It was interesting, therefore, to find that, in the presence of albumin, as little as 0·32 µg. per ml. of P.A.S. prevented, over a period of five weeks, the shift in the end-point to isoniazid which occurred in the same medium containing isoniazid alone (see table V).

Inactivation of Isoniazid in Uninoculated Media

We have found that in aqueous solution isoniazid withstands autoclaving at a pressure of 10 lb. per sq. in. for 10 minutes without apparent loss of activity (see table VI).

The stability of isoniazid in Dubos medium was studied by incubating solutions containing 4 µg. per ml. of isoniazid in distilled water and in Dubos medium under sterile conditions at 37°C for four weeks. At the start of this experiment and at the end of each week a sample of each isoniazid solution was tested for its drug content. Doubling dilutions in fresh Dubos medium were made, inoculated with a ten-day-old culture of H37RV, and incubated at 37° C for seven days. The highest dilution of the drug in which growth was inhibited was then recorded. Table VI shows that in distilled water the highest dilution producing inhibition of the test organism remained constant, even though the drug had been incubated for varying periods before the assay. In Dubos medium, on the other hand, the inhibitory dilution altered with each subsequent assay. As the test organism used for each weekly assay was of known and

TABLE IV—THE EFFECT OF STREPTOMYCIN ON THE SENSITIVITY OF H37RV TO ISONIAZID

Isoniazid in the presence of streptomycin 0·05 µg. per ml.

Weeks at 37°C	Concentration of isoniazid (µg. per ml.)										Control
	8	1·6	0·8	0·4	0·2	0·1	0·05	0·025	0·012	0·006	
1	0	0	0	0	0	0	0	0	0	0	+
2	0	0	0	0	0	0	0	0	tr.	++	++
3	0	0	0	0	0	0	0	0	++	++	++
4	0	0	0	0	0	0	0	tr.	++	++	++
5	0	0	0	0	0	0	0	++	++	++	++

Isoniazid alone

Weeks at 37°C	Concentration of isoniazid (µg. per ml.)										Control
	8	1·6	0·8	0·4	0·2	0·1	0·05	0·025	0·012	0·006	
1	0	0	0	0	0	0	0	0	0	0	+
2	0	0	0	0	0	0	0	0	++	++	++
3	0	0	0	0	0	0	tr.	++	++	++	++
4	0	0	0	0	0	0	++	++	++	++	++
5	0	0	0	0	±	++	++	++	++	++	++

In the streptomycin control in this experiment, the inhibitory concentration was found to be 0·1 µg. per ml.

TABLE V—THE EFFECT OF P.A.S. ON THE SENSITIVITY OF H37RV TO ISONIAZID (IN THE PRESENCE OF BOVINE ALBUMIN)

Isoniazid in the presence of P.A.S. 0·32 µg. per ml.

Weeks at 37°C	Concentration of isoniazid (µg. per ml.)						Control
	10	1	0·1	0·01	0·001	0·0001	
1	0	0	0	±	+	+	+
2	0	0	0	±	+ +	+ +	+ +
3	0	0	0	±	+ +	+ +	+ +
4	0	0	0	+	+ +	+ +	+ +
5	0	0	0	+ +	+ +	+ +	+ +

Isoniazid alone

Weeks at 37°C	Concentration of isoniazid (µg. per ml.)						Control
	10	1	0·1	0·01	0·001	0·0001	
1	0	0	0	+	+	+	+
2	0	0	0	+ +	+ +	+ +	+ +
3	0	0	0	+ +	+ +	+ +	+ +
4	0	0	+ +	+ +	+ +	+ +	+ +
5	0	+ +	+ +	+ +	+ +	+ +	+ +

In the P.A.S. control, some inhibition of growth occurred in 40 µg. per ml. (see text).

constant sensitivity, any apparent loss of sensitivity of that organism each week was clearly due to progressive decay in the activity of the drug resulting from previous incubation in the uninoculated medium. In table VI the drug content at the end of the first assay is given as 100%, but it is clear that even during the period of this and later assays inactivation of the drug must take place.

Further experiments are being done to determine the constituents responsible for this inactivation of the drug in uninoculated media. The following facts can be mentioned at this stage:

(1) Inactivation in uninoculated media increased as the temperature was raised from 32° to 42°C (see table VII).

(2) The inactivation of the drug in uninoculated media was not prevented by the addition of streptomycin.

Development of Resistance to Isoniazid in H37Rv

The experiments that have been described show that inactivation of the drug undoubtedly does occur in the absence of any organisms. Although this accounts for part of the shift in the end-point on prolonged incubation of inoculated media, it does not account for all of it. When this shift in the end-point was first noticed, it was thought to be due entirely to the presence in the bacterial population of large numbers of isoniazid-resistant strains which were being selected in the higher concentrations of the drug. An attempt was made to breed out these isoniazid-resistant strains to test: (1) the ease with which they could be produced; (2) their permanence; and (3) their resistance to streptomycin.

Production of resistant strains.—As described in a preliminary communication (Goulding, King, Knox, and Robson 1952), a culture of the H37RV strain was inoculated into a series of tubes of Dubos liquid medium, containing falling dilutions of isoniazid. During the first two weeks of incubation, growth was inhibited by a level of 0·01 µg. per ml., but after twenty-five days there was profuse growth in the tube which had contained initially 1·6 µg. per ml. From this tube one drop of culture was inoculated into a fresh set of drug dilutions in Dubos medium. In this series, the organisms grew within a week in dilutions up to 0·32 µg. per ml. and then to 1·6 µg. per ml. When further subculture was made from this tube into a fresh set of dilutions, growth was rapid in concentrations of isoniazid as high as 25 µg. per ml. Finally, on subculture from this tube after only ten days' incubation in fresh Dubos medium containing isoniazid, good growth occurred after only seven days' incubation in 62·5 µg. per ml. of the drug. The organisms therefore were now about 6000 times more resistant than in the original culture. This strain was subcultured into drug-free medium and retested for its sensitivity to isoniazid; this was found to lie between 8 and 40 µg. per ml. In similar experiments we obtained, from the original culture of H37RV, cultures which grew in 31·25 µg. per ml., but which failed to grow in 62·5 µg. per ml. of isoniazid. On more than one occasion we have observed lysis of the growth in tubes containing these high concentrations of isoniazid, but this has appeared irregularly.

TABLE VI—DESTRUCTION OF ISONIAZID IN UNINOCULATED MEDIA AT 37°C

Weeks of incubation at 37°C before assay	Medium			
	Distilled water		Dubos medium	
	Highest dilution inhibiting growth (µg. per ml.)	Drug remaining (%)	Highest dilution inhibiting growth (µg. per ml.)	Drug remaining (%)
1	0·015	100	0·015	100
2	0·015	100	0·031	50
3	0·015	100	0·062	25
4	0·015	100	0·125	12·5

Initial concentration of isoniazid in each medium: 4 µg. per ml. (see text).

We have found it possible to isolate isoniazid-resistant strains more easily than streptomycin-resistant strains, though the degree of resistance finally obtained with streptomycin has been greater than with isoniazid. In the case of streptomycin we have been able to obtain a strain resistant to 4000 µg. per ml., whereas the highest degree of resistance that we have so far obtained with isoniazid has been of the order of 62·5–125 µg. per ml.

TABLE VII—DESTRUCTION OF ISONIAZID AT DIFFERENT TEMPERATURES IN UNINOCULATED MEDIUM

Weeks of incubation at each temperature before assay	Temperature of incubation					
	32°C		37°C		42°C	
	Highest dilution inhibiting growth (µg. per ml.)	Drug remaining (%)	Highest dilution inhibiting growth (µg. per ml.)	Drug remaining (%)	Highest dilution inhibiting growth (µg. per ml.)	Drug remaining (%)
1	0·031	100	0·031	100	0·031	100
2	0·031	100	0·062	50	0·250	12·5
3	0·125	25	0·250	12·5	0·5	6·2
4	0·250	12·5	0·50	6·2	2·0	1·5

Initial concentration of drug at each temperature: 4 µg. per ml. (see text).

Permanence of resistance.—The isoniazid resistant strain obtained by the method described above was subcultured into drug-free medium at regular intervals of fourteen days, and at each subculture its sensitivity was retested. After the sixth transfer, the isoniazid sensitivity was unchanged, and lay between 8 and 40 µg. per ml.

Development of Resistance to Isoniazid in Freshly Isolated Strains

We have also investigated the development of resistance to isoniazid in strains freshly isolated from patients. The development of resistance in patients has already been reported by several workers (Steenken et al. 1952, Goulding, King, Knox, and Robson 1952), and is now described briefly by Joiner et al. (1952). We have also found that sensitive strains freshly isolated from patients can be trained in vitro to become resistant in the same way as can the H37RV strain.

DISCUSSION

Our results fully confirm the American reports that soniazid has a powerful inhibitory effect on the tubercle acillus. The drug initially inhibits the growth both f the H37Rv strain of tubercle bacillus and of strains reshly isolated from patients in very low concentrations about 0·01 µg. per ml. or less). Its activity against the ubercle bacillus is of at least the same order as that of enicillin against the Oxford staphylococcus. With a nolecular weight of 137, it is initially about 8–10 times nore efficient against the tubercle bacillus than streptomycin (molecular weight 579) when compared in equivalent molecular concentrations, and 30–40 times more fficient when compared on a weight-for-weight basis.

Its low molecular weight, its ready solubility in water, ts low toxicity, and the ease with which it is absorbed by mouth are all properties highly desirable in a drug. But its most remarkable property is its specificity. So far as is known it acts almost uniquely against mycobacteria; and within the mycobacteria its efficiency is greatest against the pathogenic members, especially the human tubercle bacillus.

For these reasons, then, quite apart from the hopes that it raises of widening the limited field in the chemotherapy of tuberculosis, the drug offers intriguing problems to both clinician and microbiologist. It became obvious at once that its success in the treatment of the disease would hinge on the ease with which resistant strains developed in patients receiving the drug. It is now well known that resistant strains develop rather rapidly in laboratory cultures (Middlebrook 1952, Hobby and Lenert 1952, Knox, Maclean, and Robson 1952) and in patients (Steenken et al. 1952, Goulding et al. 1952).

In this connection the phenomenon of the shift in the end-point and the "escape" from the effects of the drug shown in vitro by cultures of *Myco. tuberculosis* would seem to be of some importance. Some shift in the end-point has been mentioned by Hobby and Lenert (1952) and Aitoff (1952); but its possible extent and importance do not seem to have been appreciated. We know that two processes may be involved in this phenomenon: (1) a steady inactivation of the drug, occurring in uninoculated media during prolonged incubation (table II); and (2) the development of resistant variants, which can be obtained without much difficulty by appropriate methods of subculture. If the first process alone were to account for the shift in the end-point we should have to suppose that the drug was bacteriostatic and not bactericidal, that the inoculated organisms lay dormant but alive until such time as the drug concentration fell below the critical level, and that the organisms which finally grew out consisted of the original inoculum of sensitive cells. On the other hand, the second process could account for the phenomenon if nearly all the cells in the original inoculum were killed and if the growth which finally occurred were due to the multiplication of a small number of highly resistant cells in the original inoculum. The truth almost certainly lies somewhere between these two extremes.

To decide whether a drug is bactericidal or bacteriostatic is not always easy (Klarmann 1950). To some extent, it is a matter of degree. An organism exposed to an inhibitory agent for long enough will die of inanition. If removed from the influence of the drug after only a short exposure the bacterial cell may recover and, in a suitable medium, start growing again; but after long exposure it may have suffered irreversible damage and so fail to multiply even in an optimal medium.

It is still too early to say much about the way in which isoniazid acts—whether its action is mainly bactericidal or bacteriostatic, with what frequency resistant variants develop, and how their development can be arrested or delayed in different conditions.

It has been stated that isoniazid in relatively high concentrations is bactericidal (Steenken and Wolinsky 1952, Middlebrook 1952). Since, however, the drug is effective against sensitive tubercle bacilli in very low concentrations there is always a risk that even in subculture sufficient drug may be carried over to exert a continued bacteriostatic effect. The difficulty of deciding how the drug acts is increased by the inactivation which we have shown to occur on incubation in Dubos media, by the fact that the only available method of estimating it in minute quantities is microbiological assay in a similar medium, and by the fact that we have not yet discovered a reliable way of inactivating the drug so as to remove organisms at will from its continual influence. These problems are now being investigated in this laboratory.

The effect of temperature is interesting. We have shown that in uninoculated medium the drug is inactivated on prolonged incubation, and that the speed of inactivation *increases* over the range of 32–42°C. On the other hand the shift in the end-point which we have described *decreases* as the temperature of incubation is raised—in inoculated media the sensitivity of *Myco. tuberculosis* remains unchanged on prolonged incubation at 40°C, in contrast to the unstable end-point which we have found at lower temperatures.

At 35°C the initial activity of the drug appears to be many times greater than at 37°C and 40°C, though on continued incubation the shift in the end-point is even greater at 35°C than at 37°C. This is interesting in view of the claim by Eseltine and Rahn (1949) to have shown that the bacteriostatic action of some drugs is greatly *increased* at low temperatures whereas bactericidal action is more effective at higher temperatures.

Something of this kind may occur with isoniazid. Our experiments suggest that at 35°–37°C the drug is predominantly bacteriostatic, but that increase in temperature profoundly modifies its action either by making it more bactericidal or by suppressing the mechanism whereby resistant organisms become selected.

We have recently discussed the effect of heat in suppressing certain adaptive processes—e.g., penicillinase formation—which may be essential for the survival or growth of the bacterial cell, and we have suggested that quite small changes of temperature may be important in vivo as well as in vitro (Knox and Collard 1952). If isoniazid is more bactericidal at temperatures above 37°C, this would help to explain why it is the toxic pyrexial patient who responds most dramatically to the drug (Robitzek et al. 1952), and perhaps why experimental tuberculosis of the cornea (Goulding and Robson 1952) is more efficiently controlled by isoniazid in the rabbit (with a body-temperature of about 38°C) than in the mouse (with a body-temperature 4° lower). The remarkable influence of temperature on the action of isoniazid on the tubercle bacillus would seem to be an interesting field for further investigation.

The remarkable effectiveness of streptomycin or P.A.S. in preventing the shift in the sensitivity of H37Rv to isoniazid suggests that the combination of either of these substances with isoniazid may prove more effective than isoniazid by itself in the treatment of tuberculosis. How subinhibitory amounts of streptomycin act with isoniazid in preventing the shift in the end-point is being investigated further. We have found that isoniazid continues to be destroyed in Dubos medium in the presence of streptomycin. Thus the combination must act either by preventing isoniazid-resistant mutants from appearing in the culture or by turning a bacteriostatic action of isoniazid into a bactericidal effect. It looks, therefore, as though the combination acts in the same kind of way as raising the temperature of incubation.

These results together with the experimental and clinical results published in accompanying papers

(Goulding and Robson 1952, Joiner et al. 1952) indicate that, whereas isoniazid is likely to be of limited value by itself, in combination with other substances it represents an outstanding advance in the chemotherapy of tuberculosis. The remarkable specificity of its action should provide a valuable clue to the metabolism of the tubercle bacillus and in the search for other compounds with similar or even greater activity to which resistance develops less readily.

SUMMARY

These studies confirm the American statement that isoniazid has a powerful and specific inhibitory effect on *Myco. tuberculosis*. In Dubos liquid medium the growth of *Myco. tuberculosis* H37RV and of many strains freshly isolated from patients was inhibited initially by as little as 0·01 µg. per ml.

The "sensitivity," must, however, be read after a standard period of incubation, such as fourteen days, since with continued incubation the end-point shifts. This is due to two processes: (1) inactivation of the drug, which occurs even in uninoculated Dubos medium at 37°C, though in distilled water the drug is stable at that temperature and withstands autoclaving; and (2) the emergence of resistant organisms.

The speed of inactivation of isoniazid in uninoculated Dubos medium varies directly with the temperature of incubation. On the other hand, the shift in the end-point in inoculated media at 35°C and at 37°C is almost completely suppressed at 40°C.

Streptomycin or P.A.S. has the same effect as increase of temperature in delaying the shift in the end-point; yet streptomycin does not prevent the inactivation of isoniazid in uninoculated Dubos medium. It seems likely that both increase of temperature and drugs such as streptomycin or P.A.S. convert a predominantly bacteriostatic action of isoniazid into a more nearly bactericidal action.

Isoniazid-resistant strains have been isolated in vitro without difficulty, though the degree of resistance is not so great as that obtained eventually with streptomycin. Isoniazid-resistant strains retained their original sensitivity to streptomycin, and vice versa. Isoniazid resistance was found to be retained after six subcultures in drug-free medium.

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TITRATION OF STRAINS OF TUBERCLE BACILLI AGAINST ISONIAZID

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THE widespread use of isoniazid (isonicotinic acid hydrazide) in the chemotherapy of tuberculosis has presented various problems to the laboratory worker. The most important aspect is likely to be the estimation of the sensitivity of strains of *Mycobacterium tuberculosis* to the drug. The purpose of this paper is to describe certain conditions which may influence any test which is employed, and in particular the effect of variations in the composition and pH of the medium, the stability to heat of the drug, the influence of the size of the inoculum, and the occurrence of resistance to streptomycin or *p*-aminosalicylic acid (P.A.S.) resistance in the strains being tested.

METHODS

Strains of Myco. tuberculosis

The virulent human strain H37RV was used for most of the work. It was obtained in 1947 from the Depot of Standard Cultures of Tubercle Bacilli, Saranac Lake, U.S.A., and was maintained for two years on Proskauer and Beck's synthetic medium and, since then, on Löwenstein-Jensen medium. Several recently isolated strains of tubercle bacilli were also employed.

Media

The following media were used: (1) a modified Dubos and Davis liquid medium containing 'Tween 80' and bovine albumin (Medical Research Council 1948), referred to as Dubos medium; (2) the same medium without the addition of Tween 80; (3) Dubos oleic-acid albumin solid medium (Dubos and Middlebrook, 1947); (4) Herrold's (1931) egg agar medium; and (5) Löwenstein-Jensen medium.

Isoniazid

This was supplied as 'Nydrazid' by Messrs. E. R. Squibb & Sons, London. A stock 1% solution was sterilised by filtration through a Berkfeld candle and was stored at 4°C.

Sensitivity Tests to Streptomycin and P.A.S.

Streptomycin sensitivity was determined by the Medical Research Council (1948) technique, and P.A.S. sensitivity by a similar method in which the inoculum was ten times smaller. The results are expressed relative to those obtained with H37RV, which was usually inhibited by 0·5 or 0·25 µg. per ml. both of streptomycin and of P.A.S.

TABLE I—SENSITIVITY TO STREPTOMYCIN AND P.A.S. OF STRAINS TESTED FOR SENSITIVITY TO ISONIAZID IN DUBOS MEDIUM

Strain	Number of times less sensitive than H37RV	
	Streptomycin	P.A.S.
H37RV	1	1*
1	1	1*
2	1	1
3	8	1
4	8	1
5	64	1
6	128	1*
7	> 8000	1*
8	1	128*
9	4	128*
10	32	256

* Strains also tested in Dubos medium without Tween 80, Herrold's medium, and Dubos oleic-acid albumin agar medium.

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* In receipt of a grant from the Medical Research Council.

RESULTS

Sensitivity of Strains in Various Media and Effect of Duration of Incubation

Serial twofold dilutions of isoniazid were made with -ml. amounts of Dubos medium and of Dubos medium without Tween 80 in $^1/_4$-oz. screw-capped bottles. Similar dilutions in Dubos solid medium and in Herrold's medium were prepared in $^1/_2$-oz. bottles. To each bottle was added 0·02 ml. from a ten-day culture of six strains of tubercle bacilli. In addition a further five strains were tested in Dubos medium alone. The sensitivity of these strains to streptomycin and P.A.S. is shown in table I.

After ten days' incubation the strains were inhibited in Dubos medium by 0·012 or 0·025 µg. per ml. isoniazid. In Dubos medium without Tween 80 all strains were inhibited by 0·025 µg. per ml. On the solid media the highest drug concentration on which maximum growth occurred was 0·012 or 0·025 µg. per ml. although sparse growth usually occurred on the slope with the next highest concentration.

After fourteen to twenty-eight days, as incubation continued, growth began to appear in progressively higher concentrations of isoniazid up to 1·6 µg. per ml., but not in higher concentrations even after incubation for seventy days. On solid media only very scanty colonies developed on slopes containing between 0·2 and 1·6 µg. per ml. isoniazid.

TABLE II—EFFECT OF INOCULUM SIZE ON SENSITIVITY TO ISONIAZID TESTED ON LÖWENSTEIN-JENSEN MEDIUM

Dilution of inoculum suspension	Days of incubation	Concentration of isoniazid (µg. per ml.)					
		0	0·025	0·05	0·1	0·2	0·4 and over
Undiluted ..	10	+ +	+ +	+ +	0	0	0
	28	+ + +	+ + +	+ + +	+	0	0
	56	+ + +	+ + +	+ + +	+	5	0
1 : 10 ..	10	+	+	0	0	0	0
	28	+ +	+ +	+ +	0	0	0
	56	+ +	+ +	+ +	3	2	0
1 : 100 ..	10	0	0	0	0	0	0
	28	+	+	+	4	3	0
	56	+	+	+	7	3	0
1 : 1000 ..	10	0	0	0	0	0	0
	28	8	11	8	0	0	0
	56	8	11	8	0	0	0

+ + + to + = degrees of growth. The numerals under concentration indicate the numbers of colonies on the slopes. In each case the results after seventy days' incubation were identical with those at fifty-six days.

The addition of 1 µg. per ml. of either *p*-aminobenzoic acid or of nicotinamide to Dubos medium did not alter the sensitivity of H37RV to isoniazid.

Effect of Different Inoculum Sizes

Sets of bottles of Dubos medium containing twofold dilutions of isoniazid were inoculated with fivefold dilutions of an eight-day Dubos culture of H37RV. After ten days' incubation the minimal inhibitory concentration in bottles which had received 0·1 and 0·02 ml. was 0·05 µg. per ml., whereas it was 0·025 and 0·0125 µg. per ml. in those which had received 0·004 and 0·0008 ml. respectively. With further incubation, growth appeared more rapidly and in higher concentrations of the drug in bottles which had the larger inocula.

A series of slopes of Löwenstein-Jensen medium were prepared to which isoniazid had been added before a single period of about one hour's inspissation at 80°C. These were inoculated with a 3-mm. loopful of a suspension of H37RV prepared by grinding up growth from solid medium in distilled water. The suspension was of almost equal opacity to that of a ten-day Dubos culture. The results are shown in table II. Here again it will be noted that inoculum size had little effect on the inhibitory end-point.

TABLE III—EFFECT OF pH ON THE ACTIVITY OF ISONIAZID IN DUBOS MEDIUM

pH of medium	Minimal inhibitory concentration of isoniazid (µg. per ml.) after incubation for		
	9 days	14 days	21 days
5·0	0·06	0·025	0·025
5·5	0·025	0·025	0·025
6·0	0·025	0·025	0·05–0·1*
6·5	0·025	0·05	0·4–0·8*
7·0	0·025	0·05	0·1–0·4*
7·5	0·025–0·05*	0·05	0·4
8·0	0·025	0·05	0·1–0·4*

* Where two figures are given they are those obtained when the duplicate readings did not agree.

Effect of pH

The pH of batches of Dubos medium was adjusted by the addition of hydrochloric acid or sodium hydroxide so that the final pH, after addition of albumin, ranged from 5·0 to 8·0, as measured with a Muirhead pH meter. Each batch was then distributed in 3-ml. amounts and isoniazid added in a range of twofold serial dilutions. Every set of tubes was set up in duplicate. Each bottle was inoculated with 0·02 ml. of an eighteen-day Dubos culture of H37RV. The minimal inhibitory concentration of isoniazid after incubation for nine, fourteen, and twenty-one days is shown in table III. Alterations in pH clearly have little effect on activity, if one takes into account the slower growth of the strain at pH 5·0.

Heat Stability

Incubation at 37°C.—Sets of bottles containing a range of twofold serial dilutions of isoniazid in Dubos medium were prepared under identical conditions. One collection of sets was stored at 4°C and the other at 37°C. At intervals two sets of bottles were taken from each collection and inoculated with 0·02 ml. of a Dubos culture of H37RV. The minimal inhibitory concentration of isoniazid found after ten days incubation is shown in table IV. There was no evidence of destruction at 4°C; but there was a considerable loss of activity when tubes were stored at 37°C, only about 5% of the activity being present after six weeks.

Autoclaving and steaming.—Sets of tubes containing dilutions of isoniazid in Dubos medium without albumin were prepared under identical conditions. Pairs of sets were subjected to steaming for ten and thirty minutes and to autoclaving at 15 lb. per sq. in. for fifteen, thirty, and sixty minutes. A control pair of sets was untreated. Albumin and an inoculum of 0·02 ml. of a Dubos culture of H37RV were then added to all the tubes. The minimal inhibitory concentration of isoniazid found after twelve days' incubation was 0·05 µg. per ml. in each set. Growth was considerably heavier in tubes containing 0·025 µg. per ml. which had been autoclaved for thirty and sixty minutes than in those receiving the milder treatments. This suggests that there may have been a slight loss of activity after prolonged autoclaving.

TABLE IV—EFFECT OF INCUBATION AT 37°C ON THE ACTIVITY OF ISONIAZID IN DUBOS MEDIUM

Period of storage (days)	Minimal inhibitory concentration of isoniazid (µg. per ml.) after storage at	
	4° C	37° C
0	0·05	
7	0·05–0·1*	0·1–0·2*
21	0·05–0·1*	0·2–0·4*
42	0·1	1·6–3·2*

* Where two figures are given they are those obtained when the duplicate readings did not agree.

DISCUSSION

The degree of sensitivity of strains of *Myco. tuberculosis* and the lack of cross-resistance to streptomycin and P.A.S. agree well with the reports of Steenken and Wolinsky (1952) and of Pansy et al. (1952). The occurrence of growth in progressively higher concentrations of the drug with increasing periods of incubation can be explained by the presence of small numbers of resistant organisms in the original inoculum, since subcultures from tubes containing 0·4–1·6 µg. per ml. yielded strains which were less sensitive to the drug. The behaviour of these resistant strains will be discussed elsewhere. Similar findings have been reported by Pansy et al. (1952), Steenken and Wolinsky (1952), and Rist et al. (1952).

The rather small effect of changes in inoculum size resembles that found for streptomycin, but is different from that found with P.A.S. where sensitivity to the drug changes distinctly with changes in the size of the inoculum. The most pronounced effect of increasing the inoculum size was to increase the speed of appearance of resistant variants in tubes containing higher concentrations of the drug.

Alterations in pH have been shown to have little effect on the activity of isoniazid. This behaviour differs from that of streptomycin, whose activity is greatly diminished in acid media, and may be important in the treatment of tuberculosis since caseous material is often acid. Loss of activity found during incubation at 37°C has also been reported by Goulding et al. (1952). It is remarkable that there is so little loss due to heating at higher temperatures for up to an hour.

From these findings a few comments can be made on techniques for determining the sensitivity of tubercle bacilli from patients under treatment with isoniazid. It seems safe to incorporate the drug in Löwenstein-Jensen medium before inspissation. The activity will not be altered appreciably either by the heating or by alterations in the pH—a difficult factor to control in egg media. Since resistant strains obtained both in vitro and in vivo have been found to be unstable on culture in media free of isoniazid (Pansy et al. 1952, and personal observation) it would be wise to test their resistance as soon as possible after isolation. However the plating-out of sputum concentrates directly on medium containing a range of concentrations of isoniazid may be inadvisable for the following reasons:

1. The period of incubation before appearance of colonies is more variable on primary culture than on subculture. If this period is prolonged there might have been an appreciable loss of activity of the drug during incubation at 37°C.
2. An inoculum containing a small number of bacilli would yield an unreliable result, and a further test from the control tube would then have to be set up. It is at present doubtful whether such a result could be compared with the results of a direct test.

For those reasons the technique outlined by the Medical Research Council (1952) is recommended in which growth from the primary culture is inoculated directly on to Löwenstein-Jensen slopes containing a range of isoniazid contractions. The results of such tests, though not necessarily reflecting the true degree of resistance of the strains, would at least allow comparison of the results between tests and would minimise any loss of resistance during subculture.

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THE CORRECT PHYSIOLOGICAL BASIS ON WHICH TO COMPARE INFANT AND ADULT RENAL FUNCTION

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In order to compare certain aspects of renal function within the same species but in members of very different age and size, there has been a desire to find a method by which the absolute measurements may be reduced to some common basis. It was suggested by McIntosh, Möller, and van Slyke (1929) and by Holten (1931) that the comparisons should be made per unit of surface area, because in both young and old the weight of the kidney and the basal metabolic rate were proportional to this. It was found by these workers, moreover, and confirmed by others (Payne and Shukry 1934, Cullen et al. 1935) that, if surface area was used as the basis of comparison, the urea clearance of a child above the age of one or two years had the same numerical value as that of an adult. Schoental et al. (1933) found the relationship to hold for children as young as two months, and its physiological correctness and clinical value for older children have never been seriously questioned.

McCance and Young (1941) showed that, if a factor based upon surface area was used to make the comparisons between adults and very young infants, even healthy infants appeared to have lower glomerular filtration-rates and clearances of urea than adults. There were two ways of interpreting these findings. One was to suppose that the infants, although healthy, were physiologically undeveloped—i.e., that the functional capacity of the kidney of the infant had in some way lagged behind its anatomical and other physiological development. The other was to assume that surface area was not the correct basis on which to make the comparisons. McCance and Young (1941) considered various bases on which the comparisons might be made and discussed the possibilities of body-weight, kidney weight, total basal metabolic requirements, &c., and finally adopted surface area as appearing at that time the most reasonable one.

The experimental results of McCance and Young (1941) have been amply confirmed and extended (Dean and McCance 1947, Barnett et al. 1948, Rubin et al. 1949), and surface area has continued to be used as the basis of comparison (H. Smith 1951), although with some reservations (C. A. Smith 1951). This has led to the idea that there is something almost unphysiological about the healthy infant's kidney and certainly that it is an inefficient organ by adult standards. Several papers have been written, for instance, on the maturation of renal function in the first year or two of life (West et al. 1948, Rubin et al. 1949). The kidney of the newborn may be inefficient when the organ is subjected to some stress, or when some test load is applied to it (see below), and there may be differences between the tubular and glomerular adjustments of infants and adults (McCance 1950); but the following considerations suggest that the real understanding of juvenile renal function has been delayed by the selection of an incorrect basis of comparison.

EXCRETION OF UREA

If the function of the kidney is regarded as pre-eminently the regulation of the constancy of the body-fluids, three things must be borne in mind:

(1) The concentration of urea in the body-fluids varies ttle from day to day, or indeed from decade to decade.

(2) The concentration of urea in the body-fluids depends n its rate of formation and its rate of elimination.

(3) Urea is dissolved in the whole of the water in the ody, and for present purposes its concentration in this may be taken to be the same throughout.

To maintain the amount of urea in the body within ormal limits, the rate of excretion by the kidney must keep pace with the rate of formation. If in this state of dynamic quilibrium the urea formed per minute is equivalent o the amount dissolved in x ml. of the body-water, the kidney may be regarded as clearing x ml. of the body-water every minute, and it is accordingly suggested that the urea clearances should be expressed per unit of total body-water. If this be done, it becomes possible to compare the results for old and young, large and small, within any one species, by a method which is physiologically sound. Functions, moreover, on which the clearances of urea depend, such as the glomerular filtration-rate, may also very properly be compared on this basis. The excretion of water will receive special consideration later.

The accompanying table gives the average urea clearances and glomerular filtration-rates which have been found by McIntosh et al. (1929), Cullen et al. (1935), Dean and McCance (1947), Barnett et al. (1948), and Rubin et al. (1949). They are expressed in terms of the total body-water of an "average" adult as well as in terms of the adult surface area. The figures for body-water were obtained by assuming that the body of an adult weighing 70 kg. contains 60% of water—i.e., 42 litres (McCance and Widdowson 1951); that the body of a child above six months of age also contains 60% of water; and that the body of an infant under six months of age contains 69–77% of water according to its weight (Widdowson and Spray 1951). The figures obtained by Barnett et al. (1948) and Rubin et al. (1949) for healthy infants, which were well below those of adults when they were expressed per 1·73 sq. m. of surface area, are equal to those of adults when they are expressed per 42 litres of body-water. The clearances of children aged 138–356 days (Barnett et al. 1948), which were a little lower than those of adults on the basis of surface area, are higher per 42 litres of body-water, and the urea clearances of older children, which were equal to the urea clearances of adults per 1·73 sq. m. of surface area, are considerably higher than those of adults when expressed per 42 litres of body-water. This is only to be expected on physiological grounds, since the protein intake of children per kg. of body-weight, and hence per kg. of body-water, is much higher than that of adults. A comparatively small amount of this protein is required for growth in older children; and, were the clearances not higher, the concentration of urea in the body-water would normally be about 70 mg. per 100 ml. at the age of five years, which it certainly is not. It may be the level of protein metabolism in children which determines the magnitude of the glomerular filtration-rates and urea clearances. An increase or a decrease in the protein intake materially raises or lowers the glomerular filtration-rate in seals (Ladd et al. 1951), dogs (Jolliffe and Smith 1931, Shannon et al. 1932), and rats (Dicker 1948), and although the effect is much smaller in human adults it may be large in children. A high-protein diet certainly leads to renal hypertrophy in young animals (H. Smith 1951). If the renal clearances of newborn infants respond rapidly to the protein intake, the low clearances obtained by Dean and McCance (1947) (see table) may be explained, for the children used by them had been deprived of food for fifteen or sixteen hours before the tests were made.

If this physiological basis for comparing renal function of small and large individuals is adopted, some of the results and many of the conclusions about juvenile renal function will have to be re-examined. This is now being done. It goes without saying that, if the urea clearances are expressed per unit of body-water for physiological purposes, it does not prevent them from being given as a percentage of normal in clinical reports.

EXCRETION OF WATER

It is usual to study the excretion of water by administering a test dose, and to follow the response of the organism to this disturbance in the amount and composition of its body-fluids. It is clear therefore that the dose administered should be calculated in relation to the total volume of the body-water. The organism gets rid of water not only by the kidneys but also by the lungs and skin. The last two are likely to be more important in the infant than in the adult, but the figures given by Levine et al. (1938)—admittedly for older babies—show that they are relatively unimportant in the few hours following a large test dose. If, however, the organism is weighed at suitable intervals before and after the test dose, and if the volumes of water excreted by the kidney are also recorded, both the renal and extrarenal losses may be measured and distinguished.

Since the object of the experiment is really to compare the rates at which the kidney restores the composition of the body, and therefore the amount of the body-water, to normal in infancy and in adult life, the correct basis of comparison must surely be the percentage of the dose excreted, or the ml. excreted, per unit volume of total body-water. Suppose, for example, that a 70 kg. adult and a 3·6 kg. infant are given 3500 and 180 ml. of water respectively, and that they excrete respectively 3500 and 90 ml. by the kidney within the next five hours. The volumes excreted are absolute amounts, have real meaning in relation to the dose given, and are equal to 3500 and 1500 ml. if expressed per 42 litres of body-

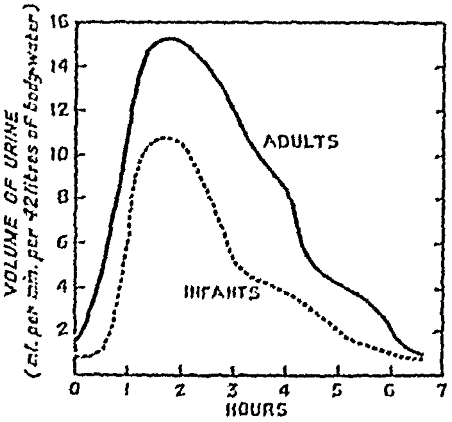
UREA CLEARANCES AND GLOMERULAR FILTRATION-RATES

("Maximum" clearances only used)

Reference	Figures averaged	Age of children	No. of children	Urea clearance (ml. per min.)		Glomerular filtration-rate (ml. per min.)	
				Per 1·73 sq. m.	Per 42 litres of body-water	Per 1·73 sq. m.	Per 42 litres of body-water
Dean and McCance (1947)	Table 4	2–8 days	4	17	42	34	82
Barnett et al. (1948) ..	Table 1B, BA, RA, PI A and B, MA, RO, PA	3–13 days	7	34	78	48	109
Rubin et al. (1949) ..	Table 1A, p. 1147	2–22 days	11	29	71	49	122
Barnett et al. (1948) ..	Tables 1 and 1A, ML, GR, GO, KE twice	8–28 days	4 (one twice)	34	77	51	116
Rubin et al. (1949) ..	Table 1A, p. 1148	54–118 days	9	35	77	67	149
Rubin et al. (1949) ..	Table 1A, pp. 1149 and 1150	138–356 days	12	55	104	100	204
McIntosh et al. (1929) ..	Table 1	2–12 years	8	72	115	—	—
Cullen et al. (1935) ..	Table 1	5–13 years	61	78	123	—	—
Normal adult value				75	75	120	120

water. If, however, the figures are expressed per 1·73 sq. m. of surface area, the first remains 3500 ml. for the adult and the second becomes 630 ml. for the infant; the latter is misleading since it represents the infant as having a poorer renal function than it in fact has. McCance and Wilkinson (1947), Heller (1947, 1951), Dicker and Heller (1951), Ladd et al. (1951), and others have expressed the dosage and excretion of water per unit of body-weight. This basis is theoretically not more correct than that of surface area, but the results given by it are much nearer those based upon body-water.

Experiments recently carried out by N. J. Naylor and R. A. McCance (unpublished) suggest that the figures in the example given above are fairly near the truth for babies in the first few weeks of life. The accompanying illustration shows a comparison of the average rates of excretion of water by six infants and five adults after administering an amount equal to 6% of their body-water by mouth. The figure brings out two further points about the treatment of a large dose of water:



Minute volume of urine of infants and of adults after administration of amount of water equal to 6% of the body-water.

(1) The time relationships of the onset, peak, and course of the diuresis were very much the same at each age, and hence the absorption-rates and time relationships for the post-pituitary functions were in all probability also similar.

(2) The flow of urine subsided to its base-line in infants before the dose had been excreted, with the result that the response of the kidney came to an end while the amount and composition of the body-fluids were still abnormal. Dicker and Heller (1951) seem to have made a similar observation on guineapigs.

These findings are being further explored.

EXCRETION OF SODIUM, CHLORIDE, PHOSPHATE, AND OTHER IONS

The excretion of these substances by the kidney is a more complicated process than that of urea—at any rate less is known about it—and further experimental work is desirable before making definite suggestions about the basis on which the functions in infants and adults should be compared. A satisfactory physiological basis can only be reached if the following points are taken into consideration:

(1) The size and nature of the pool which the kidney drains.

(2) The concentration of the substance in that pool.

(3) Unless the pool is getting larger or smaller (which may happen in the metabolism of sodium), or the concentration of the substance in it is changing from day to day (which may happen in potassium or phosphorus metabolism), the amount excreted by the kidney in each twenty-four hours must equal the net quantity entering the pool.

(4) There are reasons for believing that the stability of the pool is so important physiologically that mechanisms have been developed by which the amount of a substance removed daily by the kidney may be rapidly altered to prevent variations in the amount entering the pool from materially altering its size and composition. No comparisons can be made without equating these variables or allowing for them.

COMMENT

Hitherto there has been a tendency to oversimplify the whole problem of comparing adult and juvenile renal function. The approach has been too rigid, and this has led to confusion of thought and contradictory conclusions. It may not be possible to make exact comparison on the same basis, and it is certainly not reasonable to expect to be able to do so on the basis of surface area.

Even in the so-called objective sciences any proposals involving changes in established thought or practice are likely to meet with considerable opposition (George 1936, Beveridge 1950). The suggestions now put forward certainly come into the category of those which are likely to upset current conceptions, and as such will be opposed on subjective grounds. It is hoped nevertheless that they will receive at least some objective consideration.

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THE MULTILOCULAR CYSTIC TUMOUR OR ADAMANTINOMA OF THE JAW

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THERE is considerable confusion as to the nature of adamantinoma and its treatment. The old names—"multilocular cyst," "epithelial odontome," and "ameloblastoma"—seem to have been discarded for "adamantinoma," which is admitted to be inappropriate (Lucas and Thackray 1951). "Multilocular cystic tumour" is an accurate description, but "fibrocystic disease of the jaw"—a still older name—is misleading. However, "adamantinoma" is convenient and appears to have been universally adopted for some years.

I have treated 14 cases of this tumour and have studied the reports on it published in English during the past thirty years.

A true multilocular cystic tumour or adamantinoma is not malignant, in spite of the fact that it recurs readily if it is not completely excised with its capsule intact. It begins as a solid encapsulated endosteal tumour usually in the molar region of the mandible; I have seen one only in the maxilla. This tumour grows slowly until cysts begin to form, especially just under the capsule;

ut the cysts may form in any part of the tumour. The ysts begin to expand, and then the tumour rapidly ncreases in size, spreading upwards into the ascending amus of the mandible. When the cysts burst through he alveolar plates, the tumour extends into the soft issues of the floor of the mouth or into the cheek. Very arge tumours have extended from the coronoid process nto the pterygomaxillary fossa.

Specimen no. 385 in the museum of Charing Cross Hospital ledical School is a solid encapsuled nodular tumour attached o the crown of a molar tooth. *The roots of the tooth are* underdeveloped. This tumour was enucleated from the nandible of a boy, aged 5 years, fifty-one years ago. The istological section showed it to be what was then called an pithelial odontome.

HISTOLOGY

The histology of the tumour varies, but it is an pithelial tumour with follicles lined by a layer of typical palisade-like columnar cells and containing a fine stellate reticular tissue. The palisade epithelial cells resemble the ameloblasts, and the stellate tissue is like that of the enamel organ of the developing tooth germ. There is little evidence that these tumours arise from the developing tooth germ, and similar tumours have been found in the long bones of the skeleton. Coley (1949) has collected 18 such cases. I have examined the histological sections of 10 tumours and found no connection between the surface epithelium of the gum and the tumour. The fine interstitial tissue may contain groups of epithelial cells and small cysts. The groups of epithelial cells have been mistaken for carcinoma cells, but it is more common for a basal-celled carcinoma or an adenocarcinoma to be mistaken for an adamantinoma. I have known 3 basal-celled carcinomas and 2 adenocarcinomas to be diagnosed as adamantinoma. A basal-celled carcinoma arises from the surface epithelium, and the club-like processes of large epidermal cells spread into the deeper tissues. I have never seen a malignant adamantinoma. Two or more cases of metastatic growths secondary to an adamantinoma have been recorded (Coley 1949, Waterworth and Pullar 1948), but possibly the primary tumour was not a true adamantinoma. Lucas and Thackray (1951) describe eight different histological types of adamantinoma, ranging from the primitive type to the melano-ameloblastoma. Three sections of tumours which have recurred after incomplete removal (one after scraping) show a considerable increase of the epithelial cells in the interstitial tissue compared with the first tumour removed.

DIFFERENTIAL DIAGNOSIS

Clinically these tumours resemble in some ways the simple encapsuled parotid tumour. There are four different types of parotid tumour, according to the predominance of the kind of tissue forming its structure: the fibrous tumour, which is very similar histologically to the primitive type of adamantinoma; the myxomatous; the mucous; and the epithelial. The epithelial type of tumour has in the past been called an endothelioma, or cylindroma: it is now called an adenoma and is sometimes malignant. The parotid tumour has been found anywhere in the mouth, palate, cheeks, jaws, and pharynx, and in the neck.

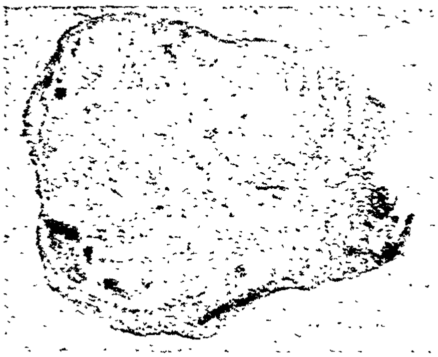
Fig. 2—Recurrence of tumour in 1951 in operation scar of 1931 (see fig. 1).

The diagnosis of adamantinoma is usually obvious—biopsy is rarely necessary, and there are good reasons for not taking a biopsy specimen from an encapsuled tumour. There is no difficulty in recognising a carcinoma or an adamantinoma during its removal. Of course a large piece of the tumour is sectioned immediately after it has been removed.

TREATMENT

Complete excision by diathermy and dissection is the most successful treatment. The coöperation of a dental surgeon is necessary because the jaw may have to be resected. Apparatus to fix the fragments of the jaw and interdental splints should be made, and septic teeth should be extracted before the operation. The tumour should be thoroughly and completely exposed and its limits defined. To achieve this, good access is necessary. Stereoscopic X-ray photographs are studied to assist in the definition of the limits of the tumour.

The choice of mouth gag is important. I prefer the Davis gag with its tongue-depressor, and it is a very satisfactory gag for an edentulous patient (Warwick James 1940). When this gag is used, the patient's head is extended over a sandbag in the position for enucleation of the tonsils. An efficient headlamp and a suction pump are essential. If the tumour is in the lower incisor region the patient is well propped up in the sitting position with the surgeon standing and looking down on the teeth. Denhard's gag is useful for a tumour in the incisor area.

Division of the lower lip in the midline does not give much better access; it causes deformity of the mouth by drooping of its angle and it is really unnecessary. Division of the upper lip for tumours of the upper alveolus gives better access without subsequent deformity. When the maximum exposure of the operation area has been obtained, a long incision of the mucoperiosteum is made down to bone at the lowest point of the cheek sulcus. The incision is made with a diathermy cutting needle from the ascending ramus to the symphysis. A similar incision is made as low down as possible on the inner or buccal surface of the mandible, and the two incisions are united well behind and well in front of the tumour to include an elliptical area of the surface mucoperiosteum, which is excised with the

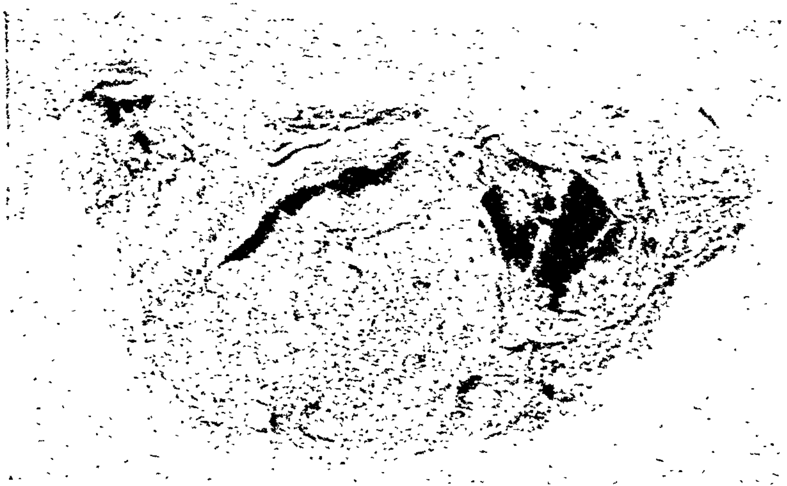
Fig. 1—Multilocular cystic tumour removed by resection of jaw in 1931

tumour. The mucoperiosteum is rasped off the bone to the lower edge of the mandible. Four or five pairs of curved artery-forceps are clipped to the edge of the mucosa and, if allowed to hang down, act as good retractors of the lip and cheek. The mucosa of the buccal surface is rasped *off the bone, and then the* thinned covering bone is removed with nibbling forceps all around the tumour and beyond its circumference and to the bottom of the bony cavity.

When the tumour is fully exposed it is dissected away with a blunt flat dissector working well outside the capsule and any of its cystic prolongations. Great care is taken to preserve the capsule intact.

I have completely excised 8 of these tumours in this way. At the end of five years there was no recurrence; in 2 cases there was still no recurrence after sixteen and twenty years. If it is found, when the tumour has been removed, that it has an inaccessible prolongation upwards into the ramus or any other part of the mandible, the jaw can be resected with a Gigli saw through a large external flap incision. Scraping and trying to enucleate the tumour with a sharp spoon is useless—recurrence is almost certain, and then it is more difficult to define the tumour and to excise it completely. If a small prolongation is left, or even if the capsule is ruptured, recurrence is probable. I am opposed to the set operation of resection of the jaw without first defining the limits of the tumour. If the tumour recurs after a complete excision, then a resection of the jaw may be necessary. In a few advanced cases the diagnosis has been too late and resection is the only possible operation which will achieve a complete removal of the tumour. The earlier the diagnosis the better the prospect of a complete removal. I have seen 2 cases of recurrence of the tumour twenty-one years and ten years after resection of the mandible.

In a case illustrated in the Middlesex Hospital museum an alleged dentigerous cyst containing two inverted teeth was incised and scraped in 1910. In 1924 a tumour recurred which gradually increased in size until in 1928 a solid tumour with a cyst was excised. In 1931 there was a recurrence, for which the jaw was resected (fig. 1). In 1951 an encapsuled globular tumour recurred (fig. 2), which was dissected out of the scar tissue by Mr. Douglas Ranger.

In my experience deep X-ray therapy has been unsatisfactory and disappointing. It is difficult to imagine that an embedded cystic encapsuled tumour should disappear with radiotherapy. The most that happens is that the cyst wall becomes fibrosed and thickened, and excision of the tumour is made more difficult. Necrosis of the bone, osteomyelitis, and burning of the mucosa and skin have occurred without any benefit, but with considerable misery to the patient. X-ray photographs after radiotherapy may show improvement by fibrosis in the superficial part of the tumour, but the more inaccessible deep portion remains. Recurrence of the growth is inevitable within a year or so.

Radiotherapy has been recommended in the extensive inoperable tumour which has burst through the bone into the soft tissues and inaccessible areas—for example, in an old man who has had a coronary thrombosis or is in bad physical condition. I prefer to treat this type of case by draining the cysts through large openings.

I am indebted to the Ferens Institute of Otolaryngology and to Dr. A. C. Thackray, of the Bland-Sutton Institute of Pathology, Middlesex Hospital, for the opportunity of studying specimens and sections; also to Mr. B. W. Fickling and Mr. Rainsford Mowlem.

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PLASMA-ESTERASE AND PLASMA-LIPASE LEVELS IN NUTRITIONAL ŒDEMA SYNDROME (KWASHIORKOR)

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THE effect of malnutrition on the production of enzymes by tissues has been receiving increasing attention in recent years.

Hutchinson, McCance, and Widdowson (1951) found the serum-cholinesterase level below normal in undernourished Germans in Wuppertal. According to them an insufficiency of calories was responsible for decreasing the pseudo, and to a lesser extent of the true, cholinesterase activity; the deficiency of neither protein, nor fat, nor carbohydrate, nor any of the major dietary constituents was considered to be specifically involved.

Hutchinson (1951) observed that undernutrition did not alter the levels of true cholinesterase, phosphatase, catalase, or glyoxalase in red blood-cells, although there was some indication of a slight increase in the level of carbonic anhydrase. However, in dogs and rats, even in severe malnutrition, the serum-pseudocholinesterase level was not lowered.

Veghelyi (1948) observed by duodenal intubation a diminution in the output of pancreatic enzymes in malnourished children in Vienna. The first enzyme to diminish and then to disappear was the lipase, and the last the amylase. He also observed that the blood-lipase and blood-amylase levels were considerably lowered in protein-deficiency states. Dietary treatment with milk powder brought about clinical improvement and a recovery of the enzyme activity.

Thompson and Trowell (1952), who compared by duodenal intubation the pancreatic enzyme activity in 24 African normal children and 59 cases of "a type of kwashiorkor," found the activity of pancreatic amylase and lipase in the kwashiorkor group much lower than in the normal children. In most cases the enzyme activity returned to normal after successful treatment with whole milk, skim-milk, or milk protein alone.

A syndrome similar to, and probably identical with, kwashiorkor has been under investigation at Coonoor for the last four years (Ramalingaswami et al. 1948, Gopalan and Patwardhan 1951). So far, 80 cases have been investigated and treated. In a fairly large number of these the plasma-lipase and plasma-esterase levels were estimated.

We present here the results of our observations in 17 normal children and in 33 with nutritional œdema resembling kwashiorkor.

METHODS

Plasma-esterase was estimated by the method of Cherry and Crandall (1931).

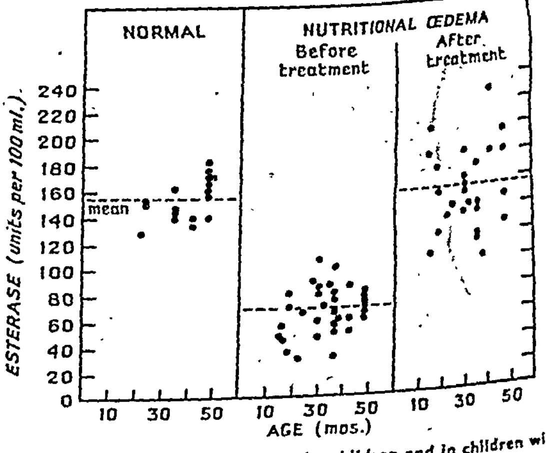
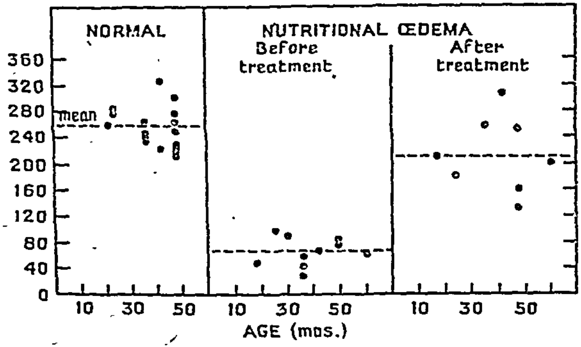


Fig. 1—Plasma-esterase levels in healthy children and in children with nutritional œdema.

TABLE I—PLASMA-ESTERASE AND PLASMA-LIPASE LEVELS IN KWASHIORKOR AND IN HEALTHY CHILDREN

	Age range	Plasma-enzyme level (units per 100 ml.)							
		Before treatment				After treatment			
		No. of cases	Range	Average	Standard error	No. of cases	Range	Average	Standard error
rase :									
n kwashiorkor ..	From 1 yr. 3 mos. to 4 yr.	33	30–105	66·7	± 3·25	27	100–230	154	± 6·64
n healthy children ..	From 1 yr. 10 mos. to 4 yr.	17	130–180	153·5	± 3·61	—	—	—	—
ase :									
n kwashiorkor ..	From 1 yr. 6 mos. to 5 yr.	10	30–100	67·0	± 6·80	8	130–305	211	± 20·10
n healthy children ..	From 1 yr. 10 mos. to 4 yr.	17	215–325	258·5	± 7·30	—	—	—	—

Plasma-lipase in the earlier part of the investigations s estimated by the method of Goldstein et al. (1948); t it soon became apparent that, owing to its non-cificity, the method could not give correct values for ase. Certain modifications were introduced, the most portant being the addition of sodium tauroglycocholate the reaction mixture in a final concentration of × $10^{-3}M$ containing tributyrin and plasma. In the esence of tauroglycocholate at the given concentration e esterase activity of plasma towards tributyrin is mpletely inhibited; hence the estimation gives a asure of lipolytic activity alone. The procedure and nterpretation of results obtained by this method are escribed elsewhere by Srinivasan and Patwardhan (1952).



g. 2—Plasma-lipase levels in healthy children and in children with nutritional œdema.

MATERIAL

The patients investigated were children, aged 15–48 onths, of stunted growth, with œdema and diarrhœa. n addition, enlarged liver, dermatosis, and depigmentaion of hair—the other features of typical kwashiorkor—ere present singly or together in a fair number of cases. he diarrhœa was non-infective and the œdema not of ardiac or of renal origin. Plasma-esterase and plasmaipase were estimated in blood obtained on admission nd on discharge. All the cases were treated with econstituted skim-milk, the quantities of which were radually increased according to the tolerance of the atient. In the later stages the skim-milk was supplemented by the hospital diet. On discharge, when a second ample of blood was taken for enzyme studies, the œdema had completely disappeared, the liver, if previously enlarged, had receded, and dermatosis had esponded.

RESULTS

The results of observations of enzyme activity are summarised in table I and figs. 1 and 2. The plasmaesterase and plasma-lipase levels, by age-groups before nd after treatment, behave (figs. 1 and 2) very much ike those of the pancreatic enzymes (amylase, lipase, and trypsin) as described by Thompson and Trowell (1952).

Plasma-esterase levels in 33 cases on admission were 30–105 units per 100 ml., with a mean of 66·7 units. After treatment the observations were repeated in 27 cases only, the levels being 100–230 units per 100 ml., with a mean of 153·8 units. Statistically this difference is significant ($P < 0.001$). The range and the average levels in a comparable age-group of normal and apparently healthy children are also given in table I, from which it is clear that, when treatment produced distinct clinical improvement, the plasma-esterase level returned to *normal.*

Plasma-lipase levels were estimated according to our modification of the method of Goldstein et al. (1948) in only ten cases before treatment and in only eight cases after treatment. From table I it is clear that the changes in plasma-lipase levels are similar to those in plasma-esterase levels.

DISCUSSION

Plasma-esterase

Whipple (1913) suggested that the plasma-esterase level could be used to measure liver function. Holmes and Trowell (1948) reported the failure of liver-cells from biopsy specimens to store glycogen in the presence of liberal amounts of glucose in their cases of kwashiorkor. Waterlow (1950) found a low cholinesterase activity in liver-biopsy specimens in his two cases with fatty liver. These observations make it probable that in kwashiorkor, which seems to be invariably associated with structural and functional damage to the liver, the plasma-esterase level is below normal.

In table II an attempt has been made to compare the degree of fatty infiltration of the liver with the plasma-esterase level in cases where liver structure in biopsy material could be examined. Although it may be too early to draw any conclusion, it does seem possible that some relation may exist between the degree of liver damage and the activity of plasma-esterase. At present not enough biopsy material has been collected before and after treatment to allow comparison in greater detail between the increase of plasma-enzyme activity and alterations in liver structure.

The plasma-esterase levels in patients before treatment show a wide divergence. On the other hand, in every case investigated a distinct rise in the plasma-esterase

TABLE II—PLASMA-ESTERASE AND FATTY INFILTRATION OF LIVER

Case no.	Esterase (units per 100 ml.)	Fatty change *
	(Before treatment)	
1	50	+ + + +
2	65	+ + +
3	60	+ + +
4	75	+ + +
5	75	+ +
6	70	+ +
7	75	+ +
8	80	+ +
9	100	+

* The severity of fatty change was graded as follows:
+ Tiny sudanophil droplets in the cytoplasm of liver-cells.
+ + + + Coalescence of sudanophil droplets in adjoining liver-cells, giving the appearance of large fat cysts.
Intermediate stages were graded + + and + + +.

level was observed after treatment. The final levels after treatment compare favourably with the normal levels in a comparable group of apparently healthy children.

Plasma-lipase

This enzyme probably has its origin in the pancreas. Ordinarily a very small part of the pancreatic enzymes enters the circulating blood, and this is normally excreted in the urine. In conditions like pancreatitis, pancreatic lithiasis, and cancer of the head of the pancreas, increased amounts of amylase circulate in the blood and can be found in the urine in higher concentrations than in normal people (Peters and van Slyke 1946). In these conditions the acinar function is normal, but the secretion of the enzymes into the ducts, or their entry into the duodenum, is interfered with. It might be expected that, in conditions where the capacity of the acini to elaborate the enzymes is impaired, the levels of pancreatic enzymes in the blood would be lower than normal. Davies (1948) has described the structural changes in the pancreas in kwashiorkor, the lesions varying from minor degenerative changes to advanced fibrosis and atrophy. Diminished pancreatic function has been observed by Veghelyi (1948) and Thompson and Trowell (1952) in kwashiorkor. These observations would explain the diminished plasma-lipase activity. According to the latter workers, successful treatment improves pancreatic function, a finding which seems to fit in with the improvement of plasma-lipase levels observed by us. Estimation of plasma-lipase levels may prove to be a more convenient method of determining the state of pancreatic function in kwashiorkor than is duodenal intubation. However, further work, including the estimation of plasma-amylase and plasma-trypsin levels, must be done before this can be accepted.

The plasma-lipase and plasma-esterase levels did not reveal any correlation with total plasma-protein or with plasma-albumin or plasma-globulin. The total-protein levels in 11 cases in the present series were 3·35–5·67 g. per 100 ml., with an average value of 4·8 g., before treatment, and 5·75–7·7 g. per 100 ml., with an average value of 6·87 g., after treatment.

SUMMARY

The plasma-esterase and plasma-lipase levels have been studied in 33 children with nutritional œdema, a condition similar to and probably identical with kwashiorkor, and in 17 apparently normal children who were comparable in age and derived from the class of people in whom this condition is prevalent.

In all the children with nutritional œdema the plasma-esterase and plasma-lipase levels were well below normal.

Therapy with skim-milk restored the levels to normal.

The possible cause of the lowered levels and their relation to nutritional œdema are discussed.

We gratefully acknowledge the assistance received from the nutrition clinic and the pathology department of the Nutrition Research Laboratories in the conduct of this investigation.

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Heart-disease and Pregnancy

AT the first meeting of the session, on Oct. 7, Prof. J. CRIGHTON BRAMWELL was inducted as president and delivered a presidential address on Heart-disease and Pregnancy.

Professor Bramwell referred to the part a medical society might play in helping to close the gap between consultants and general practitioners, and in bringing the practitioner into closer touch with the growing-points of knowledge. He suggested that the wealth of clinical material in Manchester imposed a corresponding obligation on those working there to undertake clinical research.

Over 1600 pregnant women with organic heart-disease had been investigated in his clinic at the Manchester Royal Infirmary during the past twenty-five years. The first 350 cases had been analysed by Dr. Edith Longson and himself in 1938, and 500 of the more recent cases had been similarly analysed by Dr. Morgan Jones.

The risk of pregnancy in patients with heart-disease depended on the severity of the disease, and could usually be assessed by the patient's tolerance for exercise before pregnancy. In patients with trivial heart-disease the risk was negligible; in those whose tolerance for exercise was reduced to a greater or lesser extent the added risk was appreciable; while in those who had suffered from heart-failure the risk was prohibitive. Pregnancy was contra-indicated in patients with active rheumatic carditis and in those whose cardiac condition was deteriorating rapidly. Intercurrent infection, especially bronchial infection, and anæmia were important and preventable causes of heart-failure. The prospect of successful pregnancy must also be considered. I the more recent series, 4 out of 5 pregnancies had yielde living children; whereas in 53 patients with advance heart-disease who were seen too late for pregnancy to b terminated, or who were unwilling to have it terminate only 1 in 4 was successful. Acute pulmonary congestio in patients with mitral stenosis constituted a grav emergency which was liable to develop very suddenl and often resulted in death; if it was recognised in th first trimester, pregnancy should be terminated. Valvotomy was now a possible alternative to termination o pregnancy. In addition to the clinical evidence, X-ray screening was invaluable in the early recognition of this condition.

Auricular fibrillation did not add so greatly to th risk as most earlier workers had imagined. Unde favourable conditions it should not be regarded as a bar to pregnancy.

In patients who had never actually had heart-failure, but whose tolerance for exercise was much restricted assessment of the risk was most difficult; and factor other than the severity of the heart-disease—namely age and parity, temperament, and economic conditions—all had to be taken into consideration. The addition o an aortic lesion to mitral stenosis did not add to th risk. Opinions varied regarding the importance o cardiac enlargement, but many patients who died o acute pulmonary œdema had little cardiac enlargement

A case follow-up in the more recent series showed tha about 90% of patients who survived had no evidence cardiac deterioration as the result of pregnancy.

With regard to treatment, Professor Bramwell believe that the two most important things were: (1) never t interfere with pregnancy in a patient with heart-failu until everything possible had been done to relieve t heart-failure; and (2) to ensure adequate antenat supervision in every case. If heart-failure was recognise early it responded well to treatment. In the antenatal cardiac clinic the almoner played a most important part.

It was now known that in the last few weeks of pregnancy blood-volume and cardiac output diminished, and that the strain on the heart was correspondingly reduced. There was therefore no justification, in this respect, for anticipating normal delivery by inducing premature labour or by cæsarean section. All recent work showed that in patients with heart-failure cæsarean section carried a heavier mortality than normal delivery.

New Inventions

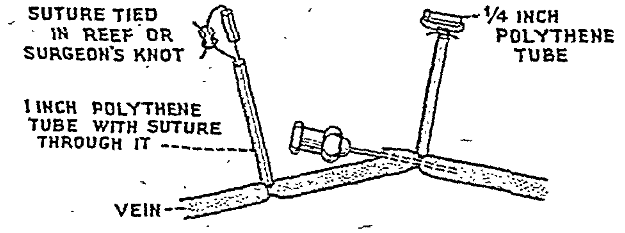
A TECHNIQUE FOR SAVING THE VEIN

FOR administering continuous intravenous fluids to children it is usual to cut down on a vein and tie it off. The method described here is designed to preserve the patency of the vein for subsequent intravenous therapy. It is based on the assumption that after a few hours' intravenous therapy little bleeding will take place, because of spasm and sometimes thrombosis of the vein.

As an alternative, it has been suggested that after a vein has been dissected out, it may simply be needled without tying; but I have found this unsatisfactory because of bleeding round the needle at the point of puncture.

The usual cutting-down apparatus is required, and also a piece of 'Polythene' tube. The polythene is cut into four lengths, two of 1 in. and two of $^1/_4$ in. The size of the polythene tubing is not important, but no. 3 is quite satisfactory.

The vein having been exposed, two catgut sutures are placed round it in the normal way. The ends of these sutures are threaded loosely through the long pieces of polythene (see figure), and artery forceps are applied to the polythene. A snick is made in the vein and the cannula is introduced. The two sutures are now drawn tight through the polythene, one being placed round the cannula and one distal to it (the artery forceps having been removed). One end of each suture is threaded through the smaller piece of polythene, and the suture is secured with a surgeon's knot. It will be seen that this is a modification of the Bowden-wire principle.


SUTURE TIED IN REEF OR SURGEON'S KNOT
1/4 INCH POLYTHENE TUBE
1 INCH POLYTHENE TUBE WITH SUTURE THROUGH IT
VEIN

When the transfusion is finished, the cannula is extracted and an attempt is made to suture the vein wall. Then the sutures are cut and removed. Even if it is impossible to suture the cut in the vein, bleeding can be easily controlled by skin sutures and a pressure bandage.

The method has been applied successfully in the treatment of infants with gastro-enteritis who have required intravenous therapy. The long saphenous vein has been used. At the conclusion of the transfusion it has always been found possible to remove all the sutures without untoward effects, and there has been no leaking from the vein during the infusion. The method was also used in giving blood to a boy with acute leukæmia who had a hæmorrhagic tendency shown by widespread ecchymoses and purpuric spots. There was slight bleeding from the vein at the conclusion, but it soon stopped when a tight bandage was applied at the site of the incision.

I have had an opportunity of using this method for a second time on the same vein. A child, aged 1, was transfused during the treatment of an ulcerating hæmangioma affecting both legs. A second transfusion was needed three months later, and I cut down on the same vein. There was no real difficulty in introducing the cannula and though the lumen of the vein seemed a little narrower the transfusion was entirely satisfactory.

This method might appeal to those who have to give repeated transfusions to the same patient over several years—e.g., in congenital hypoplastic anæmia.

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Reviews of Books

Principles and Practice of Medicine

A Textbook for Students and Doctors. L. S. P. DAVIDSON, M.D., F.R.C.P.E., professor of medicine and clinical medicine, University of Edinburgh. Edinburgh: E. & S. Livingstone. 1952. Pp. 919. *32s. 6d.*

Professor Davidson, with the staff of the medical department and clinical units at Edinburgh, has compiled a textbook embodying the teaching of this school over the past twenty years. This volume is clearly produced and simply designed. A similar descriptive pattern is used for each disease, giving concise ætiology, pathology, clinical manifestations, diagnosis, and treatment. As would be expected from this group of teachers, the physiological background is well covered and special emphasis has been laid upon treatment: it is indeed pleasant to find this aspect so well handled. The selection of material is admirable, and the student will find enough about rare diseases to serve him for his final examinations.

The printing and production is first-class. Some readers may wish for more illustrations, but they must remember that the price is remarkably low for all this volume provides. Davidson's textbook will assuredly take its place as a real contribution to British medical teaching.

Oestrogens and Neoplasia

HAROLD BURROWS, C.B.E., PH.D. Lond., F.R.C.S., formerly *experimental pathologist, Chester Beatty Research* Institute, The Royal Cancer Hospital, London; E. S. HORNING, M.A. Oxfd, D.SC. Melb., reader in experimental pathology, University of London, at the institute. Oxford: *Blackwell Scientific Publications.* 1952. Pp. 189. *30s.*

IN addition to its main theme this volume includes an account of the chemistry of œstrogens by C. W. Shoppee and a brief summary of experimental tumour chemotherapy by W. C. J. Ross. A preliminary chapter sets out the natural sources of œstrogen from plants and animals, as well as factors controlling its supply in the body and influence in stimulating mitosis, hyperplasia, and benign and malignant growths. From observation of human and experimental conditions, the authors support the view that continuous secretion of, or exposure to, œstrogen rather than intermittent excessive output or application is the effective hormonal factor causing spontaneous or induced neoplasia. Among other special conditions cited are species and organ variation in sensitivity and response and, within the same species, differences depending on heredity and inbreeding. In the case of heritable mammary tumours of mice the effective cause is infection with the milk factor aided by œstrogen. Subsequent chapters summarise systematically knowledge of the neoplastic influence of œstrogen on its target organs. A short account of œstrogen-producing tumours is included. Numerous subheadings and cross-references help the reader to extract and to trace to source any special information required. There is a bibliography of 957 references.

Surgery of the Œsophagus

R. H. FRANKLIN, M.B., F.R.C.S., senior lecturer and surgeon, Postgraduate Medical School of London. London: Edward Arnold. 1952. Pp. 222. *42s.*

IN this work Mr. Franklin has considered the œsophagus as a whole, and he has used his experience to draw into reasonable perspective the work in this field of the ear, nose, and throat surgeon, the thoracic surgeon, and the abdominal surgeon.

He writes with authority on the operative treatment of congenital atresia, and it is interesting to note that he has now a preference for the transpleural as opposed to the extrapleural approach. In his brief but clear discussion of the technique of œsophagoscopy he emphasises its potential dangers in incautious hands. Apart from diagnosis, endoscopy plays an important part in the removal of foreign bodies, but there are some complications which require the use of open surgery. He considers the syndrome of reflux œsophagitis, resulting from a shortened œsophagus with herniation of the stomach, in the light of recent work, and illustrates the difficulties of treatment. In the description of the operative treatment of carcinoma of the cervical and thoracic œsophagus, the absence of many figures and results make it difficult to determine the appropriate technique for each case.

The illustrations are well selected. All interested in the œsophagus should read the book, for it is a valuable contribution to a subject which is rapidly developing.

Psychology, the Nurse, and the Patient

Doris M. Odlum, M.A. Oxfd, B.A. Lond., M.R.C.S., D.P.M., senior psychiatrist, Elizabeth Garrett Anderson Hospital, and consultant psychotherapist, West End Hospital for Nervous Diseases, London. London: *Nursing Mirror* Publications. 1952. Pp. 114. 7*s.* 6*d.*

This pocket-size book should be of real help to student nurses, for it covers the syllabus in psychology for the preliminary examination for State-registered nurses. It could also be read with advantage by medical students and their seniors. After a brief outline of modern psychological theories the nurse is shown how this can be applied to the whole gamut of the *patient's* experience of illness and hospital life; so that she is led step by step to a realisation of how psychology can be of real use in understanding and ministering to her patients. The chapter on Some Special Problems is particularly good and deals with the surgical case, preparation for operation, anæsthetics, the care of the patient after operation, alleviation of pain, getting up, the use of sedatives and hypnotics, patients' questions about dying, the long-stay case, the elderly patient, and relatives and visitors. There is also a good chapter devoted to the nursing of children; the need for avoiding unnecessary separation of the young child from its mother is emphasised, though not, perhaps, forcibly enough. Some account of the good results obtained in children's wards where the mother is encouraged to visit daily and assist with settling the child down for the night might well have been included.

The whole book is written around the patient (a fact which is not suggested by the phrasing of the title) and this is specially commendable.

Nutrition and Climatic Stress

H. H. Mitchell, professor of animal nutrition, University of Illinois; Marjorie Edman, instructor in animal nutrition, in the university. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 234. 50*s.*

This monograph was originally written for the United States Armed Forces, to summarise what is known of the influence of nutrition on the ability of men to endure climatic stress. The subject has an obvious bearing on the proper rationing of troops; but, as the authors point out, it has much wider implications than that. They have studied and summarised a great deal of work, published before October, 1949, on diet in a cold environment, a hot environment, and at altitude. Each section begins with the physiological effects of the form of stress under consideration, and then gives an account of what is known of the effects of this stress on nutrient requirements in animals and man. The very large bibliography refers mainly to American work, but some other sources are quoted. At the end of each section the authors have weighed up the evidence available at the time, and have offered some practical conclusions—such as that carbohydrate, especially when backed up by fat, is more effective than protein in keeping out the cold, that there is no statistical evidence to show that men voluntarily eat less protein in hot climates, that vitamin supplements seem to make little difference to tolerance of either heat or cold, and that for those going up to 15,000–17,000 feet carbohydrates are the thing, though perhaps inclined to cause trouble from flatus. A table occupying 16 pages summarises the effects recorded of treatments other than nutritional on altitude tolerance, noting the subject (whether animal or human) used, and the results. This shows at a glance which measures look promising and which may as well be given up. It also bears out the authors' contention that animal experiments do not offer a satisfactory guide to human nutritional requirements.

Human Nature

Its Development, Variations and Assessment. John C. Raven, M.Sc. London: H. K. Lewis. 1952. Pp. 226. 12*s.* 6*d.*

In this book Mr. Raven, the author of the well-known Progressive Matrices test, gives a good introductory account of the development of human personality from birth to maturity and old age. His style is leisurely and reflective, and much of what he says will stimulate the reader to fresh thought on well-worn topics, without ever shocking the most devout disciple of William James or McDougall. The section on mental testing in its various forms, with the assessment of their value, is authoritative. An appendix deals with the statistical techniques used in psychology, but even this is palatably administered. The book includes references to further reading at the end of each section, and a useful glossary and index.

Fitness and Injury in Sport (London: Skeffington. 1952. Pp. 189. 16*s.*).—During the last few years a number of books have appeared on the subject of athletic training written by men who must have had considerable practical experience in the preparation of athletes and in the prevention and treatment of injuries. Their aim, they invariably say, is to convey to athletic trainers in simple language the essential scientific principles and their application. That is a praiseworthy ideal, but in their anxiety to emphasise "the scientific approach" they usually include details of anatomy, physiology, and pathology out of all proportion to the requirements of potential readers. The difficulty is that moderate knowledge of a subject like physiology does not equip anyone to write a simple treatise for a layman, for this is one of the most difficult of all scientific literary achievements, and demands the profound knowledge of a professor.

There are so many flowery bypaths into which a writer can stray, and Mr. S. S. Knight, who is general secretary of the Physiotherapists' Association, unfortunately strays a good deal. Thus in the chapter on Food and the Athlete he begins by saying that "there is no known or certain way of improving athletic performance by means of food," and ends 14 pages later with the remark: "it is my experience that it is what you like in food that does you good providing there is enough of it." This being so, he might as well have omitted the intervening account of food analyses and calorie values. Nor does he make up for this waste of space in the section on prevention of injuries, for practical details here are scarce. He gives a brief but good summary of modern ideas on physical fitness. His proposed course for athletic trainers would occupy four to five terms, each of 12 weeks' full-time study. It seems a lot.

Proceedings of the Third International Congress of the International Society of Hematology (London: Heinemann Medical Books. 1951. Pp. 593. £3 10*s.*).—This is the English edition of the proceedings. It does not differ at all from the American edition, edited by Dr. Carl V. Moore, reviewed in *The Lancet*, 1951, ii, 868.

Interrogation (Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 164. 35*s.*).—Captain Harold Mulbar is a senior officer of the Michigan State Police who has had much experience of getting at the truth by interrogating reluctant people. He has written, in admirably direct style, a well-informed guide to the practice of this art. Besides describing the procedures and artifices of ordinary questioning within the American police system, he gives much sensible information about the use of the polygraph, in Chicago and elsewhere, for "lie detection." His book is eminently practical, full of wrinkles and warnings, and assumes throughout that the investigator will have to produce his evidence for an American court. He is outspoken in condemning third-degree methods, which, it seems, might better be called torture and brutality.

THE LANCET

LONDON: SATURDAY, NOV. 1, 1952

Isoniazid

It is little more than six months since the news of the antituberculous action of isoniazid (isonicotinic acid hydrazide) and some of its related compounds was announced, but much work has already been published both on the clinical and on the laboratory side. As a result, certain preliminary conclusions have been fairly well established,[1] and they can now be examined in the light of two trials which have lately been undertaken in this country. The first and larger of these is described in an interim report[2] of the Medical Research Council's tuberculosis chemotherapy trials committee; and the second, a combined clinical, pharmacological, and bacteriological investigation at Guy's Hospital, is reported in three articles which we publish this week.

For the initial stage of the M.R.C. trial, 331 patients suffering from very different degrees of pulmonary tuberculosis were divided into two groups: one group of 173 patients received isoniazid (alone), and the remaining 158 had streptomycin and *p*-aminosalicylic acid (P.A.S.). After three months' treatment the isoniazid group showed an average gain in weight of 11 lb. compared with 6 lb. in the streptomycin-P.A.S. group—a highly significant difference. On the other hand, there was little difference in the response to treatment as judged by general condition, erythrocyte-sedimentation rate (E.S.R.), temperature, and radiological appearances. The M.R.C. report concludes that "judging wholly from short-term results . . . isoniazid is a very effective drug in pulmonary tuberculosis; but given alone it is not more effective than streptomycin plus P.A.S." Further reports are promised on the results of this investigation and on the various trials of combined therapy which are now in hand.

In the meantime, the clinical trial started by Dr. Joiner and his colleagues at Guy's Hospital carries us a good deal further. It is much smaller than the M.R.C. investigation, but it has certain features which make an interesting contrast. "Clinical assessment, sedimentation-rate, and weight estimation were recorded weekly by the same physician, while specimens of sputa from each patient were examined twelve times each month, so that the criteria for a negative microscopic result were strict." The patients corresponded to group 3 in the M.R.C. trial—the chronic type of patient who lives in "unhappy symbiosis with the organism" or whose general condition is slowly deteriorating. The conditions of the trial were "those under which most patients suffering from the type of disease have to be treated today." A preliminary investigation was designed to test the effect of isoniazid given alone for a very short time. Capsules of isoniazid (250 mg. per day) were given to 12 patients for six weeks, while another 10 had identical capsules of lactose. During the six weeks several patients in the first group showed a striking improvement in their general condition: they put on weight, and the number of tubercle bacilli in their sputum fell, though the changes in E.S.R. and in X-ray appearances were slight. In the control group most patients slowly lost ground. At the end of the six weeks the 10 patients who had been having lactose, together with 1 newcomer, were started on a course of isoniazid (250 mg. daily) plus 1 g. of streptomycin six times a week: the 12 patients who had been having isoniazid alone continued as before. The progress of these two groups was then assessed for eighteen weeks in all, and they showed definite differences. Isoniazid alone, even in the rather low doses used, produced in the first four or five weeks a striking improvement in most cases; but the effect on the sputum was only temporary, for some patients were already relapsing by the fifth week, and isoniazid-resistant strains were cultured from their sputum. On the average these patients gained weight until about the twelfth week; thereafter their weight remained stationary and their clinical condition began to deteriorate. On the other hand, those treated with isoniazid plus streptomycin not only showed the same initial response but maintained their improvement throughout the eighteen weeks; their general condition got steadily better, their weight continued to go up, the E.S.R. went down to normal in most cases, and the sputum-count showed very few bacilli or none at all. Another group of 16 patients was investigated: 9 had isoniazid plus streptomycin and 7 P.A.S. plus streptomycin. Both groups showed about the same improvement in clinical condition, in E.S.R., and in sputum-count during fourteen weeks' treatment, but those on isoniazid plus streptomycin gained much more weight than the others. Both these investigations at Guy's are continuing, and further reports will be published.

The Guy's results must be analysed by methods quite different from those used in the M.R.C. trial: each group of patients, though small, served in a sense as its own control. The patients who were treated with isoniazid alone, after a rather dramatic improvement, nearly all relapsed in an equally convincing way. Most of the patients in the initial control group were going slowly but steadily downhill, but this decline stopped immediately when treatment with isoniazid plus streptomycin was started; in fact they improved for the rest of the trial. An inspection of the record of each patient who had isoniazid plus streptomycin shows the characteristic "triple response" of gain in weight, fall in E.S.R., and decrease in sputum-count. Clearly the conclusion to be drawn from this clinical trial is that isoniazid alone cannot be recommended as a treatment for pulmonary tuberculosis, but that isoniazid plus streptomycin promises to be highly effective. This conclusion finds support in the field of experimental chemotherapy. The pharmacological branch of the work at Guy's Hospital has dealt with the effect of isoniazid, alone and in combination, on experimental tuberculosis of the cornea in rabbits and mice. The methods used have already proved valuable in examining the merits of promising antituberculous drugs.[3] On another page of this issue, Dr. GOULDING and Professor ROBSON describe how the development of corneal tubercles in mice inoculated intracorneally with a virulent strain of *Mycobacterium tuberculosis* was completely arrested while the mice were having isoniazid; but the lesions appeared after the usual interval when the drug was stopped. With streptomycin alone the disease was almost entirely prevented, though occasional lesions appeared even during treatment; and when the streptomycin was stopped, it was uncommon for lesions to develop later. But a combination of isoniazid and streptomycin was much more efficient, and no lesions developed at all either during or after treatment. A combination of P.A.S. and isoniazid was no more effective than isoniazid alone.

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[1] See *Lancet*, 1952, i, 546; *Ibid*, p. 1293; *Brit. med. J.* 1952, i, 858.
[2] *Brit. med. J.* Oct. 4, 1952, p. 735.

In the third paper of this series Professor KNOX, Dr. KING, and Mr. WOODROFFE describe their work on the in-vitro action of isoniazid on the tubercle bacillus. They found that the apparent sensitivity of *Myco. tuberculosis* to isoniazid in Dubos liquid medium depended on the length of incubation of the culture, and for that reason a standard period of incubation was essential. When the sensitivity was read after incubation for fourteen days or less, growth was usually inhibited by a concentration of 0·01 µg. per ml. (1 part in 100 million). With longer periods of incubation, growth was eventually seen in tubes which originally contained up to 1·6 µg. per ml. They have shown that this unstable end-point is the resultant of two processes: (1) an inactivation of the drug, even in uninoculated Dubos medium at 37°C; and (2) a selection of organisms with increased resistance to the drug. In another article in this issue, Dr. MITCHISON reports a similar inactivation of isoniazid in uninoculated Dubos medium at 37°C, and a comparable shift in the end-point in the inoculated medium. Commenting on the difficulty of deciding with certainty whether a drug is mainly bactericidal or bacteriostatic, KNOX and his colleagues say that the in-vitro action of isoniazid was profoundly modified by quite small changes of temperature, and they suggest that a rise of temperature from 37° to 40°C increases its bactericidal action. They think that this is no mere test-tube phenomenon, for isoniazid has a miraculous effect on toxic patients with high temperatures, and, moreover, GOULDING and ROBSON found interesting differences in the action of isoniazid on animals with different body-temperatures. The laboratory evidence, though not yet complete, suggests that isoniazid alone, in vitro, and in concentrations close to those which inhibit growth, is bacteriostatic rather than bactericidal; that resistant variants can be quickly and easily produced; and that a combination of isoniazid and streptomycin is more nearly bactericidal and delays the development of strains resistant to both drugs.

All this evidence points to the same general conclusion: the initial attack of isoniazid on the tubercle bacillus is perhaps the most powerful of all the weapons yet discovered, but the drug must not be used alone except for very special reasons. Attention is now being concentrated on the urgent question of how best to combine it with other drugs. The final answer is most likely to come from extensive clinical comparisons of the kind started so promptly by the M.R.C.; but valuable information can be gained and a great deal of time saved by smaller combined investigations on the Guy's pattern.

Management of Disseminated Sclerosis

NOWADAYS associations of patients suffering from a particular disease, and of those interested in their welfare, are springing up, and doing good service by passing round useful information. One such association, the National Multiple Sclerosis Society of America, was founded in 1946 by a group of physicians and patients to stimulate research into the demyelinating diseases in general and disseminated (multiple) sclerosis in particular. This society, which has already sponsored some thirteen research projects in university hospital centres in the United States, has now published five important manuals by Dr. EDWARD E. GORDON, of the department of physical medicine and rehabilitation of the Bellevue Medical Center, New York University. One is addressed to doctors, while the other four, addressed to patients, are home programmes for those confined to bed, those who can manage life in a wheel-chair, those able to walk with mechanical aids, and those able to walk alone.[1]

The striking thing about these publications is their hopeful and confident attitude towards a disease which we in England are apt to regard despondingly. Dr. CORNELIUS H. TRAEGAR, medical director of the society, in his foreword to the home programmes points out at once that the life-expectancy of these patients does not differ much from that of normal people, and is a great deal longer than that in most other chronic diseases. Instead of speaking vaguely of "remissions of varying duration" he declares roundly that great numbers of patients, at first severely disabled by the disease, have recovered spontaneously, either wholly or in part. These are no mere encouraging tales for patients; much recent work supports them[2]; and Dr. GORDON reiterates them in his introduction to the manual[3] addressed to doctors, and adds this important statement:

> "Since doctors are not prophets it cannot be predicted that the termination of a given acute episode is not the last of the disease for a given patient. When a patient with multiple sclerosis recovers from an acute episode, the doctor, for the purpose of rehabilitation, must *promptly* and *enthusiastically* begin a programme of rehabilitation."

This manual discusses in detail how the patient may be taught to live his life in spite of his handicaps, by exploiting his remaining powers. It is a programme demanding hard work from both patient and doctor. The chief enemy of the patient's life is infection—bronchopneumonia, bladder sepsis, bedsores—and the strong ally of infection is inactivity. The doctor's duty, then, is to get the patient on the ove and keep him moving. The first thing to do is to ssess the degree of disability; and in Dr. Gordon's iew this is no matter of getting a rough general idea. The manual includes a chart which can be used for rading spasticity, strength, and range of movement f the joints of the upper and lower limbs, neck, and runk. The completed chart serves for comparison t the next examination. Spasticity is of particular nterest, not only because it varies according to the osition and previous activity of the patient but also ecause it is increased by anxiety. If the patient's motional difficulties—whether these preceded the ppearance of his disorder or are its outcome—can e resolved, his general tension may be much reduced nd with it his spasticity. Other methods of lessening pasticity include gentle stretching, heavy exercise f the unaffected muscles, and in a few cases special races designed to increase the patient's skills. Weak nuscles are easily fatigued, and in a series of trials heir power may progressively decline. Such a decline an be recorded in figures, as 4→3→2→1, where 5 is ormal, 4 good, 3 fair, 2 poor, and 1 a trace or a light muscular contraction with no motion. In ddition, it is important to note contractures, and ny weakness due to overstretching in the antagonists f contracted muscles. The degree of ataxia and ncoördination may be difficult to evaluate if obscured by muscular weakness or spasticity; Dr. Gordon thinks it more useful to concentrate on the activities of daily living. Thus a positive Romberg test gives information about standing balance; but it is more useful to know whether the patient can stand safely with his feet a little apart and his eyes looking ahead than that he falls when he has his feet together and his eyes shut.

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[3] Rees, R. J. W., Robson, J. M. *Brit. J. Pharmacol.* 1950, 5, 77.

[1] Published by the National Multiple Sclerosis Society, 270, Park Avenue, New York 17, N.Y., U.S.A.

[2] See *Lancet*, 1952, i, 1196.

[3] Multiple Sclerosis: Application of Rehabilitation Techniques.

Activities depending on body position include, for example, ability to roll to either side in bed, to sit up, to get out of bed or out of a chair and stand, to sit down in a chair or a wheel-chair from the standing position, and to get down on the floor and up again. Those depending on reach and grasp include ability to dress, tie the shoelaces, brush the hair, eat with a knife and fork, write, telephone, and turn a tap. For those using a wheel-chair progression depends among other things on the ability to get into and out of the chair, propel it, and move from it to the toilet seat and back again; while for those walking with or without crutches progression depends on the ability to walk forwards, backwards, and sideways, to open and close a door, and to go up and down stairs. These and similar activities are charted, with the date on which each is achieved—a great encouragement to the patient.

The reablement programme is energetic and directed to clearly defined ends. The patient, Dr. Gordon reminds us, expects to find in his doctor a strong and resourceful counsellor. Objectives will differ according to the patient's physical status—whether he is confined to bed, restricted to a wheel-chair, able to walk with aids, or able to walk alone. If he is bedfast and cannot sit, it is pointless to begin by teaching him to use a spoon: he must first learn to sit up in bed. If he can sit in a wheel-chair he must learn to reach and grasp before he learns to walk.

To take a specific example, suppose a patient who can sit up is clumsy at carrying food to his mouth. The first step will be to study the muscle-groups which subserve grasp, supination, flexion on the elbow, and abduction of the shoulder, and to treat them for any weakness, spasticity, or contractions which may be present; the second step is to give the patient integrated training in performing the whole motion under realistic conditions. If incoördination is also present, then training in coördination must be included. If these measures produce no change for the better, it is time to think of mechanical devices to help him over the difficulty—e.g., aids for grasping, and for lifting and stabilising the arm.

The doctor must not overwhelm the patient with responsibility for his entire course of training: he must present him with attainable objectives, one or two at a time. The patient has his own responsibility—to carry out faithfully the exercises the doctor prescribes; and details of how he is to do it, and what simple equipment he will need, are set out in the home programmes.

A simple pulley with two stirrup-shaped handles can be used to exercise the arms; and if the patient cannot grasp the handles he can wear a glove which straps the fingertips down to a wristband and so holds the hand closed. One stirrup can be replaced by a child's bucket holding graded weights, and the arm can then be exercised against weight resistance. Coördination can be practised by moving small objects to numbered squares on a chessboard, and by the use of Montessoric apparatus designed to give practice in fastening buttons, tying laces, or fastening hooks and eyes.

We are too apt, in dealing with these patients, to think of failure of function in purely structural terms, forgetting that the conscious person in charge of the structure can find ways of getting round a difficulty, and moreover that the nervous system is wonderfully adept in spreading its tasks among the available neurones, much as a hospital matron during a staff epidemic deploys her remaining nurses. The patient with disseminated sclerosis can and should work at his own reablement; and Dr. Gordon is not among those who think heavy exercise will harm him. He points out that studies of cases of lower-motor-neurone injury have shown that fatigue does not interfere with axon regeneration.

Mechanical aids may be used in two ways—either to start a patient off in acquiring the next skill (thus a crutch and leg-irons may help to start a patient walking, though he may be able to discard them later), or as a substitute for a power finally lost.

Dr. Gordon advises on crutches and crutch gaits, leg braces, night splints for hands, wrists, and legs, types of wheel-chair, sling suspensions which allow patients to use weak hands, devices for holding spoons and knives and forks, a knife and fork conjoined, long spoons and forks conjoined at an angle, thick-handled pencils, cups with lids perforated so that the patient can drink without fear of spilling, pivoted arm-rests, long shoe-horns, supported telephones, lazy-tongs, and many other simple and useful tools to help these patients to help themselves.

The whole tone of these manuals is inspiriting, and should start many doctors thinking afresh about the care of their patients with this disease. As Dr. Gordon puts it, "the techniques and devices developed in the field of rehabilitation can be employed so that the patient's life may be made productive; if not productive, self-dependent; and if not self-dependent, at least tolerable." The National Multiple Sclerosis Society send the appropriate manuals to doctors or patients without direct charge, though they mention that subscriptions to further their work will be welcome.

Control of Filariasis

FILARIASIS, due to *Wuchereria bancrofti*, is a scourge of most of the hot and damp parts of the tropics; but it can now be hopefully attacked in two ways—by destroying the worms with dimethylcarbamazine ('Hetrazan,' 'Banocide') or by destroying the mosquitoes (which transmit it) with insecticides. Progress on these lines is now being made in different parts of the world. On another page a correspondent describes what is being done in Tahiti, where a joint American and French team are studying modern methods of control.[1] In that island, it seems, a third of the population over 5 years old carry microfilariæ in the blood, and 8–20% of the men between 30 and 50 years of age suffer from elephantiasis. Small experimental areas each containing about 60 persons were treated by various combinations of dimethylcarbamazine, general sanitation, and D.D.T. The dimethylcarbamazine was given as 2 mg. per kg. body-weight three times a day for seven days. (This schedule must have been difficult to supervise to ensure that all doses were actually taken.) A year later the percentage of people with microfilariæ had fallen from 34 to 20 and the microfilarial density in those remaining positive had fallen to less than 10% of its original level. The treatment, however, did not reduce the frequency or severity of clinical filariasis. The drug is said to have been well tolerated, though more than half the patients suffered transitory reactions on account of the compound itself or of allergic reactions to the microfilariæ which had been destroyed. Presumably the people were conscious of the dangers of the infection and so were prepared to undergo some discomfort in order to be rid of it. The other measures, of sanitation and of spraying with D.D.T., did not have an effect upon microfilarial rates or densities in the course of a single year, though they probably reduced the mosquito population. These are measures which act slowly, and their full benefit cannot be estimated soon.

A trial of dimethylcarbamazine which was restricted to a single village of about 700 persons has been reported from the Gambia in West Africa.[2] A preliminary survey by blood films taken at night showed that 40–54% of the people over 10 years old carried *Mf. bancrofti*, but only 6 (about 1%) showed signs of elephantiasis, or hydrocele. Dimethylcarbamazine, 5 mg. base per kg. once daily for five days, was administered under strict supervision to the microfilaria carriers. A year later 64% of the treated carriers had become free of microfilariæ and the total microfilaria count was reduced by 94% (9% of people previously free from microfilariæ now showed them). Some of the patients who had been treated with the drug had also contained *Mf. perstans*, and a year later the total microfilaria count for *perstans* had been reduced by 90%. Although *perstans* is non-pathogenic and so unimportant, this demonstration of the action of dimethylcarbamazine on it is interesting. Unfortunately many of the persons receiving the drug experienced minor toxic reactions such as headache, nausea, or anorexia. Very few of these were sufficiently severe to have been noticed by inpatients at a hospital; but among healthy villagers, who were not much *conscious of filariasis or its sequelæ*, they were enough to cause great reluctance to complete the course of treatment. In villages where the doctor was not personally known and trusted, they would make such mass-treatment impossible. In this investigation it was concluded that dimethylcarbamazine (in this dosage) had been effective in greatly diminishing the potential transmission of the infection, but its unpopularity and expense would be great handicaps to widespread use.

From East Africa comes the annual report of a research unit set up in 1949 by the Colonial Medical Research Committee under the High Commission of East Africa for the study of filariasis.[3] This report covers a wide field. Much attention has been devoted to the optimum dose schedule for dimethylcarbamazine and to its absorption, blood concentration, and excretion. Two field trials have been begun, one at Kyela near Lake Nyasa and another on the island of Ukara in Lake Victoria. *In the first a total dose of* 70 mg. per kg. (divided into two-hourly doses) was given during a single day. This caused much vomiting; and for practical use the report recommends a dose of 0·5 mg. base per kg. per hour so that a total of 35 mg. per kg. is given during three days. (This was the dose which was used for most of the patients on Ukara.) Fifteen months later the total microfilaria count at Kyela had been reduced by 96% although 80% of the patients still contained a few microfilariæ. The results on Ukara were similar, though the period of follow-up is not yet so long. The expense of such treatment would, however, be a serious obstacle to its wide use. As was expected, dimethylcarbamazine had no effect on clinical filariasis, hydrocele, or elephantiasis. Trials were also made of an antimony compound called 'Protostib,' which is pentavalent N-methyl glucamine antimoniate. This was given intramuscularly to 164 patients in doses as high as 20 ml. of the 30% solution daily for ten days. In 4 cases the patient developed mild and transient exfoliative dermatitis, but none the less the treatment seems to have been popular among the local inhabitants. There has not yet been enough time to evaluate the full effect of this treatment, which is designed to destroy the adult worms; but after four months there was a diminution of the total microfilaria count by 50–80% and the general outlook is promising. However, this treatment is too expensive and too toxic for use in field eradication work.

During filarial surveys, microfilariæ of *bancrofti* were found in 2 infants of less than 12 months old, who must be the youngest carriers yet recorded. Attempts to facilitate the diagnosis of the infection by antigens—e.g., by skin reactions or complement fixation—were unsuccessful; both these tests were unreliable. Dimethylcarbamazine has also been used to treat onchocerciasis (a disease which is important because of the blindness it causes); but a more effective way of controlling this infestation seems to be the eradication of the vectors, *Simulium neavei* and *S. damnosum*, by treating infected streams with D.D.T.

Altogether the present work on filariasis is remarkable for its wide geographical distribution, its diversity, and its promise of ultimate (though perhaps delayed) success.

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1. Beye, H. K., Edgar, S. A., Mille, R., Kessel, J. F., Bambridge, B. *Amer. J. trop. Med. Hyg.* 1952, 1, 637.
2. McGregor, I. A., Hawking, F., Smith, D. A. *Brit. med. J.* Oct. 25, 1952, p. 908.
3. Filariasis Research Unit Annual Report 1951. East Africa High Commission.

Annotations

NOBEL PRIZE

Prof. Selman Waksman, director of the Rutgers University institute of microbiology, New Brunswick, has been awarded the Nobel prize for medicine and physiology for the discovery of streptomycin. This discovery, in 1943, was the outcome of work begun in 1915, when Professor Waksman found in soil the actinomycete later named [illegible]. He has since developed neomyci[illegible] *fradiæ.*

TRANSPYLORIC PROLAPSE OF THE GASTRIC MUCOSA

Radiological examination sometimes shows an inconstant filling defect in the base of the duodenal cap, resembling a mushroom, cauliflower, or umbrella, due to linear folds of gastric mucosa passing through the pylorus and, as it were, pouting into the duodenum. This pouting is inconstant in shape and it may be present only during antral contraction; serial radiographs show a continually changing pattern that can be further modified by pressure over the antrum or duodenal cap and by altering the position of the patient.

As long ago as 1923 Forsell[1] drew attention to the mobility of the mucosa on the muscular wall of the stomach and to its independent changes in shape. Soon afterwards it was shown[2] that prolapse of the gastric mucosa through the pyloric sphincter into the duodenum could be recognised radiologically and confirmed at operation. As often happens with radiological appearances, increasing familiarity has been followed by reports showing an increasing proportion of positive findings. Thus, Rees[3] found 4 instances in 3000 patients, Scott[4] just over 1% in 1000 patients, Ferguson[5] 7% in nearly 300 patients, and Rappaport et al.[6] 15·5% in 1000 patients. In this country New[7] has reported this change in nearly 3% of 1700 patients, while in Belgium Wellens and Spyckerelle[8] found it in 5% of their patients. Rappaport et al. cite a case in which characteristic appearances were seen in only one of fifteen radiographs of the pyloric antrum and duodenum; and such inconstancy suggests that sometimes the normal is being confused with the abnormal.

Manning and Gunther[9] described six cases of mucosal prolapse examined post mortem. In none of these did this disorder account for death, though in 1 gastric hæmorrhage was a contributory factor. In 5 cases the antral rugæ were thickened, hypermobile, and redundant, with microscopic evidence of mild to severe chronic inflammation in the mucosa or submucosa. In 1 case congestion and multiple small superficial ulcerations were present on the prolapsed folds. Thickening of the pyloric muscular ring with apparent narrowing of the pyloric canal was seen in 4 of the 5 cases examined microscopically. In 4, the entire circumference of the pyloric mucosa was involved in the prolapse; the other 2 showed only tongue-like projections.

Norgore and Schuler,[10] described 2 cases treated by partial gastrectomy on account of vomiting and epigastric pain made worse by solid foods. Levin and Felson[11] found 18 cases of prolapse in 100 patients with no digestive complaint. Of the 1000 patients examined by Rappaport et al., only 28 had no gastro-intestinal symptoms, and of these 3 showed mucosal prolapse; of 118 with lower abdominal symptoms only 16 had mucosal prolapse; while of 854 with upper abdominal symptoms 136 had prolapse. The proportional differences between the three groups are small. Of the 155 patients with mucosal prolapse 91 showed one or more further definite abnormalities in the gastro-intestinal tract; hiatus hernia, cholecystitis or gall-stones, and peptic ulcers were the most common. Of the remainder 39 had chronic recurrent dyspepsia consisting of periodic epigastric fullness, generally after heavy or spicy food, flatulent discomfort, and heartburn; discomfort was felt soon after a meal and actual pain was rare. Bicarbonate of soda gave much relief, but aluminium hydroxide gel gave little. Gain of weight before the onset of symptoms was not uncommon. All these 39 patients had notable evidence of neurosis, and said that their symptoms were often induced by emotional disturbance. 4 patients (not all in this series) were treated surgically, but relapsed afterwards. A further 25 patients in the series with positive radiological findings had only transient epigastric discomfort or no upper abdominal symptoms at all. Gastric analysis and gastroscopy gave no definite information. As in New's[7] series the appearances were more often seen in men than in women, and were most usual in the fourth and fifth decades.

It thus seems that prolapse of the gastric mucosa into the duodenum may give rise to either no symptoms at all or to mild symptoms, especially in the neurotic. There is no evidence that this disorder is a hazard to the patient's life.

GENERAL PRACTICE IN SCOTLAND

The Scottish Medical Practices Committee issued its fourth report this week. The committee welcomes a substantial increase in the number of principals in practice: on July 1, 1952, there were 2379 doctors providing general medical services in Scotland, compared with 2328 a year before; and of this year's total 2127 also provided maternity medical services, as against 2063 in 1951. The latest figures show that the average number of patients per doctor in Scotland is about 2150; the corresponding figures for England and Wales at the beginning of this year give an average of about 2400 per doctor, but, as the annual report of the Ministry of Health[12] points out, the total number of patients on doctors' lists is still inflated by duplicated and out-of-date entries. Moreover the Scottish average is reduced by the figures for the isolated areas where a doctor is needed even though his list is very small; the doctor on the island of Coll, for example, has a list of only 209. There are many places, chiefly in the industrial areas, where doctors still have more patients than the committee thinks desirable, and the report hopes that when the proposed changes in the distribution of the central pool come into effect, new doctors will find it easier to gain entry into established practices in these areas.

On the question of ways into general practice, the evidence before the committee in the past year has strengthened its view that "the likeliest method for a young doctor to establish himself in general practice is to be assumed into partnership, preferably after an initial period of assistantship." Doctors who have set up new and independent practices (even in districts which had been included in the list of underdoctored areas) have often, in the committee's experience, had a hard time of it, and the proportion of doctors who apply to start practice on their own account is decreasing. The committee granted 148 applications for admission to executive councils' lists during the year under review, and only 31 of these were from doctors going into independent practice, whereas in the previous year the proportion was 20 out of 74.

Scottish executive councils advertised 25 practice vacancies during the year, and they received over 500 applications. There were not, of course, over 500 doctors looking for a permanent place in general practice, because many were applicants for more than one vacancy; but nevertheless "the Committee have been concerned to note the difficulty still experienced by many doctors anxious to become settled as principals." Roughly 70% of the applicants were already engaged in general practice, either as assistants or as principals who sought to change the type or locality of their practice; 10% were hospital doctors; 10% were doing locum appointments of various kinds; and the remaining 10% were employed in the public-health service, Government medical services, and comparable work. A further analysis of 21 of the advertised vacancies shows that 17 of them went to doctors under the age of 40. The corresponding committee for England and Wales observed last year[13] that, in the matter of openings in general practice, "the scales are now more than balanced fairly in favour of the younger doctors"; and the position in Scotland justifies the same remark.

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[1] Forsell, G. *Amer. J. Roentgenol.* 1923, 10, 87.
[2] Eliason, E. L., Pendergrass, E. P., Wright, V. W. M. *Ibid*, 1926, 15, 295.
[3] Rees, C. E. *Surg. Gynec. Obstet*, 1937, 64, 689.
[4] Scott, W. G. *Radiology*, 1946, 46, 547.
[5] Ferguson, I. A. *Ann. Surg.* 1948, 127, 879.
[6] Rappaport, E. M., Rappaport, E. O., Alper, A. *J. Amer. med. Ass.* 1952, 150, 182.
[7] New, P. F. J. *Brit. J. Radiol.* 1951, 24, 441.
[8] Wellens, P., Spyckerelle, G. *J. belge Radiol.* 1949, 32, 157.
[9] Manning, I. H., Gunther, J. U. *Amer. J. Path.* 1950, 26, 57.
[10] Norgore, M., Schuler, I. J. D. *Surgery*, 1915, 18, 452.
[11] Levin, E. J., Felson, B. *Radiology*, 1951, 57, 514.

[12] See *Lancet*, Oct. 11, 1952, p. 729.

SALINE INFUSION

In his challenging letter on p. 883, Dr. Murphy raises the question whether we are allowing patients to die for want of adequate saline infusion. He dismisses the dangers of overloading the circulation as a bogy, at any rate in patients with no primary cardiac or renal failure. He points out that normal people can readily get rid of large loads of salt and water; and he might have added that normal people can withstand infusions of saline, plasma, or blood up to 2 litres without any notable symptoms.[14] The weakness of his argument lies in the implied transfer of the homœostatic powers of a healthy person to one who has just sustained a major operation. There is clear evidence that in the post-operative period both water and salt are excreted abnormally slowly;[15] and the patients are in the grip of a major metabolic disturbance.[16] Pathologists are familiar with the sodden lungs of patients exposed to excessive intravenous saline, even when that unfamiliar tool, the stethoscope, has not revealed pulmonary œdema during life.

The crux of the matter would seem to lie in accurate diagnosis of salt depletion before beginning treatment. There is no excuse for saline treatment as a routine post-operative measure, and little doubt that saline infusion can be dangerous to a patient who is not salt-depleted. In the salt-depleted patient, on the other hand, saline infusions are well tolerated and beneficial, and the amount of saline required to restore circulation and well-being may, as Dr. Murphy claims, be very large. The diagnosis of severe salt depletion must be based on a history of salt loss (usually from the alimentary tract, but sometimes in the urine, as in diabetic coma) and on clinical dehydration and collapsed veins. In severe salt depletion the serum-sodium is low, and chloride is often absent from the urine. Given the clinical context and the signs of serum-sodium depletion, it is safe to press on boldly with saline infusion. The deficiency of sodium associated with severe dehydration is of the order of 1000 m.eq., representing some 60 g. of salt. Saline infusion on this scale is only justified by an accurate previous assessment of the deficit. In patients with acidosis about half the necessary sodium should be given as lactate; and potassium should also be given during massive saline infusion, which increases the urinary excretion of potassium. Potassium should be administered by mouth when possible; but the greatest problems of electrolyte replacement arise in patients with paralytic ileus or fistulæ, and for these intravenous potassium may be needed. Cooke and Crowley[17] have lately given a practical account of the management of electrolyte loss from the gastro-intestinal tract.

So far as electrolytes are concerned, improved post-operative management depends on taking more care with the individual patient and adjusting our treatment to his needs, so far as we can discover them.

ONE MAN'S MEAT

In the days when travel was possible, one could leave one's customary diet of bread and tea to travel north and eat scones and haggis. One could then cross the sea for the pastries and dairy produce of Denmark, go south for the crêpes and snails of France, and on for the potatoes and beer of Germany, and then either east for the rice and chow-mein of China or west for the breakfast cereals and soft drinks of the U.S.A.; one could even taste the corn and fat-back of the southern States before passing into Mexico to gorge on tortillas and chillies. Nevertheless, these foods of civilised peoples are all much of a muchness. It is among less civilised races that diet becomes either very monotonous or very varied: very monotonous if only one foodstuff is to be had throughout most of the year (as with Eskimos), or very varied if one downs almost anything that can be chewed and is not subject to a taboo.

On Oct. 18 the Nutrition Society devoted a day to the discussion of unusual foods. Some would have us eat grass (euphemistically called leaf protein), some green algæ, some synthetic fats made from coal. Mr. W. A. P. Black, PH.D., stated the case for seaweed. To the analyst this seems an excellent food: 15% protein, some fat, a high mineral content, a liberal supply of vitamins including apparently vitamin B_{12} (or cyanocobalamin as we now should call it), and plenty of agar to add bulk. Furthermore it contains not only 1% iodine but also 3 : 5-diiodotyrosine ready-made for the thyroid. However, the dietists present were not told how to cook it. Should it, one wondered, be fried in deep fat, or perhaps be chopped, boiled, and served with grated cheese? Mushrooms and toadstools were championed by Mr. J. Ramsbottom, D.SC. In any country other than this such fungi would not be classed as an unusual food; and the widespread fear of them is not justified, since only *Amanita phalloides* and two related types are poisonous. Mushrooms are not rich sources of nutrients, and only the epicure would pay the price of 16*s.* a pound which was reached in the war. Probably Dioscorides was right in classifying mushrooms into those which were poisonous and those which were not, and leaving it there. After this vegetarian start the meeting passed to a meat dish with an authoritative discourse on insects as food from Mr. W. S. Bristowe, D.SC. A zoological blind eye was apparently turned on this address, which was more about spiders than insects. The important point was that "insects" taste nice: the flavour of the lizard is musty, but a giant water-bug tastes like a strong gorgonzola, only more so; the so-called "bird-eating" spider, without its jaws and toasted, tastes like excellent marrow, and there is quite a lot to be said for boiled locusts. The question of taste was obscure to Mr. A. L. Bacharach, who thought that the "meaty" flavour was always accompanied by a backbone and that invertebrates always tasted vegetable.

Mr. F. Aylward, PH.D., described investigations by the Massachusetts Institute of Technology into the excellent dietary of the inhabitants of Central America; the plants eaten by the Mexicans are much richer in nutrients than are those in the U.S.A. Dr. H. M. Sinclair then took the meeting to visit the Eskimos and Canadian

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13. *Ibid*, 1951, ii, 982.
14. Sharpey-Schafer, E. P., Wallace, J. *Brit. med. J.* 1942, ii, 304.
15. Coller, F. A., Campbell, K. N., Vaughan, H. H., Iob, L. V., Moyer, C. A. *Ann. Surg.* 1943, 119, 533.
16. Wilkinson, A. W., Billing, B. H., Nagy, G., Stewart, C. P. *Lancet*, 1949, i, 640.
17. Cooke, R. E., Crowley, L. G. *New Engl. J. Med.* 1952, 246, 637, see *Lancet*, Sept. 20, 1952, p. 574.

Indians. From the dietary of seal and fish consumed by Eskimos a century ago he calculated the aliments and nutrients obtained. It seems that they fared very well provided they could catch the seals, and there was certainly no deficiency of vitamins. Although the diet was very rich in protein, rich in fat, and poor in carbohydrate, there was no reason why it should give rise to ketosis; but it was perhaps surprising that arteriosclerosis was so rare. Indeed, the other diseases of civilisation (such as diabetes mellitus, tuberculosis, appendicitis, cancer, and dental caries) were extremely rare among the Eskimos, and still are in those few places where they have not been contaminated by white men. Importation of the white man's diet brings with it his diseases. This has been particularly obvious in the case of the Indians: the Crees visited by Dr. Sinclair in 1943 used to be hunters subsisting on an excellent carnivorous diet; but now their dietary is mainly bannock, white flour, lard, and sodium bicarbonate, mixed together in haphazard proportions. This fate has also overtaken the Australian aborigines, whose food was discussed by Mr. G. H. Bourne, D.SC. Now they consume white flour and sugar, whereas previously they subsisted on various animals ranging from marsupials and buffalo to moths and caterpillars. In the last paper, Dr. B. M. Nicol discussed the protein in the diet of the Isoko tribe of the Niger Delta. Here again was a tribe largely carnivorous in habits who consumed fish, snails, snakes, and lizards; but to these they added yams, cassava, palm oil, and palm wine.

It is perhaps unfortunate that there was not enough time to correlate the dietaries of these different peoples with the incidence of diseases among them: this is a subject of great interest to which far too little attention has been paid. Sometimes dietary and culinary habits are dictated by expediency: the Eskimos obtain large amounts of vitamin C from the skin and stomach contents of the animals they eat, and most of their food is eaten raw. These habits arise, not from a knowledge of dietetics, but from the necessity of eating as much as possible of the slender food-supply and from the difficulties of cooking in an igloo. Physiologists might well study the Eskimo further, particularly when such interest is being taken in survival under Arctic conditions. And some of the problems appear to concern physicists; for Dr. Sinclair mentioned that the Yakuti are alleged to be able to eat 36 lb. of beef and 18 lb. of butter (about 120,000 calories) in under three hours. Throughout this interesting discussion it appeared that there were serious gaps in our knowledge, severe limitations in our choice and enjoyment of food, and a surprising difficulty in describing tastes. It is doubtful if we have advanced much beyond the problem of cooking a snark.

PORPHOBILINOGEN

PORPHOBILINOGEN, the Ehrlich-reacting material which appears in the urine of acute porphyria, has long been one of the veiled figures which haunt the course in clinical pathology. It has some diagnostic and prognostic interest to the clinician, but its main importance is its association with the whole subject of porphyrin chemistry. In this connection the biochemist has had it on the list of "wanted" substances for some time, and now a particularly elegant piece of research by Westall[1] has culminated in its crystallisation. This is a considerable feat, since the insolubility of porphobilinogen in most non-aqueous solvents and its instability make it very unmanageable. Its isolation has been made possible by the development of ion-exchange resins as chromatography media, and by the observation that porphobilinogen can be precipitated from urine by mercuric acetate.

Porphobilinogen has usually been thought to give rise, under certain circumstances, to uroporphyrin. This view, recently contested by Hawkinson and Watson,[2] has now been proved correct. The change takes place on boiling at any pH between 1 and 8, the largest yield being obtained in $0{\cdot}5N$ HCl. On standing at room-temperature, porphobilinogen is slowly converted to the reddish non-porphyrin pigment, porphobilin.

The importance of any substance which can give rise to porphyrin lies in the possibility that it may be a natural intermediate in porphyrin synthesis. The number of these known or suspected precursors is growing—recent work by Weatherall[3] at the London Hospital, for instance, strongly suggests that in the lead-poisoned rabbit all the urinary porphyrin is present as precursor at the moment of excretion. The nature of porphobilinogen has been the subject of several guesses. The most popular has been that it is a monopyrrole or more probably a dipyrrole—possibly a dipyrrylmethane of the type postulated theoretically as an intermediary in porphyrin synthesis. This guess can now be tested. Whether porphobilinogen in the urine is an overflow of a normal metabolite which is produced in excess, or whether it is in itself an abnormal material, cannot yet be settled. But some interesting light on porphyrin synthesis and on congenital errors of metabolism is likely to come from further work on porphobilinogen which is now in progress.

FIFTY YEARS OF MIDWIFERY

IN 1900, out of every 300 London mothers giving birth, one died; in 1950 one died out of every 1880. The first Midwives Act, which set in train the events which led to this extraordinary change, was passed in 1902; and on Oct. 28 the Royal College of Midwives entertained the Minister of Health at their celebration of the golden jubilee of this momentous piece of legislation. Before it was passed, as the *Manchester Guardian* (Oct. 27) recalls, women who could not afford to pay a doctor to attend them in confinement relied on the Gamp, who was sometimes kindly and experienced, but all too often cut to the pattern of the immortal Sarah. It is true that in 1872 the Obstetrical Society of London, after failing to persuade the Government to take action, started their own examination for midwives, though they could not compel women practising midwifery to take it; and when the Midwives' Institute, now the Royal College of Midwives, was founded in 1881 it immediately undertook the further training of women who held the Obstetrical Society's certificate. It took eleven years, and all the money the institute could raise, before the Act making it an offence for an uncertificated woman to attend a delivery (unless she was working under a doctor) reached the statute-book. The official qualification became the certificate of the Central Midwives Board; and after 1910 the board recognised the institute as a lecture centre for pupil and postgraduate midwives. The increasing work of the institute in the interests of maternity and child welfare led to its change of status, in 1941, to the College of Midwives, and in 1947 to the royal recognition.

Today the mother has many services at her command. The midwife, however, remains a key figure in the team, and may fairly take much credit for the fall in the maternal mortality-rate. Nor has her part been small in the saving of infant lives: since 1902 the infant-death rate has fallen from 133 per 1000 live births to 23 per 1000 in the third quarter of this year—the lowest figure on record.

THE ASSISTANT EDITOR OF THE LANCET

WITH great regret we announce that Dr. Edward Clayton-Jones, because of continuing ill health, has resigned. The Proprietors have appointed Dr. Ian Douglas-Wilson to succeed him as assistant editor from Nov. 1.

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Special Articles

THE GROUP INTERVIEW IN THE SELECTION OF MEDICAL STUDENTS

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THE suggestion has several times been made (Biesheuvel 1947, Millar 1948, Brinton 1951, Warburton 1952) that the group interview might be adapted for use in the selection of medical students, and it may, therefore, be of interest to record some experiments with it at University College, London.

It is a generally accepted principle that candidates should be interviewed before being offered a place in a medical school. This implies the recognition of the great importance of personal qualities in a doctor, and the assumption that these can be assessed by interview. The unreliability of the conventional interview has, however, often been clearly demonstrated—by Hartog and Rhodes (1936) for instance. Nevertheless the interview is probably the only safe way of choosing those candidates whose personal qualities recommend them for a medical career. The question then arises: how can the interview be improved, or supplemented, so that we can select more successfully?

One of the difficulties is that we are attempting to predict, from the candidate's behaviour at the interview, what his behaviour will be as a student and doctor—and he may behave very differently in different situations. This difficulty stimulated the development of some of the procedures used by the War Office Selection Board and the Civil Service Selection Board; here candidates are observed in situations more like those in which they will do the work for which they are being selected. There are obvious difficulties in using such methods for medical students, because we could not hope to test them for the skills that a doctor needs, but only for the capacity to develop these skills during their training. One way of meeting the difficulty is to extend the process of selection into the early part of the training period, as advocated by Brinton (1951). Another way is to watch the candidate in a number of different situations, so that his assessors get a better idea of the range of his behaviour; and various forms of group interview could be used for this purpose.

COMPARISON OF INDIVIDUAL AND GROUP INTERVIEWS

In the individual interview the candidate is seen reacting to one person, or to a board, and in general he is expected, and he expects, to behave as a junior to a senior. It is proper that his behaviour in this rôle should be tested, for a good deal of a student's time, and part of a doctor's, will be spent in this way. Most people, however, do not behave towards juniors or contemporaries in the same way as they do towards seniors—some people behave very differently indeed—so the value of such an interview, *in indicating how the candidate will* behave to patients or to colleagues, is limited.

In a group interview the candidate is seen in a much more complex social situation, for he is reacting to several other candidates, who are contemporaries, as well as to his assessors, who are seniors. Thus, the group interview samples the candidate's behaviour in a different social setting. It differs from the individual interview in another very important respect. The etiquette of the individual interview is fairly well established: the candidate usually speaks only *in answer to a question,* or when invited to make a statement; the assessor takes the initiative and the candidate responds. In group interviews, however, the candidate must form his own judgment of the situation and how to conduct himself. The assessor plays a much less active rôle, and the candidate a much more varied and autonomous one.

DEVELOPMENT OF THE GROUP INTERVIEW

Testing by various group methods was developed during the last war (O.S.S. Assessment Staff 1948, Harris 1949). Group interviews are now an established part of the Civil Service Selection Board procedure (Vernon 1950). They are also being used in several other ways—e.g., in the selection of applicants for training as teachers at Dudley Training College (Jordan 1950) and at Manchester University (Herbert 1951); in making various appointments in industry (Fraser 1950); in choosing dental students at Manchester University (Warburton 1952) and medical students in the U.S.A. (Wood et al. 1949).

GROUP INTERVIEW AT UNIVERSITY COLLEGE

The group interview can be used in different ways; the main aim may be to test leadership, or simply to see how well candidates get on together. For each purpose modifications of technique are of course necessary. In our interviews we were mainly concerned with testing social adjustment, and the ability to think effectively *about an abstract scientific topic.*

The candidates were interviewed in groups of eight, sitting round a table with two assessors. The selection procedure (Aitken and Johnson 1952) was explained, and we told them that we were trying this rather complicated method of three interviews because candidates often felt that in the usual interview lasting ten minutes or so they did not have time to do justice to themselves. By this method they would be interviewed in all for about one and a quarter hours. We tried to reassure them as much as possible by saying that we appreciated that most people found any interview an ordeal, and if they were not used to discussions they might find this kind particularly difficult. Their final assessment, however, would not depend on any one test alone. They were then asked to discuss as freely as possible the topic printed on a slip of paper given to each candidate.

The Topic

We have experimented with the kind of subject the candidates are asked to discuss. To give everybody a fair chance, we avoided subjects about which the knowledge and experience of candates might vary; and controversial subjects were excluded because we did not want to test ability to debate or argue. "The qualities necessary in a doctor" was used for some time, but we found this subject too general to be discriminating. Such topics as "The results of an experiment cannot be wrong" and "In science the primary duty of ideas is to be useful and interesting even more than to be true" *were stimulating though difficult.* They seemed to have the following advantages:

(1) It is probable that they are equally unfamiliar to most candidates so none would have an unfair advantage.

(2) They invoke the kinds of thinking we wanted to test, and allow discrimination between candidates.

(3) We were developing a method of teaching certain *scientific skills by group discussion* (Johnson 1950, 1952), and we could call on our experience of the ways students talk about such problems to help to assess the candidates.

The Behaviour of the Assessors

This is of great importance in any interview, and it was our aim to make the candidates feel as much at ease as possible, so that they could concentrate on the problem. They would almost certainly feel themselves as competitors, so we maintained a neutral position, showing no approval or disapproval, agreement or disagreement, *but at the same time trying* not to appear aloof or unsympathetic. We found it best to say very little in the early stages of the discussion in order to give candidates the opportunity of taking the initiative. Later we would take a more active part, if necessary trying to draw out any specially silent people, or confirming the impressions we had already formed. Finally, with the aim of relieving any feeling of frustration which the participants might have at grappling with such a difficult subject, we would attempt to clarify confusions, point out discrepancies between statements, or reconcile different views, and show how the discussion had been concerned with problems of very fundamental scientific importance. With rare exceptions the assessors found the discussions extraordinarily interesting.

There is obviously a need to experiment with the part that the assessors play in group interviews. The experience of those who have studied some of the complex interactions between participants in interviews can be extremely useful in helping one to understand some of the difficulties involved (Oldfield 1941, Rogers 1951).

Assessing the Candidates

First, the two assessors separately graded the candidates on the five-point scale (Aitken and Johnson 1952). They then discussed them, and agreed on the grade which was to be presented at the final meeting of selectors. The assessment is based on the observation of a complicated piece of social and intellectual behaviour, certain aspects of which can be considered separately.

Adjustment to a difficult situation.—The topics are difficult, and the whole situation in which the candidate finds himself is very trying, but a doctor's life is, after all, not one of uninterrupted ease, and it seems legitimate to assess candidates on their ability to cope with some kinds of stress.

A few candidates, in spite of encouragement, say so little during the 50-minute interview that any assessment of them is bound to be unreliable. Nevertheless, it is probably fair to assume that such a candidate has less claim to a place than one who can cope satisfactorily with the same situation; and in fact none of the four candidates who made no contribution to the discussion did well in the individual interviews.

But candidates who say little do not necessarily get a low assessment. Some have an extraordinary capacity for taking in what is going on, and after saying nothing for a long time will suddenly take charge of the discussion, clarifying and summarising what has been said. Others seem to ruminate apart, and then produce a new idea which leads the discussion into different channels. It is scarcely necessary to add that those who say a lot do not always get a high assessment.

Personal relations.—Some candidates seem to establish good relations with others easily, while some are aggressive or overcompliant; some are consistently helpful and sympathetic, others carping and destructive; some seem to be generally liked, even if they are obviously more competent than the rest, and others seem to put everybody's back up. A very few seem to be uncoöperative, or at least not very tactful—e.g., those who appear bored and listless, or those who persistently talk too much so that others do not get a chance. Social factors have to be taken into account in assessing the ease of personal relationships, and the information supplied on the application form and referee's report are helpful here. We are attempting to assess what Dr. C. F. Harris (1951) described as the "capacity to fit in with and to surmount obstacles in his environment . . . the capacity of a public school boy to live down the worst pitfalls of a public school education, or of a miner's son to remain on equal terms with those coming from an entirely different home background."

Understanding other people.—Some candidates listen attentively to what others say and seem to understand easily; others ignore, override, or misunderstand them.

Ability to understand the topic.—Some people often refer to the typed slip, and try to make sure they are discussing the subject given; others read the statement inaccurately and may fail to discuss it properly.

For instance, it is common for at least one person in each group to talk as though the topic "In science the primary duty of ideas is to be useful and interesting even more than to be true" was in fact "The primary duty of science is to be useful"—i.e., to provide equipment and material of practical use in everyday life. Again, the statement "Observation is a process of selection or discrimination—a process of selecting and discarding from the sum total of presenting objects" is sometimes misinterpreted, and discussed as if it read "Selection is a process of observation . . ." and as if it was concerned with the selection of medical students.

Mistakes such as this (and indeed all the statements made) must of course be evaluated in their context. If the first person who speaks makes such a mistake he may be excused on the ground that perhaps he feels impelled to say something and does not allow himself time to consider; but a candidate who makes the same mistake late in the discussion or who persists in making it even when it has been pointed out to him is less easily excused.

The quality of the contributions to the discussion.—The points looked for here include clarity of expression; recognition of sources of confusion—e.g., that caused by using the same word in different senses; comparing and contrasting various viewpoints; bringing up new points; and reviewing the discussion at intervals. The discussion lasts long enough for us to see that some candidates are able to reconsider, and if necessary to modify, their own opinions, while others seem to be less receptive to ideas which are new to them, and tend to repeat without modification things they have said before.

CONCLUSIONS

The ideal candidate is one who adjusts himself satisfactorily to the situation; gets on reasonably well with everyone else; listens to what others say; expresses himself clearly; talks sensibly; has a good grasp of the implications of the topic and of the matter of the discussion; and is able to re-evaluate his opinions in the light of what is said. This may seem a tall order, but of the 204 candidates interviewed this year, 19 were assessed as A (very good) and 64 as B (good). Candidates considered good are of many different kinds, showing various combinations of the desirable qualities. Indeed, the group interview seems to bring out the infinite diversity of candidates.

The kind of qualities which can be assessed by this method, the nature of the topic used, and the manner in which the discussion is conducted all need further experimental investigation. The remark of Oldfield (1941) about the individual interview is also true of the group interview: "At this stage of our knowledge the prime object of discussion must be to stimulate thought. Those whose business it is to conduct interviews could render invaluable service to their art if they would reflect upon the methods they use, give expression to their views, and try to perceive clearly the psychological implications and conditions of what comes to their notice."

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FILARIASIS IN THE PACIFIC

FROM A CORRESPONDENT

FILARIASIS is widespread in Polynesia and is indeed the main bar to progress in these beautiful and fertile islands. The International South Pacific Commission set up in 1949,[1] which now has its headquarters in Naumea, New Caledonia, is concerned, among other things, with suppression of the disease. The parasite responsible is a non-periodic microfilaria, whose adult form is now known as *Wuchereria pacifica*, and it is transmitted by the day-biting mosquito, *Aëdes pseudoscutellaris* (probably in reality *A. polynesiensis* Marks).

Since 1948, American workers have been active in the study of Polynesian filariasis, especially in Samoa and Tahiti, and some results of their researches have now been published. A group of entomologists, parasitologists, and pathologists from the University of California has been working in close association with members of the French Medical Research Institute at Papeete, the capital of Tahiti.[2] In this historic island the proportion of inhabitants harbouring microfilariæ in their blood and showing clinical signs of the disease is higher than it is in any other Pacific island yet investigated. Among the large number of people examined, no male over the age of 50 was free from signs of filariasis. (In all parts of Tahiti the proportion of males harbouring microfilariæ was higher than the proportion of females, which points to some discrepancy in exposure to, and acquisition of, the primary infection.)

Following the example of Fiji, an all-out effort is being made with the eventual aim of eradicating the main mosquito vector, *A. pseudoscutellaris* (*polynesiensis*), from the island of Tahiti and its satellite Maiao (approximately 60 miles west).[2]

To assess the prevalence of filariasis, studies were undertaken in nine areas, of which eight were on the main island and one on Maiao. The indices chosen to determine the ultimate effect of control measures were based on the average number of microfilariæ per 20 c.mm. of blood per person, the proportion of persons whose blood contained microfilariæ, the number of attacks of lymphangitis or filarial fever per person in the area, and the density of *A. pseudoscutellaris* (*polynesiensis*) in the larval and adult stages as well as the rate of filarial infection in wild-caught mosquitoes. A census of the adult mosquito population was made by means of observations at three "resting" and three "biting" stations in each of the nine areas; at the former collections were made between 8 and 9 A.M., and at the latter between 1 and 2 P.M. Here the captured mosquitoes were dissected to ascertain whether they were infected. A comparison between the mosquito populations and the average number of infected larvæ found in them, before and during the experiment, provided valuable information about differences in transmission-rates.

In the nine areas the average total percentage of the population with microfilariæ in the blood before the inauguration of control measures was 32·2. (In one area in Tahiti it was 58·3, while in Maiao it was 21·1.) One area (with a percentage of 38·6) was retained as a control, while in the other eight the measures varied. In some of them sanitation alone was employed; in others sanitation plus destruction of mosquitoes with D.D.T. In some the population were given 'Hetrazan' (2 mg. per kg. body-weight three times daily for seven days); and in others both hetrazan and insecticide were used. Sanitary measures were directed to mosquito breeding-places, with the object of draining or destroying them. Anti-mosquito measures consisted mainly in spraying the interior as well as the exterior of houses with 5% D.D.T. emulsion in water every three months while all vegetation within thirty yards was treated with 1% of this insecticide.

Of the nine species of mosquito, *A. pseudoscutellaris* (*polynesiensis*) and *Culex fatigans* were the most abundant. The former was found breeding in a great variety of places, the most important being coconuts, especially when rat-eaten. It seems that neither sanitation alone, nor D.D.T. alone, reduces the numbers of this aëdes as effectively as it reduces the numbers of other species. It was found, however, that where the population of an area had been treated with hetrazan the proportion of mosquitoes with infective filaria larvæ was reduced—in one area from 10 to 0·6% in a year.

The percentage of people with microfilariæ was estimated before, at six, and again at twelve months after treatment had been instituted. In each of the four areas in which hetrazan was administered, the percentage of positives fell appreciably; but a comparison of those positive before and after treatment does not show the effect of the drug so clearly as does a comparison of the actual numbers of microfilariæ per 20 c.mm. of blood, which on the average were less than 10% of the original number. It is particularly difficult to assess the influence of the drug on the frequency of attacks of lymphangitis, but in general it may be stated that the effect on other filarial manifestations was disappointing. The investigators feel that their data do not yet permit of statistically significant conclusions regarding the absolute superiority of any single method. In the attempt to formulate a programme for the control of filariasis which must extend over a long period, many points had to be taken into consideration. Necessarily it will require years of further study in order to determine how far the clinical manifestations of filariasis are reduced by the measures adopted.

A good deal of evidence on the transmission of filariasis outside the villages has been collected by Jachowski and Otto[3] in American Samoa. There a survey of ten villages was undertaken, and four collecting-stations were established for each village at varying distances from the open green or *malae* and at various distances in the bush leading to the banana or coconut plantations. Collections made within a period of $1^1/_2$ hours on a single afternoon yielded over 2000 mosquitoes which were then dissected for larvæ of *W. bancrofti*. In the bush itself the frequency of infected mosquitoes seemed to be related to the amount of native traffic, none being found in the areas devoid of human beings. The index of transmission was obtained by multiplying the density by the proportion of mosquitoes infected. From this it appears that mosquitoes in the houses and in the open *malaes* are of little importance compared to those in nearby bush or in houses close to it. The index is very high 175–275 yards from the centre of the villages. It thus appears that, in Samoa at least, one hour spent in the bush offers greater opportunities for infection than twenty-three hours spent in the village.

The age and sex distribution of microfilaræmia in Samoans added to the habits of the people, or to the biting habits of *A. pseudoscutellaris* (*polynesiensis*), support the conception of non-domestic transmission which is common also to *W. malayi*. Consequently in American Samoa residual spraying of native houses cannot be expected to be useful. The attack on the mosquito must be made in the bush. The same appears to be true for Tahiti and other islands of the Pacific where the non-periodic microfilaria is found.

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1. See *Lancet*, 1951, ii, 1082.
2. [illegible], H. K., Edgar, S. A., Mille, R., Kessel, J. F., Bambridge, B. [illegible] *J. trop. Med. Hyg* 1952, 1, 637.
3. Jachowski, L. A., Otto, G. F. *Ibid.* p. 662.

Reconstruction

PAYMENT FOR MEDICINES IN AUSTRALIA

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It has become a political necessity to safeguard national finance from excessive expenditure on drugs. Three methods are open to a government. It can make a charge on all medicines (probably a small sum payable on every prescription); it can standardise prescriptions by means of a formulary; or it can say that only certain selected drugs will be supplied without charge. The first method has lately been introduced in Great Britain by the shilling charge on prescriptions. The second method was proposed in Australia in 1944, but the restriction of the doctor's freedom to prescribe evoked an opposition strong enough to prevent adoption of the scheme. The third method was introduced in Australia in 1950 and has operated smoothly.

THE AUSTRALIAN EXPERIMENT

In 1950, under the Pharmaceutical Benefits Act, a limited service of pharmaceutical benefits was introduced in Australia which incorporated proposals put forward by the British Medical Association in Australia. They believed that the financial burden of medicines to the individual could be eased if the government paid for costly drugs. They therefore suggested that a limited number of "life-saving and disease-preventing" drugs should be provided without charge to the patient. By Commonwealth government regulation a list of these free drugs was issued, in which there were no compounds. At first the list contained 139 items, and by March, 1951, there were 185 items. The cost of the Pharmaceutical Benefits Scheme in 1951–52, the first full year of the scheme, was £7,327,400. Of this amount £6,700,000 was paid to chemists for 6,500,000 prescriptions. In the present year (beginning July 1) the expenditure for one month came to £496,900 for 523,000 prescriptions, an average price of 19s. per prescription. The total cost includes payments to hospitals, bush nursing-centres, flying-doctor service, and those practitioners who do their own dispensing.

In 1951 the Pensioners' Medical Service was introduced which allows for all persons in receipt of an old age, invalid, or widow's pension, a Service pension under the Repatriation Act, or an allowance under the Tuberculosis Act, or their dependants, to receive compounded medicines as a charge on the Commonwealth government. The drugs offered under this service are those drugs appearing in the *British Pharmacopœia*, and proprietary preparations are not included.

The payments to chemists for pensioners amounted to £357,600 during 1951–52 and covered some 1,600,000 prescriptions. (This is only eleven months' expenditure because prescriptions dispensed in one month are paid by the Commonwealth government in the following month, and the scheme began on July 2, 1951.)

Prescriptions in Australia may therefore be issued under two Acts or supplied privately; and the three methods of issue are kept separate. The organisation has worked smoothly in practice and with general coöperation. At the same time, costs have tended to exceed estimates, largely because new and expensive drugs have been introduced. About a third of the prescriptions dispensed by chemists each year are paid by the Commonwealth government under the two public schemes.

Soon after the schemes began it was evident that excessive quantities of certain drugs were being prescribed, particularly the antibiotics. Also the government was faced with the need to save dollars—some drugs were supplied from dollar areas only—and to start a stockpile of drugs which might become scarce. Accordingly a measure of control was introduced on the doctor's freedom to prescribe.

At first in 1950 the doctor who wished to prescribe streptomycin or chloramphenicol for one of his patients had to write: "I certify that in my opinion there is no other drug available which would be equally effective in this case." Nearly three months later it was decided that the doctor could only write such a prescription after he had received a numbered authority from the director-general of health or his delegate. In each State the Commonwealth department of health operates a 24-hour service to respond to calls from doctors on the telephone and by telegraph. The minister of health is empowered to declare by regulation that a certain drug may only be prescribed in the treatment of a disease specified by him.

DISCUSSION

Unnecessary prescribing is a subtle form of abuse, seldom entirely conscious, and under a scheme such as the Australian one a doctor may overlook the fact that the free list is costly to the National Exchequer and prescribe in a way likely to save his patients' pockets. Thus there are times—and cases of mild infection may perhaps serve as an example—when the practitioner may select the more expensive free drugs in preference to simpler and cheaper drugs for which his patients must pay. On a large scale—and Great Britain has a population five times as great as that in Australia—such habits might well make the limitation of pharmaceutical benefits to a restricted list more expensive than a small flat-rate charge on all drugs. On the other hand, the introduction of a small payment on every prescription in Britain makes it difficult to avoid individual hardship, and informed opinion in Britain has shown interest in the Australian scheme. Lord Moran,[1] who opposed the flat-rate charge on every prescription, suggested that a distinction should be made between essential and non-essential drugs, and only the essential drugs issued free of charge. Yet to make such a distinction might prove difficult in practice, since drugs are prescribed for people, and it is people, rather than drugs, that have an essential need or a less essential need. To take an example: a man in employment who has pneumonia and is absent from his work for a month or so, remaining on full or half salary and in receipt of sick benefit, would probably receive free treatment with an antibiotic (considered essential). On the other hand a man with a chronic disease, such as disseminated sclerosis, who is unable to work, might be asked to pay for sleeping drugs, digestive mixtures, and other palliatives (considered non-essential) which he needs from time to time.

By legislation the State may proclaim one group of drugs as free and another group as not free, or may impose a flat-rate charge on prescriptions; but at best either scheme is clumsy and unfair in practice, and irksome to doctor and patient alike. One can only conclude that in the long run the best way of limiting the cost of prescription is through the medical profession. Only the doctor can educate the inconsiderate and ignorant patient, and only the doctor can decide when a drug is necessary and when a patient should be asked to make a small purchase at the chemist's shop instead of claiming a prescription.

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[1] *Hansard*, House of Lords, March 26, 1952, par. 990.

In England Now

A Running Commentary by Peripatetic Correspondents

Sir Heneage Ogilvie last week must have pricked the consciences of many of us consultants. I know ever since I became a consultant physician in the eyes of the National Health Service, the terminology has worried me. This is the sort of thing that happens when perhaps one is invited out to dine.

Guest: "Oh, I hear you are a doctor. How wonderful! *Are you in general practice?*"

Self: "No, I work in a hospital."

Guest: "*You are a specialist, then?*"

Self (guiltily): "Well, I suppose I am officially."

Guest: "What do you specialise in? Are you a heart specialist or a nerve specialist, or what?"

Self (embarrassed): "I don't really specialise in anything. I do general medicine."

Guest (suspiciously): "I see."

Second Guest (whose wife's second cousin is a doctor): "I know, you're a house-physician."

Self: "No. I was one many years ago, but not now."

Hostess (coming to the rescue): "You're a consultant, aren't you?"

Self (miserably—with memories of the grand old men who taught us in our medical schools long ago): "According to the regulations, I'm of consultant status but whether I'm a real consultant, I don't know."

Silence, while all the guests take this in and become convinced you are lying and have been struck off the register for an illegal abortion or for signing a wrong certificate.

I wish Sir Heneage could devise a term for us which is not too insulting. Meanwhile, perhaps Mr. Stephen Potter could tell us how to cope with the situation, and direct the attention of the famous school at Yeovil to our predicament. How does Odoreida get out of it?

* * *

I got my fellowship and my allotment on the same day; I had waited a long time for both, but there was no doubt which gave me the greater pleasure. The allotment has waxed fat; never such tasty asparagus, such succulent strawberries and tomatoes to strain at the leash of their staking. All this, of course, is a matter of pride, but for the heaviest crop of all I can claim no merit. Our *Coprinus comatus* have had a long season and seem still to be coming on. Spinach marches proudly in ordered rank and even the marrows are marshalled, but you never know where coprinus will be tomorrow; perhaps between the bean rows, or round the rhubarb, or inside and outside the cold frame. Its range extends from one plot to the west of mine to two to the east—from all of which I harvest them to the doubting wonder of the owners. Before I bought the twin slim volumes, *Edible Fungi* and *Poisonous Fungi*, I knew coprinus only as the Inky Cap, nor thought of using it for anything but the blacking of leather shoes. Even after careful identification from legend and coloured plate I cooked and ate the first takings with terror in my heart, and for three days I ate them alone. The family hastened to inspect me each morning, but my health remained excellent. Then we had a Danish guest who ate them gladly, and they were won over; so now we all eat them every day. The taste of coprinus is like that of the field mushroom but perhaps a little stronger; they fry well, are delicious steamed and served with butter, and make an excellent sauce. Perhaps next year my allotment will yield *Morchella esculenta* or even *Cantharellus cibarius*. But by then the other allotment-holders may have been given the books for Christmas and be anxious to gather their own free-given crops! Till then we shall gorge ourselves and hope that the bomb-debris that underlies our tilth will burgeon as richly every year.

* * *

Our recent attempt at the best of three falls with one of the august bodies that reside behind Southampton Row has given us a respect for the London taxidriver's powers of observation and diagnosis. Inwardly trembling, but outwardly "with merry oath and laughter and a smile upon our lips," we stepped into a taxi and asked for Queen Square. Instantly penetrating the façade, he asked "Examination 'All?"

* * *

The boy who debunked Harvey in "News from School" on Oct. 18 is a lad after my own heart. I believe that if a group of 12-year-old modern schoolboys were presented with the anatomical facts as Vesalius knew them, at least half the boys would discover the circulation of the blood in five minutes. Why then, you may ask, did not Vesalius anticipate Harvey? When you look at Vesalius's illustrations of the heart you wonder how he could have accepted Galen's teaching that the blood passed from one ventricle to the other through pores in the septum. But, after admitting he could not find the pores, he let the matter drop. There are those who say he really did discover the true function of the valves but he was afraid that publication of his opinion might invoke religious persecution. This is pretty thin. I think the true answer is to be found in "climate of opinion." Brilliant anatomist though he was, Vesalius never escaped *from* the galenical climate. Harvey escaped—probably by chance, but possibly because he was a stranger. You can visualise him, awkward, mulish, and cranky, among the elegant Italians. He never really belonged, so he did not have so far to go.

That explains Harvey, because, the more you think of it, there was nothing really *in* the circulation—nothing that Macaulay's schoolgirl couldn't figure out in a few hours. And now in return for my explanation, can you tell me which philosopher, psychologist, or scientist, writing about 1911, invented the phrase "climate of opinion"?

* * *

The general practitioner's life is not made easier by the unceasing postal bombardment with bits of blotting-paper—varied with high-grade [illegible] to impress on him the virtues of [illegible]. There is, of course, no positive harm in this [illegible]table series, and no doubt when they are taken to school by the doctor's children the status of the family is enhanced. But it is a sobering thought that these snappy pharmacological messages often occupy most of the time which a busy practitioner can spare for professional reading. Is it fair to those who taught him his job in the medical school and hospital that he should be thus deserted? We live in an age that has seen the revival of the "News Letter." Topical, concise, and informative, it often fulfils a real need for the busy man who is putting all he's got into his job. Isn't it time we had a news letter in therapeutics—perhaps on the lines of the *Army Medical Department Bulletin* that so many isolated M.O.s found useful in the late war?

And then, what fun it would be spotting the authors of these miniature annotations: nothing longer than 100 words—what a training for aspiring after-dinner speakers. Here the limpid prose of a Robert Platt, there the authoritative dicta of a Henry Cohen, and that tell-tale phrase pathognomonic of an Englishman exiled in Scotland. Are we on the threshold of a new medical literature?

* * *

International kudology needs a clear head and a quick tongue. Before going to the States I was warned that no-one would be introduced to me as plain Professor unless for some unfortunate reason he had no doctorate of any kind. And so it turned out: it was an embarrassing moment meeting him. But there came another day when I had to confess that I also wasn't a doctor. Hoping to give the right impression, I went on to explain that in England a bachelor's degree was all that was required for qualification, and that there were a few very eminent men who were satisfied with the simple letters M.B., F.R.S. "Oh!" came the reply, "we never put membership of societies after our names."

* * *

A NEW DIALOGUE

Medico: Good morning, Socrates.

Socrates: Good morning, Medico. Did I see you emerging from the hospital just now?

M.: You did, Socrates.

S.: And what have you been doing there?

M.: Removing the tonsils of a dozen children.

S.: For the reason, I suppose, that they will be better without their tonsils than with them?

M.: Assuredly.

S.: Is every man therefore necessarily better without his tonsils than with them?

M.: How not?

S.: But I am asking you, Medico, whether you think that every man should be deprived of his tonsils at birth or at some other time.

M.: No, Socrates, not every man, for then there would be no end to the removing of tonsils.

S.: I understand then that you have to select some tonsils *rather than others for removal?*

M.: Certainly.

S.: Presumably those children with bad tonsils will be selected for operation rather than those with less bad ones.

M.: How right you are, Socrates!

S.: *It follows therefore that it is better to have bad tonsils* than good ones.

M.: By what process of reasoning, Socrates, have you reached that conclusion?

S.: For, O wonderful one, it is clear that those people with bad tonsils will be deprived of them, while those with less bad ones will be left with theirs.

M.: I suppose so.

S.: And what do you do with the children after the operation?

M.: They are put into several beds in one ward where they are cared for by the nurse until the wounds are healed.

S.: There are then, or might be, O Medico, twelve children in one ward?

M.: You say true things, Socrates.

S.: And have you read the instructions of the Governing Body about the number of cubic feet to be allowed to each patient?

M.: I am afraid that I have not.

S.: You surprise me, Medico. Surely it is your duty to read the regulations of the people set to govern you?

M.: I am a surgeon, Socrates. I am not an administrator.

S.: Indeed, Medico? But you would agree that the regulations are drawn up so that good should be done to patients rather than harm?

M.: I couldn't agree more, Socrates.

S.: Then if a sufficient number of cubic feet is not allowed to each child, more harm may eventuate than good?

M.: Perhaps.

S.: But surely, my good man, you must see this. Take horses for example: are not the best trained horses the ones allotted the most stable room?

M.: Yes.

S.: And the same would apply to bees, I suppose? Surely the bees with the optimum hivage area are the best cared for?

M.: I get you, Socrates.

S.: And does not the same principle apply to youths training at the Palæstra, criminals in prisons, badgers, and swallows and nightingales in their nests?

M.: I expect so.

S.: But listen, my good friend. I am speaking of facts and not of expectations. Surely you would not wish the human race to be *less well treated than animals*?

M.: Of course not.

S.: To return to horses, therefore—

M.: Look here, Socrates, I am a surgeon. You should tell other doctors these facts: see, they are all coming from the staff room yonder. But while I am with you, O *best* of men, tell me how I may best be enabled to perform my tonsil operations with a view to doing the most good possible to my patients.

S.: I would gladly do *so, Medico, but unfortunately* I have to come up before the Thirty in a few minutes: they are proposing to accuse me of corrupting the Youth's health by evading the regulations of the Governing Body and overcrowding the hospitals. . . .

Letters to the Editor

SPECIALISTS AND THEIR QUALIFICATIONS

SIR,—Sir Harold Himsworth *from a position* of authority stresses the dangers to research of too rigid and fixed boundaries between organised subdivisions of knowledge. On a question of terminology, may I however suggest that the term "stratification" is merely the same thing. I raise the question, not just as a verbal quibble, but because there is something of a different character which may legitimately be called stratification, and which is also a danger to research by interfering with the free interchange of ideas: I refer to stratification according to the position of individuals in the hierarchy of their group, a phenomenon particularly liable to occur in clinical medicine. It is my strong impression that both dangers are less marked in American than in British medicine, and that our American colleagues are both more bold than we are in following a clue outside their own specialised departments of knowledge, and better at mixing on terms of intellectual equality irrespective of hierarchical status within the group. Finally, is it really too late to reverse the present trend towards an excess of "precisely *prescribed requirements for the training of consultants* and specialists," and to recognise that too rigid definition of temporary boundaries of convenience, and consequently of qualifications for entering within those boundaries, may in the long run be harmful to progress?

London, W.1. DAVID PATEY.

FUTURE OF THE OCCUPATIONAL HEALTH SERVICES

SIR,—Those who criticise the report of the Dale Committee do so for two reasons: first, they have not understood its terms of reference; and, secondly, the critics assume that planning as such is a good thing.

The first misapprehension is easily corrected by those who take trouble to obtain the report and read it, when they will find the committee's terms of reference were very largely confined to conservation of man-power. May I recall that the committee proclaimed the importance of industrial health services. This is more than many of its critics have done. In the difficult political circumstances at the time of the committee's appointment and during its deliberations, this cannot, in fairness, be called timid. Even to have disposed of the implications implicit in the Prime Minister's ban on developments in industrial health services pending the committee's report, is a valuable achievement.

The onus of proof that planning is good should lie on those who wish to plan. The standard of British practice in industrial health is the highest in the world. That is no reason for not trying to make it better, but it is a reason for caution. Without exception all legislation planned in vacuo has been a failure. To hamper industry (meaning all forms of work) with unsatisfactory legislation is too serious. The usual argument used by planners is "what about the small factories?" I have not heard a logical development of the argument beyond this point. Supposing the state of small factories is bad (which I do not accept), can it be improved by direct action of doctors? That is the crux of the matter. Maybe stronger enforcement of stricter *minimum* standards is needed; but that is a matter of legislation and inspection, not of medical services.

Planners must meet the following difficulties:

1. In the British tradition employers are responsible for the health, safety, and welfare of their workers. Sanctions and duties are placed by law on employers and workers; this being so, they must be free to seek advice from doctors whom they trust and of their own choice. This advice will be the

more readily accepted if it is an integral part of management. To provide this advice is the primary function of industrial health services. In spite of much political exhortation, the interests of employer and employee are the same in this matter.

2. Enforcement (not vague supervision) of minimum standards must be uniform throughout the country if differences between different parts, as between Lancashire and Japan, are not to arise. Unless the relationship between the central government and local authorities is to be profoundly altered, enforcement by the servants of local authorities (e.g., medical officers of health) is not acceptable.

3. Medical examinations (except for strictly limited objectives, such as a few toxic hazards) have, in modern circumstances, little bearing on health. Uncritical recommendations for widespread medical examinations as panaceas for all ills are too common. Since the school health service now sends young persons from school either in excellent health or with their defects known and categorised, even the appointed factory doctor's examination of young persons is of very doubtful utility. What other function is there for doctors, not part of the managerial team, to perform unless it be inspection to see that minimum standards are observed?

4. Very few doctors have the requisite knowledge and skill to give advice of the nature required by employers and workers. Vague generalisations will quickly bring medical advice into disrepute. How are the planners going to educate medical officers of health and others who wish to bring occupational medical services within their grasp?

Let me be frank. The Dale Committee's report undoubtedly disappointed many. To say that evolution is better than planning is unpopular. Evolution does not lend itself to quick paper empires. Too many persons think that industrial (or occupational) health is primarily a medical matter. To build up a large superstructure of doctors around industry would only place a useless and needless burden of bureaucracy and mediocrity on men and women at work. In the end, even the National Health Service depends on the efforts of these men and women. Accurate information, as opposed to theories and dogmatic summaries, is what is wanted. When this has been obtained, then and then only may action be taken with safety. I will forecast that action based on knowledge will be toward a small, highly skilled cadre of doctors rather than toward unwieldy and untrained regiments. My criticism of Government departments is not that they have not agreed—for they have nothing to agree on—but that one or all of them have not initiated surveys. Perhaps the coördinating committee recommended in the Dale report, if and when appointed, would do this.

Lest anyone should reply that this letter is special pleading, let me declare my interest. I was a member of the Dale Committee.

Southwell, Notts. T. A. LLOYD DAVIES.

SIR,—Your championship of occupational health is indeed welcome to all of us engaged in this field. Your contributors and your leading article (Oct. 11), however, seem to the less vocal of us to miss one essential point. The subject is treated as if it were a "service" which can be imposed from above by legislation, and quite logically the argument goes on to suggest that the answer lies with the Ministries.

The answer really lies with doctors themselves. The whole medical profession almost automatically knows its way about the stresses and strains of family life, of the life of the diabetic and the tuberculous. There are very few doctors, however, who understand the stresses and strains of modern industrial life; and until more doctors are trained in elementary industrial administration, legislation and a "service" will simply operate in vitro. Nothing I have yet read satisfies me on the in-vivo end of the stick.

Radlett, Hertfordshire. P. PRINGLE.

RECURRENT POLIOMYELITIS

SIR,—During last year's epidemic of poliomyelitis in Milwaukee, which was the most severe in the city's history, there was an instance of recurrent poliomyelitis. 49 examples of second attacks of poliomyelitis have been published, but 17 of these are considered doubtful because the details are incomplete, because a long time elapsed between the acute disease and its diagnosis, or because some other disease or trauma complicated matters.

First Attack

A white male child, aged 8 months, was admitted to South View Isolation Hospital, Milwaukee, on Sept. 15, 1950, with a story of fever for 5 days and difficulty in moving his right leg. There was moderate neck rigidity and spasm of the back muscles. The right leg was flaccid, and the right foot was moving spontaneously. The patellar reflex was absent on the right, but the ankle-jerks were present. No symptoms of bulbar involvement were apparent.

Lumbar puncture yielded a clear, colourless fluid under normal pressure; it contained 90 cells per c.mm., 84% of which were lymphocytes.

A diagnosis of acute anterior poliomyelitis was made. The boy recovered satisfactorily and regained almost normal movement in the right leg.

Second Attack

On Aug. 16, 1951, at the age of 19 months, he was again admitted to this hospital. The previous day the child vomited and became irritable and feverish.

There was bilateral ptosis, most marked on the left, an inconstant right internal squint, definite neck rigidity, tenderness and spasm of the hamstrings, and tightness of the back muscles. Generalised tremor was present; and the right leg tended to rotate medially. The previous attack had caused a slight decrease in the length and diameter of the right leg.

Clear, colourless cerebrospinal fluid was withdrawn under normal pressure; there were 62 cells per c.mm., 83% of which were lymphocytes; sugar 62 mg., chlorides 691 mg., and protein 10 mg. per 100 ml., with no rise in the globulin.

By the second day in hospital the fever had subsided, and the child began to eat well and was much less irritable. He was discharged after 10 days, but the bilateral ptosis persisted.

Fischer and Stillerman[1] estimate a rate of recurrence of 2 per 1000 cases, Nelson and Green[2] 0·66 per 1000, and Bridge et al.[3] 2·7 per 1000. They feel their rate casts doubt on the existence of any significant clinical immunity following a single attack of the disease. At South View Isolation Hospital 2343 cases of acute poliomyelitis were treated between 1921 and 1951; so with 2 recurrent cases our recurrence-rate is 1·7 per 1000. In both of our cases bulbar poliomyelitis developed in the second attack, and both times the second attack occurred within a year of the first.[4]

Hoyne and Lipton[5] quote Trask et al.,[6] McAlpine,[7] and Steigman and Sabin[8] in support of their view that immunity in poliomyelitis is specific only for the strain of virus in the original attack. However, they also think that the immunity conferred may give protection for only a short time. Still[9] also supported the idea of "minimal duration of immunity." According to Toomey[10] it is easier to reinfect monkeys with a different rather than the same strain of virus.

If we agree that poliomyelitis can occur in a subclinical non-paralytic form, it is quite possible that the apparent rarity of recurrence is due to the difficulty of recognising mild attacks. Bridge[3] agrees that, until we are better

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1. Fischer, A. E., Stillerman, M. *J. Amer. med. Ass.* 1938, 110, 569.
2. Nelson, N. B., Green, W. T. *Amer. J. Dis. Child.* 1943, 65, 757.
3. Bridge, E. M., Clark, G. H., Abbe, D. *Ibid*, 1946, 72, 591.
4. Fox, M. J., Madden, W. J., Kohn, S. E. *Ibid*, 1948, 75, 395.
5. Hoyne, A. L., Lipton, I. *J. Amer. med. Ass.* 1951, 146, 707.
6. Trask, J. D., Paul, J. R., Beebe, A. R., German, W. J. *J. exp. Med.* 1937, 65, 687.
7. McAlpine, D. *Lancet*, 1945, ii, 130.
8. Steigman, A. J., Sabin, A. B. *J. exp. Med.* 1949, 90, 349.
9. Still, G. F. *Arch. Dis. Childh.* 1930, 5, 295.
10. Toomey, J. A. *Amer. J. Dis. Child.* 1936, 52, 802.

able to diagnose the mild forms of the disease, the possibility of a second attack might well be anticipated.

It has been estimated that the incidence of second attacks of poliomyelitis is nearly the same as that of recognised first attacks in the population at large.[1–3] The number of people developing clinical poliomyelitis for the first time forms about the same proportion of the general population as those who have a second attack do of the known poliomyelitis population.

However, it seems that in undoubted recurrences the virus does not attack the same level of the central nervous system as before. This may mean that immunity has been "fixed" at a certain level or portal of entry, and that involvement elsewhere is possible. But if different strains of virus attack different levels of the nervous system, this observation may support the view that immunity is specific for specific strains and not heterologous for all strains of poliomyelitis; or it may merely mean that "the fire will not catch on burned out wood."

I am indebted to Seymour Goldberg for assistance in this review.

Department of Internal Medicine,
Marquette University
School of Medicine, and
South View Isolation Hospital,
Milwaukee, Wisconsin.

MAX J. FOX.

ADDICTION TO BARBITURATES

SIR,—I have been caused considerable embarrassment with members of the profession and others, in regard to reports which have appeared in some daily newspapers to the effect that at a meeting of the North East Metropolitan Regional Hospital Board on Oct. 22 I stated that there were hundreds of thousands of barbiturate addicts in Britain and, secondly, that barbiturate drugs could be purchased without prescription from some chemists.

I made no such statements or similar statements either at the meeting referred to or at any other time.

North East Metropolitan Regional
Hospital Board, 11A, Portland
Place, London, W.1.

JAMES GRAHAM
Senior Administrative
Medical Officer.

OVERLOADING THE CIRCULATION

SIR,—The occasion often arises when an intravenous infusion has to be administered to a patient in need of fluid replacement. This in itself usually presents little difficulty. Yet as soon as continuity with the bloodstream is effected, there comes creeping into the medical mind the dreadful thought that the circulation may become overloaded. The fear of killing the patient is greater than the hope of curing him, and encourages prompt action to reduce the rate of flow to safe limits; and commonly the recipient then has to make do on meagre measures.

Surgeons—who only employ the stethoscope to listen to bowel sounds, or its rubber parts for cavity drainage—are especially apt to fear overinfusion. Physicians, on the other hand—providing they can overcome the mechanical difficulties of setting up a drip—are much more confident, owing no doubt to their assured ability to recognise circulatory distress.

Very many textbooks stress the danger of overloading the circulation and give the impression that this is common. Having given and seen given many hundreds of infusions, I am sure I have yet to see overloading of the circulation; and I am equally sure I have seen patients die for want of fluid, which was denied them by myself and other misguided persons.

Of the many colleagues who searched their minds to recall a case of overinfusion of a patient with normal heart and kidneys, only one could remember such a case—that of an infant who received a litre of normal saline in one hour. It is well known that when the heart and kidneys of the child or adult function normally any excess of water or salts can be disposed of at a prodigious rate. In diabetes mellitus the patient may void twenty or more pints of urine per day, and there are thirsty manual workers who could deal with as great a quantity in a shorter time.

Blood-transfusion presents a somewhat different problem, and calls for a much less liberal technique—particularly in cell restoration of the chronic anæmic patient, or in the transfusion of a patient with cardiac decompensation. Nevertheless, in the more common condition of acute blood loss the tendency still remains to administer blood too slowly and in too small a quantity. It is clinically obvious during operation that the normal patient benefits by having a greater quantity of blood transfused into the circulation than has escaped from it.

A modern revaluation of intravenous infusion and transfusion therapy based on clinical observation is surely called for.

Kingston Hospital, Surrey.

W. R. MURPHY.

THE HARROW ACCIDENT

SIR,—As I have been unable to obtain a complete list of all the doctors who rendered aid to those injured in the unfortunate train accident at Harrow and Wealdstone on Oct. 8, I should be grateful for the opportunity to send my sincere thanks to all of them through the medium of your journal.

I know the names of some of them of course, whilst others preferred to remain anonymous; but, in keeping with the highest traditions of the medical profession, all of them rendered such invaluable aid that it is impossible to estimate how many more lives would have been so tragically lost had it not been for the medical attention given to them either before or immediately after they were brought from the wreckage.

I should like each and every doctor concerned to accept my very sincere and grateful thanks.

London Midland Region,
Euston Station, N.W.1.

J. W. WATKINS
Chief Regional Officer.

REACTION TO PROCAINE

SIR,—In view of the reports in your columns of severe reactions to penicillin with and without procaine,[1] the following case may be of interest.

A man, aged 47, had complained of fibrositis of the right trapezius muscle. This had not responded to simple massage with liniment, and I decided to inject 'Novutox' (a solution of procaine hydrochloride 2% and adrenaline in Ringer's solution rendered "self-sterilising" with capryl-hydrocupreinotoxin hydrochloride). I gave him a deep intramuscular injection of barely 3 ml. of novutox. Almost at once he began to feel ill. I rather disregarded this, and after about 4–5 minutes I massaged the muscle quite vigorously. About 3 minutes later he appeared about to faint. He lost consciousness, and developed a generalised tonic spasm. He became completely pulseless, and regurgitated some of the stomach contents.

About 2 minutes later he took an odd breath or two as the spasm relaxed. After a further 2 minutes or so he began to breathe again deeply, his airway having been kept clear ever since the spasm developed.

Some half-hour later he regained consciousness, but for a further 2–3 hours he felt very ill. He was taken home, after walking to the car, $4\frac{1}{2}$ hours after the injection, and by next day was up and about.

I believe that this man, who had previously withstood injections of adrenaline for asthma, which used to trouble him in his younger days, is sensitive to procaine, though he had had local anæsthetics for occasional dental extractions. The effect of this sensitivity to procaine was increased by the massage I gave him after the injection, though I am as sure as one can be that I

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1. Batchelor, R. C. L., Horne, G. O., Rogerson, H. L. *Lancet*, 1951, ii, 195. McConnell, R. B. *Ibid*, p. 402. Yuval, A. *Ibid*, 1952, i, 163. p. 1022. Bell, R. *Ibid*, p. 1072. Wylie-

did not inject into a blood-vessel. I used a no. 12 hypodermic needle. There was no local reaction at the site of the injection, even though I had first given some of the injection just beneath the dermis.

London, S.E.26. RONALD M. PENNY.

BRONCHIAL CARCINOMA

SIR,—Last week's letter from Dr. Hesling and Mr. Cruickshank draws attention to an important symptom of bronchial carcinoma insufficiently regarded. Here is the history of a patient recently in my care:

A year ago a man of 50 went to his general practitioner and said: "Doctor, I have a wheeze in my chest just *here*, which has recently appeared, and will not go away," and pointed to the upper part of his left chest. The doctor placed his stethoscope on the spot and, sure enough, heard there a rhonchus which persisted after coughing. There was no other symptom, no other sign. He promptly referred his patient to see a chest physician from a chest hospital. The rhonchus was still there. A full investigation was instituted. Chest radiographs were normal. Bronchoscopy was performed, and was negative. Finally a bronchogram was done, and reported as showing no abnormality; and the patient went home.

A year later he visited another hospital and was again examined radiographically. This time a growth of the anterior segment of the left upper lobe was manifest. It proved to be just operable; but the prognosis is poor, and in any case a year the worse. The previous bronchogram, on re-examination, showed perfect filling of the whole lung—save the anterior segment of the left upper lobe.

The lesson is simply this: a fixed rhonchus is pathognomonic of partial organic bronchial obstruction; and incomparably the commonest cause in a man of 50 is cancer.

London, W.1. GEOFFREY FLAVELL.

THE EMERGENCY OBSTETRICAL SERVICE

SIR,—Mr. Dewhurst is to be congratulated on his excellent review (Oct. 18) of the work of an obstetrical emergency service, and for emphasising several important points.

It has always amazed me to find that a doctor who tackles a difficult forceps delivery or breech extraction in domiciliary practice may hesitate to remove a placenta. Few teachings have done more harm than the one that manual removal is dangerous and only to be carried out as a last resort.

Mr. Dewhurst's condemnation of the continued misuse of pituitary extract is welcome. Surely this drug can have no place in obstetric practice, except possibly in a drip for the treatment of inertia: after delivery ergometrine has its virtues with none of its vices. Forceps delivery under chloroform anæsthesia, administration of pituitary extract, and repeated attempts to express the placenta is a shock-producing combination.

His recommendation that all patients with a history of previous postpartum hæmorrhage or retained placenta should be delivered in hospital is important. It is very disturbing to find the flying-squad being called to a patient who has been treated by it for profound postpartum shock in a previous labour. The risks in the "dangerous multigravida," and the desirability of her being delivered in hospital, are now generally realised: but it is still sometimes difficult to persuade these faithful mothers to come in.

Mr. Dewhurst rightly emphasises that a normal blood-pressure level need not be reached before the placenta is removed. The partly adherent placenta seems liable to produce shock; and if the patient's condition is improving with treatment, and open-ether anæsthesia with its supreme safety is used, the operation should not be deferred. Mr. Dewhurst mentions intravenous anæsthesia, but many anæsthetists are unwilling to use this unless an apparatus for giving oxygen is available.

There is one point, however, on which I must join issue with Mr. Dewhurst—and that is over the small amount of one or two bottles of blood which he regards as adequate for resuscitation. Although the mortality he reports is very low, considering the type of case treated, I wonder whether his results might have been better if larger amounts of blood had been given. The main difficulty here would appear to be the strain on supplies of Rh-negative blood, as unfortunately many of these patients have not been tested for their rhesus group. He does not mention plasma or plasma substitutes. It has always seemed to me unwise to run ice-cold blood rapidly into a shocked patient; and the rapid administration of dextran or 'Plasmosan' at the start of a transfusion is very valuable, and less likely to cause venospasm.

Maintaining an obstetrical emergency service in a populous area with many domiciliary deliveries throws a heavy strain on the obstetrical staff. I feel that the demands on a service and the amount of work it has to do can be greatly reduced if some of the points Mr. Dewhurst has emphasised are more generally appreciated.

Middlesbrough. BRYAN WILLIAMS.

DARK ADAPTATION FOR SCREENING

SIR,—During fluoroscopy sessions it sometimes happens that there are intervals between the screening of groups of patients when it is desirable to have some illumination, but when full dark adaptation must be preserved. I have found that two 60-watt bulbs, one coloured red and the other dark blue, burning together, give an adequate light for writing or reading, but do not disturb dark adaptation. I find that I can see the screen more clearly after having been in this light for a time than after having been in a room lit by a neon bulb, and that this method is more comfortable than wearing a dark-adaptation eyeshield with ordinary illumination; but these are subjective impressions which may not be confirmed. Others may like to try this form of lighting.

London, E.1. ALAN WATSON.

PNEUMA, PSYCHE, AND SOMA

SIR,—Dr. George Day (Oct. 11) says that "every layman is acquainted with well-authenticated stories of presumably healthy primitive men turning their faces to the wall and dying for no ascertainable organic cause, but just because a spell has been put on them." I have spent over forty years in various parts of the tropics but do not know of a single "well-authenticated" case of this kind.

Many years ago in the West Indies I investigated two cases of death which were supposed to be due to obeah spells; but there were "ascertainable organic causes" in both cases. One of the deceased was a man with pellagra: in the dementia of that disease he had turned his face to the wall and died, but the relatives were convinced that he had died of an obeah spell. I had experience of other cases in Africa.

Anyone who tries to investigate these stories of death from witchcraft or spells—they are much the same thing—will find that most of the related events took place at a distance in time or place—over the seas or beyond the hills.

I know of no part of the world where spells are recognised as causes of death either in mortality statistics or by the law; and assuredly if such a cause could be well authenticated there are many countries where recognition would be readily given, despite the difficult legal implications.

Dr. Day also appears to base much on a second proposition: "Every general practitioner is struck at some time or another by the way Darby will follow his Joan to the churchyard before the leaves have turned.' There may be something in this; but large numbers of Darbies and Joans survive their partners for a considerable time and no notice is taken of it. The odds are that a few Darbies will soon follow their Joans to the grave when both have reached the allotted span and this is more likely to receive comment and be remembered.

The progress of psychological medicine must be based on something more than popular beliefs. If such beliefs have foundations in fact these need to be supported by the evidence of experienced pathologists and statisticians.

Bantry, Eire. LUCIUS NICHOLLS.

UNSTICKING SYRINGES

SIR,—I have found a double-socketed needle invariably successful in forcing out adherent barrels of syringes that have become occluded with a large variety of agents ranging from clotted protein to crystalline deposits.

The needle is constructed simply by filing the bevel off the shaft of one hypodermic needle and cutting off the entire shaft from the head of another needle. The shaftless head is then attached to the free end of the unbevelled shaft of the first needle with silver solder.

The stuck syringe is freed by forcing fluid into it from another syringe through the special needle. The greater the difference of diameter between the stuck syringe and the freeing syringe, the easier it is to apply considerable pressure inside the stuck syringe. For this reason a long 1-ml. syringe is the most useful pressure-pump.

Tap water is quite sufficient for syringes stuck with clotted protein, while liquid paraffin may be used for a syringe stuck with crystalline deposits.

There is no danger of breaking the syringe, and slight pressure has freed all stuck syringes in this laboratory almost immediately.

Department of Experimental Medicine,
Cambridge. J. H. CORT.

RED CELLS IN ANIMALS

SIR,—In an annotation published in your issue of July 5 you discuss red cells in animals.

In cattle the red blood-cell count varies greatly not only between different animals but also in the same normal animal. The count may vary from 5 million to 13 million per c.mm. Changes occur regularly from day to day; and when plotted graphically these give a smooth curve. Furthermore, considerable changes occur in the course of a single day, and the red-cell count may vary by 2 million per c.mm. in a single hour.

With this rapid type of variation fall in the number of red cells is accompanied by reduction of the specific gravity of the plasma, and vice versa. Dried-weight estimations have shown that the reduced specific gravity is due to reduced content of solids. Plasma-volume estimations have shown that this reduction of solids is accompanied by an increase in volume of circulating plasma. The reduced red-cell count is, therefore, due to dilution of the plasma with fluid; and the volume of circulating erythrocytes in these cases is usually increased, not diminished.

When the plasma becomes diluted with fluid, a proportion of this passes into the red cells. This is easily demonstrated by mixing plasma of low specific gravity with cells separated from high-specific-gravity plasma: the specific gravity of the test plasma increases. Increase of fluid in the red-cells leads to increased mean corpuscular volume (M.C.V.), and the correlation between red-cell numbers and M.C.V. is easily explained. This also explains why the variation in the number of packed cells is less than that of the red-cell numbers.

During these changes total hæmoglobin varies remarkably little, because of variations in mean corpuscular hæmoglobin (M.C.H.); increased M.C.V. (with reduced red-cell count and reduced plasma specific gravity) is accompanied by increased M.C.H. I know that this will be considered heretical, but it undoubtedly occurs and can be demonstrated in another way. If plasma specific gravity is deducted from blood specific gravity, we get an index of red-cell weight. This shows a correlation with M.C.H., indicating that the increased hæmoglobin content is responsible for increasing the weight of the cells. On spectrographic examination, most cattle plasmas show traces of hæmoglobin. This was previously thought to be of traumatic origin. but possibly it may be due to physiological shedding by erythrocytes.

Intravenous injections of adrenaline into cattle often cause a fall of the red-cell count with the accompanying fall of plasma specific gravity. In other words the volume of the circulating blood is increased, but the fluid portion is increased to a greater extent than the cellular. The varying red-cell count in cattle, therefore, is connected with the control of water metabolism.

These findings have a wider significance than may at first sight be evident. In the first place, there would appear to be grounds for supposing that adaptation to hot climates and drought may be connected with control of water metabolism and may thus be reflected in the blood picture. In the second place, interference with the total volume of circulating plasma solids, not revealed by biochemical estimations, becomes apparent in diseases associated with anæmia.[1] The tissue degeneration of trypanosomiasis, malaria, and the kwashiorkor group of diseases can be explained much more reasonably by interference with deliveries of essential amino acids than by faulty delivery of oxygen. The anoxæmia of the "blue baby" does not cause tissue degeneration, whereas lack of methionine causes the typical centrilobular liver necrosis of trypanosomiasis. In trypanosomiasis we find further support for this view in vasodilatation and a much reduced circulation-time.

Some of these observations are to be described more fully elsewhere.

East African Veterinary Research
Organisation, Veterinary Research
Laboratory, P. O. Kabete,
Kenya. R. N. T.-W.-FIENNES.

WITHDRAWAL OF TEACHING

SIR,—Your welcome leading article of Oct. 11 comes too late to influence the fate of the mobile film units of the Central Office of Information, but you did well to keep the issue alive. You rightly emphasise the value of the film as a teaching medium; this is still, I feel, largely unappreciated by medical teachers. The inconveniences which the new restrictions place in the way of the would-be user will further discourage medical teachers from adopting this powerful and convincing medium.

While not pretending that we can offer a substitute for the mobile film units, I would like to point out that the Central Council for Health Education does specialise in helping those engaged in medical and health education on questions of technique and media: and we would be glad to help any of your readers who may wish to consult us on this or other educational matters.

Central Council for Health Education,
Tavistock House, London, W.C.1. JOHN BURTON
Medical Director.

THE CORRECT SPELLING OF MEDICAL TERMS

SIR,—The editor of an important medical journal published in London (England) questioned my spelling of *fetus*. He refused to be interested in whether *fœtus* or *fetus* was etymologically the correct form, but said that if he printed *fetus* he would have a number of protests from his British readers complaining that he was adopting American spellings.

It is quite true that the spelling *fetus* is rarely used in British medical (or lay) literature. It is nevertheless the correct form. The *Shorter Oxford Dictionary* gives both *fœtus* and *fetus* but refers to the latter as the "better form"; it is from the Latin *fetus*.

Written English is built up by "common usage"—that is, in our view, common usage by British writers, most of whom are essentially conservative and resent change. They resent the liberties taken with their language by foreigners. For instance, they *like* diphthongs, tiresome though these may be to printers; with this point of view I am in complete agreement and I shall resist to the last ditch any movement for the general replacement of diphthongs by single vowels—the American practice. But when, etymologically, the foreigner is correct and we are wrong, it would seem that by adhering obstinately to a false diphthong we are weakening our case for maintaining our justifiable diphthongs in the face of contrary "common usage" by far more than half the English-writing world.

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[1] Feldman, H. A., Murphy, F. D. *J. clin. Invest.* 1945, 24, 780.

It is admittedly about 250 years since *fœtus* first crept into English writing, but is it not time that it was gently eased out again?

Silchester. L. EVERARD NAPIER.

CURE OF TOBACCO-SMOKING

SIR,—As a doctor's wife, I should like to put forward the case for the ordinary smoker.

Smokers enjoy smoking. They do it openly and happily; they hand cigarettes to each other and most of them have a favourite tobacconist's shop where they exchange local gossip. They are not drug-addicts furtively stupefying themselves, but merry fellows who like having a straw in the mouth because they have a common nostalgia for the idleness of the yokel.

Doctors have too high a standard of human behaviour and forget that few people reach a more advanced mental age than 13 or 14 years. Ordinary people very much miss sucking sweets or chewing grasses or biting their nails.

Animals luckily do not have to change their habits with advancing years, so that we can still see an old cat spending spare time in washing its paws or sharpening its claws, or a dog in scratching or in wagging its tail, as they did in youth; but we humans are left with nothing to do with our hands or feet or teeth in those long stretches of idleness from which we all suffer when travelling or entertaining our friends. Gradually therefore the accepted consolation has become the cigarette, the substitute for paw-washing or tail-wagging or nail-biting—the ideal straw in the mouth.

London, W.1. B. W. EDWARDS.

SIR,—"Vouloir c'est pouvoir," quoted by Professor Alstead (Sept. 27), is by no means always true, I fear, of stopping smoking—even when the *vouloir* is backed by quite a lot of *savoir*!

Professor Russ's "smoker" of dummy cigarettes (Oct. 14) is indeed a rare bird. I have not seen or previously heard of one. With the important proviso, *where there is no consumption of tobacco,* I agree that "smoking" is a habit (on a par with gum-chewing).

I can assure Dr. Geiringer (Oct. 11) that life for me is not simple, though my thesis on tobacco-smoking is; but that surely does not make it less true. He asks what is the cause of mass (drug) addictions. The answer is, I *think*, mass psychological infection, which I discussed at some length. He also asks what is the balance of the good and evil effects of such (drug) addictions, and of tobacco-smoking in particular. There is no real balance of the good effects of disease. To addicts, in the case of the drug addictions, there seems to be, because addicts have fairly fixed delusions of beneficence about the effects of their drug.

Mr. Leacock (Oct. 11) accuses me of classifying smoking "among the vices of addiction." I stated that tobacco-smoking was a drug addiction—anyone who repeatedly gives himself a drug for non-medicinal purposes is clearly addicted to it—but not a vice. The phase of "gluttony" which may follow cessation of smoking usually passes after a few months. To recommend smoking as a remedy for obesity is a therapeutic crime.

The great increase in cancer of lung, and its proved association with tobacco-smoking, have been powerfully stated by Dr. Horace Joules (Oct. 18). Dramatic and tragic though cancer of lung is, the harm it causes is, in my view, much less in the aggregate than the insidious, protracted, and extremely widespread harm caused by tobacco-smoking. Pearl's table, to which I referred (Sept. 6), lends support to this view. There is clearly but *one* real solution to this problem—our prevention of tobacco-smoking.

Wallasey, Cheshire. LENNOX JOHNSTON.

SIR,—May I recall the origin of the *tobacco* plant as recorded in the *Koran*? Mahomet, while taking a stroll, found a serpent crushed under a fallen rock. He freed the serpent, which promptly rewarded him by biting his arm. Mahomet sucked his wound and spat on the ground; immediately there bloomed the tobacco plant, which contains both the venom of the serpent and also Mahomet's mercy.

Perhaps a form of agreement may thus be established between Dr. Lennox Johnston and his correspondents.

Puteaux, Seine, France. WILFRID JOULLIÉ.

FIRST-AID TREATMENT FOR NERVE-GAS POISONING

SIR,—It has been brought to my attention that anti-gas ointment will not be issued to Civil Defence Services, and hence the advice given about decontamination in the penultimate paragraphs of the memorandum entitled *Chief Characteristics of Nerve Gas with Notes on First-Aid Treatment*, published in the issue of Aug. 9, may not always be apposite.

In circumstances (e.g., in civil life) where adequate supplies of water are available and the contaminated skin can be speedily and thoroughly cleansed, washing is an effective means of decontamination for both nerve and mustard gases. If speedily applied there is, in fact, no better method for nerve gas. In Civil Defence practice any liquid contamination on the skin is speedily removed by wet swabs, and treatment is continued by thorough washing with plenty of water and soap.

Anti-gas ointment is, however, provided for Service personnel, since under active field service conditions adequate water-supplies for washing may not always be immediately available.

H. M. GARNER
Chief Scientist.

Ministry of Supply, London.

DANCKWERTS AWARD

SIR,—The many letters in medical journals concerning the Working Party Award have been most revealing, but it seems that one aspect has not been considered. Surely those who speak critically of "spoon-feeding young doctors" should consider more closely the difficulties of entering general practice today compared with before the late war.

Then, the young doctor could buy a practice and with it an established list of patients. Houses were easy to buy or to rent. Advances for purchase of both practice and house were not difficult to obtain. Having an established list, the young doctor was able through hard work to make himself appreciated by his patients and was therefore sure of recommendation to their friends. His practice grew by repute. Having risked his capital or pledged his future by mortgage he was reasonably sure of his bread and butter for many years ahead, even if his practice did not grow according to expectation.

Now, he must purchase a house, which will cost him as much as house and practice before the war. His capital is risked or his future mortgaged with no bread-and-butter list of patients to whom his care and hard work will recommend him. He is debarred from advertisement, and his initial practice allowance diminishes each year and ceases after three years.

There is no comparison in the risk. Formerly he had opportunity to show worth; now he has none. There may be in his neighbourhood several doctors with more than the maximum number of patients on their lists: patients will tend to go, not to an unknown unadvertised doctor, but by repute from one of the established doctors o another.

This, taken in conjunction with the fact that despite he award it is still more profitable to have an assistant han to take a partner, suggests that the undesired ncrease of a salaried service within general practice is ikely to continue.

Community Centre,
Farnham Road,
Slough, Bucks.
M. E. M. HERFORD.

INJECTION ROUTINE IN OPERATING-THEATRES

SIR,—The possibility of confusing gas cylinders or drugs in an operating-theatre is still a cause of concern, and may be a considerable danger to patients.

Some pharmaceutical firms issue various drugs in identical containers; and a few days ago a patient escaped an injection of a curariform drug, instead of the analgesic I had ordered, only by chance. If the ampoules had had easily distinguishable labels such a mistake would have been impossible, even in a busy and short-staffed hospital.

Lisbon.
LOPES SOARES.

*** The use of distinctive colours and labels for ampoules was discussed in our columns recently by Major-General W. E. R. Dimond and his colleagues.[1] They suggested that the risk of accidents could be reduced by colouring ampoules of certain injectable fluids used in operating-theatres. But there is an alternative view[2] that the only safeguard is to read and re-read the label, and that other devices for identification increase the danger of injecting the wrong substance. The question of gas cylinders has also been under consideration lately,[3] and a new code of colours is being introduced in this country.—ED. L.

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS

SIR,—In reply to the letter from Mr. Page and his colleagues (Oct. 18) it must be stated that in our study[4] the type of rubber tubing in the infusion sets was not controlled.

The investigation of thrombophlebitis in the surgical-unit wards began three years ago. At that time experience of a few latex sets was compared with experience of sets supplied by the North London Blood Transfusion Centre. The figures were small, but with the latex set the incidence of thrombophlebitis was no lower.

For the last two and a half years all investigations have been conducted with the standard North London Transfusion set. During this period the rubber tubing has been changed at least six times, and it was in fact changed three times during the investigation into the pH of the fluids. Despite these changes, since the introduction of the eight-hour time-limit two and a half years ago the incidence of thrombophlebitis has remained very constant.

The report by Handfield-Jones and Lewis[5] was published after the investigation into the pH of infusion fluids was completed. We propose to test the effects of different types of rubber tubing as the next step in our investigation.

With regard to the second point raised by Mr. Page and his colleagues, we found no difference in the incidence of thrombophlebitis with the fluid of pH either 5·6 or 6·05.

Surgical Unit,
University College Hospital
Medical School, London, W.C.1.
J. F. BOLTON CARTER.

EFFECTS OF LEUCOTOMY

SIR,—Your annotation of Oct. 18 on Mrs. Petrie's book, *Personality and the Frontal Lobes*, praises the care and industry of the work, as well as the lucid presentation, but then goes on to say that "the results are disappointing because almost nothing was found that had not been described before by numerous observers."

Two comments seem relevant. In the first place, clinical observation in this field, as in many others, had resulted in a plethora of descriptions which embraced almost every trait and behaviour syndrome known to the dictionary; frequently the effects postulated by one worker were the explicit opposite to those postulated by another. Under these circumstances, it is very difficult to see how any study could succeed in unearthing behaviour not previously described; it is by producing *proof* where previously we only had contradictory *opinions* that Mrs. Petrie's study is outstanding.

In the second place, even if nothing more had been done than to quantify already existing clinical belief, does such a feat really deserve to be considered "disappointing"? To compare small things with great, it might with equal justice be said that Newton, in his *Principia Mathematica*, did nothing but confirm the phenomena which "had been described before by numerous observers"—i.e., the fact that unsupported bodies tend to fall to the ground. Science proceeds by proof and systematisation; it does not necessarily require for its advancement that its detailed findings should not, up to a point, have been anticipated by common sense and clinical observation.

The importance of such quantification is best shown by another finding of Mrs. Petrie, which is dismissed in the annotation in one sentence: "The variation of operative procedure had little and only quantitative influence on the test results." But to be able to follow experimentally such relatively small changes in operative procedure is in itself an important achievement, and to demonstrate that differences are quantitative rather than qualitative is something that could not have been done convincingly on the basis of clinical observation.

In addition, no mention is made of one of the most important findings in the book, which has since been confirmed—namely, that intellectual deterioration only occurs after posterior operation. This result alone, with all its implications regarding the localisation of functions in the brain, would suffice to show that the sentence quoted in the last paragraph does not give an accurate impression of the consequences of variation of operative procedure.

Institute of Psychiatry,
Maudsley Hospital, London, S.E.5.
H. J. EYSENCK.

BUTAZOLIDINE

SIR,—Having now used this drug in 237 cases of rheumatoid arthritis attending my outpatient clinics, I am still greatly impressed by its efficacy. I have used it alone, in combination with cortisone, and as a follow-on treatment after 'Irgapyrin.'

None of this series has shown any toxic effects other than (*a*) one case of rather severe gluteal abscess, and (*b*) a few mild macular rashes which have cleared up quickly on discontinuing the drug. In all cases the erythrocyte-sedimentation rate (E.S.R.), white blood-cell count, and platelets are kept under careful observation.

None of these patients has been given a larger dosage than 2 g. per week. (The usual dosage is 1 g. injected intramuscularly twice weekly for four weeks—this course is repeated after an interval of about a month.)

The toxic symptoms reported in your columns have nearly always followed administration of at least 1 g. of butazolidine *daily*, and it would therefore appear that this dosage is too high.

There can be little doubt as to the therapeutic value of butazolidine in rheumatoid arthritis; but the only safe

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1. Dimond, W. E. R., Pollard, A., Adamson, A. C. *Lancet*, 1952, i, 410.
2. Trillwood, W. *Ibid*, p. 510.
3. See *Lancet*, July 5, 1952, p. 36.
4. Carter, J. F. B., Milne, E. H., Whittet, T. D. *Ibid*, Oct. 4, 1952, p. 660.
5. Handfield-Jones, R. P. C., Lewis, H. B. M. *Ibid*, 1952, i, 585.

way to administer this drug would seem to be by injection so that the patient can be kept under constant observation and have his white blood-cell count, platelets, and E.S.R. continually reviewed.

The dangers of the tablet preparation are that: (a) the dose of 0·2 g. is rather large for repeated use, (b) digestive disturbances may occur, and (c) the doctor may lose personal control of the supervision of the patient.

I have recently seen two cases of massive œdema of the lower limbs following the use of butazolidine tablets (1·2 g. daily) prescribed by other practitioners.

Coventry and Warwickshire Hospital. JOHN SHULMAN,

SUBLINGUAL HEPARIN

SIR,—Last year Litwins et al.[1] claimed to have increased blood-clotting time by sublingual administration of sodium heparin (125 mg.) in the form of wafers. Clotting-time reached "therapeutic levels" within 30 minutes and were maintained for 4 hours. These workers rightly pointed out the advantages of this mode of administration, especially for the treatment of frost-bite in soldiers on active service.

Because of the importance of this claim we decided to duplicate these experiments in animals.

Rabbits were anæsthetised with sodium pentobarbitone and urethane, and clotting-times were determined on samples of blood taken from the carotid arteries. Intravenous administration of sodium heparin, 1 mg. per kg. body-weight, gave an average clotting-time of 30 minutes, the peak being reached within 10 minutes. With double this dose the average peak was raised to 160 minutes. Intramuscular injection of 10 mg. per kg body-weight raised the clotting-time to about 40 minutes; the plateau was reached within 1 hour and showed no signs of decay after a further 3 hours. Sublingual administration in rabbits anæsthetised with sodium pentobarbitone and urethane had no significant effect on the clotting-time at a level of 10 mg. per kg. body-weight. Doubling the dose had the effect of doubling the normal clotting-time, but in no instance was the "therapeutic level" (20 minutes or more) reached. Likewise oral administration was ineffective.

Since the effect of parenteral administration of heparin in the rabbit resembles that in man, it is not unreasonable to assume that the effect of sublingual administration of heparin in man would be similar to that observed in the rabbit. We therefore concluded that, even should it prove possible to reach the therapeutic levels defined by Litwins and his colleagues with their suggested method of therapy, the dosage required would be massive and the cost prohibitive.

While preparing this work for publication, we were somewhat relieved to see a report by McDevitt et al.,[2] who have also been unable to substantiate Litwins's claim. Consequently we decided that detailed publication of our work was no longer necessary.

Pharmacology Unit,
Glaxo Laboratories Limited,
Greenford, Middlesex.

E. G. TOMICH
J. E. WOOLLETT.

ANTITHYROID ACTION OF P.A.S.

SIR,—I much appreciate the comments of Dr. Benstock and Dr. Freedman in your issue of Oct. 4.

If, however, it is conceded that all antithyroid drugs act by inhibiting the synthesis of thyroxine in the gland itself and that the enlargement is compensatory and due to the influence of pituitary *thyrotropic* hormone, why should we postulate that the action of P.A.S. should be different and involve a different pituitary hormone—the adrenocorticotrophic one? Unless, of course, one goes a stage further and revives the old hypothesis that there is really only *one* pituitary hormone. The various known fractions could therefore be merely artificial substances created by modern chemical and other techniques!

The exact nature of salicylate action is still sub judice. Until it is finally elucidated, I respectfully suggest that the current concept of antithyroid drug action is equally compatible.

Ilford Isolation Hospital,
Romford, Essex.

I. M. LIBRACH,
Medical Officer in Charge.

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[1] Litwins, J., Vorzimer, J. J., Sussman, L. N., Applezweig, N., Etess, A. D. *Proc. Soc. exp. Biol., N.Y.* 1951, 77, 325.

[2] McDevitt, E., Huebner, R. D., Wright, I. S. *J. Amer. med. Ass.* 1952, 148, 1123.

Parliament

Flogging for Crimes of Violence

IN the House of Lords on Oct. 22, EARL HOWE called attention to the continuation of crimes of violence towards women and other defenceless persons, and asked whether the existing penalties which the courts had power to inflict were adequate to protect the public. The number of indictable offences known to the police had risen from 283,220 in 1938 to 524,506 in 1951. He suggested that there was more consideration for the gangster than for his victim. The abolition of flogging in 1948 had been described as a great experiment and we were told that it had not yet proceeded far enough to be judged. But, he asked, how many women had to be attacked in circumstances of the utmost brutality before the experiment ended and the public were given the protection to which they were entitled?

Lord GODDARD pointed out that serious crime in this country had increased to such an extent that the criminal work to be done at assizes bade fair to throw the whole legal machine out of gear. He agreed that it was a bad thing to be constantly interfering with the penalties prescribed by law; he believed the time had come when we must consider whether it was not time to re-impose corporal punishment for certain offences, for new and horrible forms of violence were being used. As a judge he disliked having to sentence a young man of 21 or 22 to a long term of imprisonment. Formerly corporal punishment could only be inflicted, with one or two exceptions, for robbery with violence. He suggested that the superior courts should be given power in their discretion to inflict corporal punishment for all forms of felonious violence—not for unlawful wounding, but for felonious wounding, wounding of police while resisting arrest, and attempted murder. He did not want to see the use of the cat reintroduced, and did not believe in the indiscriminate use of the birch. Nor did he believe the reintroduction of corporal punishment would do away with crime, but it might substantially reduce it.

Lord SIMONDS, the Lord Chancellor, said that against the background of a century of penal reform their Lordships were now asked not only to reverse the legislation of 1948 but to extend the penalty of corporal punishment to a degree which surpassed anything that had been permissible for the last 130 years. Was not that in the nature of panic legislation? He was not in a position to say that the Government would introduce such legislation. He asked that the system instituted by the Criminal Justice Act 1948 should be given a fair trial. It provided for preventive detention for persons over thirty for 5 to 14 years, if it was expedient for the protection of the public, and there were now 868 men and 28 women under such detention. Many causes had contributed to the increase in crime; the relaxing of family discipline, the lowering of the general moral standard, and perhaps the failure of religious sanction, were causes. How large a part they played no-one could say, but the Home Secretary thought that the Act should be given a longer trial before they decided to take the step which had been advocated that day.

QUESTION TIME

B.C.G. Vaccination

Dr. BARNETT STROSS asked the Minister of Health what classes of the population were advised to receive protective vaccination by B.C.G. against tuberculosis; and for what reasons this service was not extended to those leaving school.—Mr. IAIN MACLEOD replied: B.C.G. vaccination is at present offered to hospital nurses, medical students, and, at the discretion of chest physicians or other appropriate specialists, to other individuals at special and known risk. Its use in the immunisation of children leaving school is at present the subject of a trial being conducted by the Medical Research Council.

Replying to further questions Mr. Macleod said he feared that the rate of experimentation with B.C.G. vaccine was slow, but in Scandinavia medical opinion was by no means unanimous about its effectiveness, and the Medical Research Council in this country were not yet satisfied that its full effectiveness had been proved.

Mr. P. F. **Remnant**: Is the Minister aware that a very considerable body of opinion in this country, including eminent medical opinion, agrees with this vaccine, and will he see that he is not thwarted by any dilatoriness on the part of the Medical Research Council?—Mr. **Macleod**: It is true that there is a big body of medical opinion in favour of pressing on faster than we are doing with B.C.G., but there is also a large body of medical opinion which holds that we should wait until we know fully whether it will be effective. Dr. **Stross**: Would not the Minister agree that the percentage of reactors among school-leavers is showing an increase, and that the school population therefore shows itself to be more susceptible when leaving school now than formerly? Is that not an important factor?—Mr. **Macleod**: It is a very important factor, and is probably the most valuable field of all for experimentation. The Medical Research Council are, in fact, experimenting in that field now. Mr. **Somerville Hastings**: Is there not a considerable danger in encouraging people to trust to vaccine instead of hygiene and the laws of Nature? No further reply was given.

Assistants' Salaries

Mrs. **Jean Mann** asked the Minister what portion of the Danckwerts award would be passed on to doctors' assistants and trainee apprentices; and how far, in view of this award, he considered it necessary to continue payments to doctors for trainee assistants.—Mr. **Macleod** replied: I cannot say what adjustments in the light of the Danckwerts award will be made in the salaries of assistants, which is a matter for the doctors who employ them. No changes are at present under consideration in the arrangements for paying grants to doctors who supervise the training of assistants.

Mrs. **Mann**: Would the Minister consider making changes in view of the fact that when the Danckwerts recommendations were originally put forward there was no Government grant of £1000 to doctors for what are really locums who help them in their work?—Mr. **Macleod**: I would not agree that this is just a subsidy to locums. I think it has very much more value than that. Both the original scheme and, in consequence, the Danckwerts award were attached to principals, and not to assistants.

Major E. G. R. **Lloyd**: Is the Minister aware that there is some difference of opinion in the medical profession as to how these sums of money should be allocated? Will he consider representations on this subject before the final recommendations are approved by the Government?—Mr. **Macleod**: I have already started implementing the award of the Danckwerts money. It was passed without comment by the House of Commons before the summer recess, but I shall be happy to consider any representations which are made on this important matter.

Hospital Construction

Replying to a question Mr. **Macleod** stated that the capital cost of new hospital construction and extensions, together with the number of additional beds to be provided, in schemes approved by his department since October, 1951, in England and Wales was £5,100,000. The corresponding figure for the previous year was £7,500,000.

Traumatic Surgery

Mr. **Hastings** asked the Minister what arrangements he had made in cases of emergency, such as the railway disaster at Harrow, to draft doctors with specialised experience in traumatic surgery to hospitals in the immediate vicinity, so that the best known treatment might become available to sufferers.—Mr. **Macleod** replied: I am sure the hon. member will agree that the medical aid rendered in this disaster was prompt and efficient. The general surgeons at the hospitals concerned, though not specialists, are experienced in traumatic work. Further help of this nature was offered but not required. The tragedy will be closely studied to see what lessons can be learnt from it. Mr. **Hastings**: Does the Minister realise that traumatic surgery is a specialty of its own? As an instance of that, there are several accident hospitals. Is it not of the greatest importance that people who suffer unexpectedly in this way should in all cases have the very best treatment?—Mr. **Macleod**: I have great sympathy with the hon. member's point of view, but, as I pointed out in my answer, such skilled specialist help was offered and in this case was not required. We will certainly see if there are any lessons that we can learn from this disaster.

Visits to Children in Hospital

Replying to a question, Mr. **Macleod** stated that of the 1300 hospitals admitting children, all except 70 fever hospitals and 75 others allowed regular visiting; 300 allowed daily visits, and the great majority of the remainder allowed visits more than once a week.

Mental Hospitals Accommodation

Replying to a question, Mr. **Macleod** stated that on Jan. 1, 1952, the bed space in use in mental hospitals was overcrowded by 16,000 patients, an average of 13·5%. At the same date the number of unstaffed beds was 1700. The present shortage of staff was about 3500 men and 7700 women. A year ago it was estimated at about 3000 men and 8000 women. The problem was being closely studied by the Mental Health Advisory Committee of the Ministry of Health.

Health-centre Schemes

Replying to a question, Mr. **Macleod** said that since October, 1951, one health-centre scheme had been approved, and this centre and two others approved before that date had been completed.

New Treatment for Cataract?

Mr. J. A. **Sparks** asked the Minister what steps he was taking to make available to persons suffering from cataract blindness the new cure discovered by the New York Cataract Institute in the use, by injection, of protein substances from the lenses of fishes' eyes.—Mr. **Macleod** replied: I am advised that the claims made for this treatment are so far unsubstantiated.

Toxic Effects of Detergents

Dr. **Stross** asked the Minister what evidence was available of the toxic effects following the use of detergents in cleansing glass and crockery; and what figures he had as to the incidence of dermatitis following their use.—Mr. **Macleod** replied: I am not aware of any. Dr. **Stross**: Has the Minister not been made aware that detergents tend to cause dermatitis, chapped hands, and so on? Is he not aware that it is agreed that if glasses and crockery are not adequately washed after being dipped into detergents a cumulative dose is gradually taken into the human body and that that is not good for it?—Mr. **Macleod**: I do not dispute that, but that is not the question that I have been asked. I have inquired from the Minister of Labour and the Minister of National Insurance and they have no such evidence as was referred to in the question.

Foot-and-mouth Disease

In the House of Lords on Oct. 21, replying to the **Earl of Listowel**, Lord **Carrington**, joint parliamentary secretary to the Ministry of Agriculture, said that in recent weeks the amount of foot-and-mouth disease in this country had been so much reduced that after midnight of that day, if all went well, there would be only one infected area left. In September there were 13 outbreaks, compared with 19 in August and 51 in July. So far in October, there had been only 3 outbreaks, all in Hampshire, and no outbreaks had been reported since Oct. 6. Since Nov. 1, 1951, there had been 582 outbreaks in all, and the compensation payable to farmers amounted to about £2,738,000. On the whole, the position in Western Europe was much less ominous than a year ago, and there was at present no reason to expect this autumn a major invasion of the disease from the Continent such as was experienced last autumn and earlier this year.

He added that at an international conference convened by the Food and Agriculture Organisation of the United Nations at which 13 European countries, including the United Kingdom, were represented, it was agreed to recommend that a European Commission for foot-and-mouth disease should be appointed to stimulate and coördinate national and international control of this disease. This recommendation still had to be studied in detail by the governments concerned, but a body of this kind could, he thought, do much to prevent a repetition of last year's disastrous epidemic in Europe and minimise the risk of disease spreading to this country.

Vitamins in Food

Replying to Dr. STROSS, Mr. MACLEOD, Minister of Health, said that the report of the Standing Committee on Medical and Nutritional Problems on the possibility of excessive consumption of vitamins due to food fortified by these substances had been referred to the departments concerned for their consideration. It appeared from the report that in present circumstances there was no danger of excessive consumption of vitamins due to food fortified with these substances.

Children and Tuberculosis

In answer to a question Mr. MACLEOD stated that a survey conducted by a committee of the Medical Research Council in 1949–50 in 22 selected areas on a sample basis showed that 56·1%, over all, of children aged fourteen and 48·5% of those aged fifteen to sixteen were tuberculin-negative, and that there was some evidence that these percentages were increasing.

Public Health

Shortage of Health Visitors

THE public-health section of the Royal College of Nursing thinks that the present complement of health visitors is quite inadequate to carry out the wider duties implicit in the National Health Service Act. Where the annual number of new recruits should be 900 it is now little more than 500, and some 25% of places in approved centres are not taken up. In addition, and partly as a result of this shortage the health visitor's proper sphere is being invaded (it is felt) by a host of other workers with a shorter training and higher remuneration. Though this discrepancy in pay is certainly a contributory factor, the main deterrent to newcomers to the service is believed to be the sense of frustration and disillusionment to be found among the health visitors themselves.

The council of the college is asking the Minister of Health to set up a committee to review the training, employment, and prospects of the health visitor, and to clarify not only her position under the local health authority but that of others working in kindred fields and also fields which the health visitor feels to be her own. The Minister will shortly have the results of the Nuffield analysis of the work on which the health visitor is at present engaged; and the moment is appropriate in view of his recent pronouncements on the need to strengthen the clinic, domiciliary, and family-doctor services as a means of relieving pressure on costly hospital beds. Much has been done to improve the position of hospital nurses, but too little, it is felt, to capture the imagination of possible recruits to public-health nursing.

Examination of Coalminers

Draft regulations issued by the Minister of Fuel and Power (Coal Mines [Medical Examinations] General Regulations, 1952) lay down that all those under 21 entering employment in or about coalmines shall be medically examined, with certain exceptions. The regulations prohibit the employment of anyone in work for which he is found on examination to be unfit. The draft regulations do not specify the form of examination, nor do they mention repeated examinations throughout the period of employment.

Statistics for England and Wales

In England and Wales during the June quarter[1] the birth-rate was 16·0 per 1000 population. This was the lowest rate since 1942; the average for the five years 1946–50 was 18·8. The stillbirth-rate—22·4 per 1000 live and still births—was the lowest ever recorded for a June quarter in this country. The death-rate was 10·6 per 1000 population, compared with 11·1 in the two previous June quarters. The infant-mortality rate of 25·1 per 1000 related live births represented a drop of 3·6 from the rate in the June quarter of 1951, and was the lowest yet recorded for the quarter in this country. The excess of births over deaths was 58,683, compared with 72,066, 60,552, and 59,660 in the June quarters of 1949, 1950, and 1951.

The Registrar-General has also reported provisional figures for the third quarter,[2] which, together with the corresponding figures for earlier years, are as follows:

Third quarter of		*Live births per 1000 pop.*		*Stillbirths per 1000 total live and still births*		*Deaths per 1000 pop.*		*Deaths of infants under 1 yr. per 1000 related live births*
1952	..	15·3	..	21·5	..	9·0	..	23·0
1951	..	15·2	..	21·8	..	9·1	..	23·4
1950	..	15·4	..	22·5	..	9·3	..	23·9
1938	..	15·2	..	37·0	..	9·9	..	42·5

Thus the fall in the birth-rate since 1947 has been arrested. The death-rate was the lowest since the September quarter of 1947. Both the stillbirth-rate and the infant-mortality rate were the lowest ever recorded for any quarter in this country.

Infective Hepatitis in the U.S.A.

In the U.S.A. the total number of cases of infective hepatitis in the thirty-nine weeks of this year up to Oct. 4 is provisionally estimated at 11,868.[3] The incidence was highest in the winter and spring months, and in the States of Alabama, Georgia, Kentucky, and West Virginia. Epidemics have been reported most often from States with large rural populations, and commonly in schools. In two outbreaks water was regarded as the vehicle of infection; but in most instances epidemiological evidence has pointed to person-to-person spread. In one instance handling of soiled linen used by infectious patients in hospital seems to have been the means of transmitting infection.

Obituary

WILFRED WATKINS-PITCHFORD

M.D. Lond., LL.D. Witwatersrand, F.R.C.S., D.P.H.

Dr. Watkins-Pitchford, the first director of the South African Institute for Medical Research and a former vice-president of the British Medical Association, died on Sept. 29 at the age of 84.

He was educated at St. Olave's Grammar School in Southwark, where his father was vicar of St. Jude's, and in 1891 he qualified from St. Thomas's Hospital. After holding resident appointments there he took his F.R.C.S. in 1897, but he was deflected from a possible career in surgery by the offer of an appointment in Natal, where his brother Lieut.-Colonel Herbert Watkins-Pitchford was chief veterinary officer. He spent the next few years advising the government of Natal on the plans for the establishment of their new bacteriological laboratory. In 1898 he was appointed as a special plague officer to the government of Bombay. After serving as a civil surgeon during the Boer War he returned to England in 1901, to take the D.P.H. at Oxford. While he was at home the smallpox epidemic of 1902 occurred, and in view of his experience in the Far East he was appointed consultant to the London County Council. The same year he took his M.D. Lond. in State medicine.

Shortly afterwards he returned to Natal as assistant bacteriologist to the government, and in 1907 he became pathologist and analyst. In 1911 he moved to Johannesburg, where he became government pathologist and bacteriologist to the Transvaal. He also held the posts of municipal public analyst and of honorary pathologist to the Johannesburg General Hospital.

When the South African Institute for Medical Research was set up in 1912 he was appointed its director. In 1914 he published a monograph on *Industrial Diseases of South Africa*, and when the Miners' Phthisis Board was formed in 1916 he became chairman of the medical bureau. His contributions on silicosis, published in the annual reports of the board, described what was at that time the most comprehensive and intensive inquiry ever made into the occurrence of any disease.

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[1] Registrar-General's Quarterly Return for England and Wales: Quarter ended June 30, 1952. H.M. Stationery Office. Pp. 27. 2s. 6d.

[2] Registrar-General's Weekly return for England and Wales: Week ended Oct. 18, 1952. H.M. Stationery Office. Pp. 20. 1s.

[3] Morbidity and Mortality: Weekly Report, Federal Security Agency, Public Health Service: Oct. 10, 1952.

During the 1914–18 war Watkins-Pitchford added to his heavy burden of work the task of editing the *South African Medical Journal*. He saw bacteriology as a discipline of the science of preventive medicine, and his appointments outside his specialty included membership of the Union of South Africa's Council of Public Health and Leprosy Advisory Committee. He was also honorary professor of pathology and bacteriology in the University of Witwatersrand, and on his retirement in 1926 he received from it the honorary degree of LL.D. His work for the British Medical Association during his years in South Africa was recognised by his appointment as vice-president in 1923.

On his return to England he settled at Bridgnorth in Shropshire, where his friends were able to watch with pleasure the improvement in his health and the increasingly active part he was able to take in local affairs.

A. J. O. writes: "Two outstanding services were rendered by Wilfred Watkins-Pitchford: he was the first director of the South African Institute for Medical Research, and he was the first chairman of the Miners' Phthisis Medical Bureau. When he was appointed director of the S.A.I.M.R. there was a fine building designed by the late Sir Herbert Baker, a small amount of elementary equipment, and no staff. Soon there was a staff of half a dozen. From this grew the present great institute. When he retired Watkins-Pitchford left the institute in full swing. The Medical Bureau was established in 1916, the first institution of its kind in the world. It was, and still is, the sole authority for the medical examinations of miners, pre-employment, periodical, and for certification of the presence and degree of silicosis. With the late Louis Irvine, Watkins-Pitchford laid down the plan of work for the bureau which for many years continued to function admirably. A modest man of much personal charm and kindness, he had many friends in South Africa, few of whom, alas, are still alive."

Dr. Watkins-Pitchford married in 1905 Olive Mary Nicholl. They had a daughter, and a son who is a doctor.

Sir TRENT CHAMPION de CRESPIGNY, D.S.O., F.R.C.P., a former president of the Royal Australasian College of Physicians, died at his home at Adelaide, on Oct. 27, at the age of 70. For many years he was dean of the faculty of medicine of Adelaide University, and he was also chairman of the council of the Institute of Medical and Veterinary Science of Adelaide.

Births, Marriages, and Deaths

BIRTHS

BROMFIELD.—On Oct. 22, at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, to Anne (née Powell), wife of Dr. Frank Bromfield—a son.

FISHER.—On Oct. 12, to Sylvia, wife of Dr. J. A. Fisher, of Clonelly, Magherafelt, co. Derry—a daughter.

LITTLEWOOD.—On Oct. 15, to Elizabeth, wife of Dr. Arthur William Littlewood, of Gillits, Natal, South Africa—a daughter.

MILTON.—On Oct. 19, at Southchurch, Haslemere, to Joan, wife of Dr. R. Milton—a son.

WALKER.—On Oct. 19, to Elizabeth (née Barton), wife of Dr. Richard Walker, of Whitchurch, Hants—a son.

MARRIAGES

MACDONALD—DAVIES.—On Oct. 18, at Bolney, Sussex, Duncan [illegible] B., to Rosemary Ann Davies.

[illegible]—On Oct. 18, at Chiswick, Geoffrey [illegible] B., to Teresa Elizabeth Tomlinson.

DEATHS

BAYON.—On Oct. 20, at Little [illegible] Henry Peter Bayon, M.D. Genoa and Ca[illegible]

BURT-WHITE.—On Oct. 20, at [illegible] Burt-White, M.D. Lond., F.R.C.S., M.R.C.O.G.

EASTERBROOK.—On Oct. 25, at Gowanbrae, Eskbank, Dalkeith, Midlothian, Alexander Maitland Easterbrook, M.B. Edin., aged 83.

REDMOND-HENDERSON.—On Oct. 21, Sidney Redmond-Henderson, husband of Dr. Winifred Redmond-Henderson.

SILLAR.—On Oct. 23, William Cameron Sillar, M.D., B.SC. Edin., of the Gables, Wheatley, Oxon, aged 88.

SMEED.—On Oct. 25, Edward Smeed, M.R.C.S.

TALENT.—On Oct. 17, at Newlands, Grange over Sands, John William Talent, M.D. Edin.

THOMAS.—On Oct. 19, Frank Leslie Thomas, M.B. Lond., of the Square, Barnstaple.

WALKER.—On Oct. 21, at Springbank, New North Road, Huddersfield, Albert Edward Walker, M.B.E., M.D. Edin., aged 89.

Notes and News

ALCHEMY

"Let chemists toil like asses," Gay's highwaymen sing, "Our fire their fire surpasses, and turns all our lead to gold." We, who know at last that metals really can be transmuted, declining from uranium to lead, are yet apt to wonder at the passion with which our learned ancestors, with very little to go on, believed in the Philosophers' Stone. And indeed the mystery which hangs about alchemy is real and strange, as Mr. F. Sherwood Taylor, PH.D., makes clear in his little book, *The Alchemists*,[1] For one thing, only the meaner sort among them were seeking gold. The true alchemists were feeling their way blindly towards perfection—of the base metal, certainly, but also and chiefly of their own natures. Moreover, they believed it to be a lost perfection, which men had once known how to recover. Where we are looking anxiously forward they were looking nostalgically back. No-one could hope to be an alchemist until he had been instructed by a master of the art; for though there were texts available—some ancient and of great authority—which gave recipes for making the red and the white stones, with their marvellous properties, they were written in a style so deliberately obscure that the uninitiated could not understand them. Even now it is impossible to decipher more than a fraction of their meaning. Yet after instruction, it seems, the neophyte could follow them without difficulty. That is not to say he was forthwith in reach of making the Philosophers' Stone. The method was so lengthy and the risks to apparatus so formidable that he was likely to spend years in failing and starting afresh—years which he expected to use in preparing himself spiritually for the responsibilities of success. It is not possible for us to suppose that anyone ever succeeded; yet there are circumstantial accounts by those who say either that they did, or that they were given a tiny particle of the stone by an alchemist and worked the marvel of transmutation with it. Of course they had no exact means for assaying gold—which accounts for the readiness with which they accepted recipes for "doubling" gold (actually by debasing it with other metals in alloy).

Alchemy is often said to be the forerunner of chemistry; and certainly the alchemists had opportunities to observe a multiplicity of chemical reactions. Their attention, however, was elsewhere, and they have left us no record of these changes. What they did bequeath us was some first-class laboratory equipment—stills, flasks, furnaces, lamps, water-baths, ash baths, reverberatory furnaces, crucibles, dishes, beakers, pestles and mortars, strainers, filters, stirring-rods, and much other convenient apparatus still in use today. They had no conception of the freemasonry among scientists which we are now losing, and which made every new discovery the common property of the scientific world. But then, their reason for secrecy was a better one than ours: they feared that if knowledge of the art was put within reach of unscrupulous men, it might not be used for the glory of God and the benefit of mankind.

EMERGENCY BED SERVICE

THIS year, during the winter months, we shall again be publishing in our news columns figures showing the number of applications for beds for acute cases dealt with each week by the London Emergency Bed Service. The applications include those from general practitioners and from hospitals wishing to transfer patients from their casualty outpatient departments. The gap between the number of applications and the number of admissions is not composed entirely of cases that fail to be admitted: some cases are withdrawn by the doctor or the hospital while the service is still looking for a bed, and some patients refuse to go to hospital when a bed has been found, or die before admission.

HOSPITALS YEAR BOOK

ANOTHER October has brought a new edition of the Institute of Hospital Administrators' yearbook (obtainable from the Institute, 35, Portland Place, London, W.1: 1952. Pp. 1402. 45*s*.), and, though there may be more exciting reading for fireside evenings, anyone who is interested in our health services will find in its pages many useful facts set out in easily accessible form. The addresses and names of the chief officers of the bodies which administer the health service are given, from the Ministry in Whitehall to the executive council in Zetland and the hospital management committee at Morgannwg, and the list of less formal voluntary bodies who lend a valuable helping hand ranges from ASLIB to the W.V.S. In the section on reference information for the hospital administrator the value of the list of statutory instruments, memoranda, and circulars is increased by a useful index. As Mr. J. F. Milne, the editor, in his opening survey points out, it would be unfortunate if the present natural and perhaps inevitable concentration of interest on finance were allowed "to obscure the achievements which the national hospital service, in the comparatively short space of four years, has already to its credit." In offering so much useful information about our health services the yearbook reminds us that there is now a good deal to be informative about.

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[1] London: Heinemann. 1952. Pp. 246. 12*s*. 6*d*.

HEBERDEN SOCIETY

ON Oct. 25, Lord Horder delivered the Heberden oration taking as his subject Rheumatism—a National Problem. Sir Henry Cohen, the president of the Society, presented the Heberden medal to Lord Horder for his original observations and research in rheumatism.

DIRECTORY OF RESEARCH

IN 1946 a list of the research being carried out in British universities was prepared for an Empire scientific conference. The list was taken over by the British Council for its own use, but there have been so many requests for copies that the Department of Scientific and Industrial Research has now arranged to publish it each year. The British Council will continue to collect the material. *Scientific Research in British Universities 1951–2*, which is now available from the Stationery Office (8*s*., by post 8*s*. 6*d*.) gives details of research work in universities and colleges in the United Kingdom. It covers all fields of science and technology, including medicine. The names of the staff working on each problem and enough description to show the scope of the research are given in the main list, which is arranged according to university. There is also an index of names at the end so that any worker may be easily traced to his academic base.

FRIENDS' WORK

IN *Quaker Relief*[1] Mr. Roger Wilson, general secretary of the Friends Relief Service, modestly but effectively describes the many kinds of work which some 1200 men and women chose as an acceptable way of rendering their National Service other than in the Armed Forces. Not all of them were Quakers, but all had accepted the full implications of the pacifist rôle, and they were allowed to do this service as conscientious objectors. He explains a good deal about the background of committees, for nothing goes on its sober Quaker path without the appropriate committee backing. But delightful touches tell us of how, here and there, the headstrong team, or individual, would act first, and see about the permission later; and it seems as if the general secretary was able to suit his blind or watchful eye to every occasion.

In this country the work was usually some form of social service—among hop-pickers, among evacuees, in air-raid shelters, or for new settlers on housing estates. Abroad, teams, largely of American Friends, helped refugees after the Spanish Civil War and from Alsace in 1940. The Friends Ambulance relief team worked with the 21st Army Group, alongside the British Red Cross. In Greece a domestic school for girls remains a very successful piece of work. Episodes in Germany, Austria, Holland, Poland, and (outside Europe) Palestine and East Africa round off a tale of absorbing interest.

The members of the relief service, by the ability to live and work together, to forego comfortable living, and to share physical discomfort with their victims, gave their work a particular quality of sincerity and effectiveness. Reading this book one is reminded of Bunyan's hymn: "He who would valiant be, 'gainst all disaster." And what a telling quality valiance has in a disaster.

FILM ON HEMIBALLISMUS

A COLOUR film on *Hemiballismus in a Woman aged 71 Years* records the case of an old lady with severe choreiform movements of one side of the body. The movements are well shown, and there is a diagram depicting the site of the lesion in the subthalamic nucleus. Although some of the shots are rather long and some are reduplicated, this is nevertheless an excellent teaching film. The film (16 mm., silent) was made in 1950 for the National Hospital, Queen Square, by the department of medical illustration, Guy's Hospital, London.

A NEW JOURNAL OF PROJECTIVE TECHNIQUES

THE origins of the Rorschach test are to be found in several countries: the doctor-poet Justinus Kerner published his book on *Kleksographien* in Germany a hundred years ago, Alfred Binet provided a French contribution in 1895; and since Rorschach's brilliant work, investigators in America, England, and many other countries have illuminated the subject. Articles have appeared in widespread journals, including the *Rorschach Research Exchange* (now known as the *Journal of Projective Techniques*). The appearance of *Rorschachiana*, an international review of Rorschach and other projective techniques (Berne and Stuttgart: Huber), is to be welcomed, for it was in Switzerland that the notable studies of Hermann Rorschach were carried out. This well-produced quarterly has a strong Swiss backing but a widely representative editorial board, and should provide a forum not only for Rorschach studies but for reports on other projective methods developed since his untimely death. The languages to be used will be English, French, German, and Latin (and possibly also Spanish). In the opening number there are instructive contributions by Professor Bleuler, Dr. Loosli-Usteri, and Dr. Kadinsky, in the three main languages of today; except on the front page and the last, there is nothing to suggest that readers of the journal need to brace themselves forthwith for a tussle with the Latin periods of some expert reared in the grand traditions; at all events, since Mr. K. W. Bash, the editor, threatens to reject any paper that is not "stilistically correct," there is no danger that the writers of a debased Silver Age style—"Ulpian at the best"—will be allowed to affront the international Rorschach public.

THE EVOLUTION OF PLANTS

CERTAIN non-living chemical substances can interact to produce other substances very difficult to distinguish from living matter. Protein is supposed to have arisen in this way. If a particle of protein interacted with other substances to form more protein like itself it would be a virus. If this was indeed the way in which living organisms first came into being, it means that the earliest of them were not autotrophic (making their organic food from inorganic substances) but heterotrophic (obtaining their organic food from organic material) and that autotrophic organisms evolved from heterotrophic. Possibly some heterotrophic organisms gradually acquired the power of setting up chain reactions, and such an organism would gain if it could prevent dispersal of the products of earlier reactions in the chain likely to be required for the later reactions. Thus any organism which acquired a protective envelope would have a better chance of survival than most, and this would be the beginning of the cell and its semipermeable membrane.

The next step would be towards sexual reproduction, which enormously increases the rate of evolution by natural selection. Every organism that reproduces sexually has its life-cycle divided into two parts—haploid, with single chromosomes; and diploid, with double chromosomes. But these parts are not equal. In almost all animals the organism is mainly diploid, with but a brief haploid phase without mitosis. In many of the simpler plants the opposite is true, but in most plants both haploid and diploid cells undergo mitosis (alternation of generations). These facts suggest that sexual reproduction evolved before animals and plants diverged from one another—in fact, in a unicellular organism. The simplest form of sexual reproduction would be the fusion of two unicellular haploid organisms to form a diploid one, followed by meiosis producing haploids, and *da capo*.

A multiplicity of algal types shows that before vegetable life invaded the dry land it had undergone a long and complicated evolution. Whitehouse[1] suggests that the land plants have evolved from a fresh-water plant with a protected egg-cell enabling it to withstand a period of drought. The three classes of land plants—(1) mosses and liverworts, (2) ferns, club-mosses, and horsetails, and (3) seed-plants—have in common five important features: a protected egg-cell, alternation of generations, a cuticle, stomata, and air-spaces. Algæ do not share these features, which suggests that land plants are not descended from algæ but from a common ancestor shared with algæ. Of the three classes of successful land plants the mosses and liverworts "still show traces of their aquatic ancestry in their mode of fertilisation, and in this respect may be regarded as incompletely adapted for life on ıd." Whitehouse calls them "a blind alley of evolution." them the haploid phase predominates over the diploid. The final step in botanical evolution was the development of ɜd-plants. The elaboration of the haploid phase in mosses d liverworts rendered these plants incapable of eliminating ə need for external water. The abbreviation of the haploid ase enabled the ferns to evolve into seed-plants. This was ne by developing two kinds of sporangia, one containing ge female spores with a plentiful food-supply, and the her containing small male spores. Sometimes the female ores were retained on the diploid plant, their food being pplied direct from the parent; then, for fertilisation to take ace, the male spores must germinate near the female orangia and not on the ground. Such features can be cognised in fossils of the Carboniferous age (c. 300 million ars ago). In the succeeding Permian age (c. 250 million ars ago) the reproductive method had evolved still further. ıe female sporangia were protected by an integument, rming *ovules* which, after fertilisation by male spermatozoids, gan to develop into new plants but stopped after a time and came *seeds* for dispersal. Moreover fertilisation no longer pended on the presence of extraneous water: the necessary quid was derived from the male spores and from the breakown of the tissues of the apex of each female sporangium. or, in remembrance of their aquatic origin, the spermatozoids plants still have to swim for it, like human spermatozoa.

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[1] London. Allen & Unwin. 1952. Pp. 350. 15*s*.

[1] Whitehouse, H. L. K. Botany from the Beginning. Thrift Books No. 20. London: C. A. Watts & Co. Ltd. 1952. 1*s*. 6*d*.

niversity of Cambridge

Dr. A. D. Gardner, regius professor of medicine in the niversity of Oxford, has been appointed Rede lecturer for 953.

Prof. H. R. Dean has been re-elected as representative of ıe university on the General Medical Council for a further ve years.

niversity of Leeds

The title of emeritus professor has been conferred on rof. J. W. McLeod, F.R.S., who lately retired from the rotherton chair of bacteriology.

Mr. P. J. Moir, who held the chair of surgery from 1940 to 946, and who has been elected dean of the faculty of medicine, as been appointed professor of surgery from Oct. 1. For the ime being Prof. Digby Chamberlain will continue to act as ead of the department of surgery.

oyal College of Physicians of London

Prof. Alan Moncrieff will deliver the Charles West lecture n Tuesday, Nov. 11, at 5 P.M. at the college, Pall Mall East, S.W.1. His subject will be Infection in the Newborn Baby.

Royal College of Surgeons of Edinburgh

At a meeting held on Oct. 22 the following officers were elected:

President, Prof. Walter Mercer; vice-president, Mr. W. Quarry Wood; secretary and treasurer, Mr. J. J. Mason Brown; members of the president's council, Prof. R. C. Alexander, Mr. K. Paterson Brown, Mr. John Bruce, Mr. Arthur Hamilton, Mr. James Jeffrey, Mr. Archibald Brown Kerr, Sir James Learmonth, Mr. Robert Mailer, Dr. David Middleton, Mr. T. McWalter Millar, Dr. Douglas Miller, and Mr. R. Leslie Stewart; representative on the General Medical Council, Sir Henry Wade; conservator of museum, Mr. J. N. Jackson Hartley; convener of museum committee, Mr. John Bruce; librarian, Dr. Douglas Guthrie.

The following were admitted to the fellowship:

Amirali Abdulkarim Alidina, Gurbux Singh Babbar, K. L. Barnes, A. K. Brown, Jitendrarao Vajendrarao Desai, Sami Salim Khoury, Manijah Khudabux, Herbert Kramer, R. C. W. Lowe, J. D. Malloch, Naizhy Noble, R. D. Oatway, F. F. Sandor, L. A. Scrivin, Gurmukh Singh Sekhon, Shailendra Kumar Sinha, J. R. Smith, D. M. Stevens, N. P. Stracey, S. E. Wijetilaka.

Royal Australasian College of Physicians

The following have been admitted to the membership:

John Beveridge, R. S. Colton, M. Faunce, Alison K. Garven, Donald F. King, G. S. Nagy, A. Jean Palmer, I. S. Wallman.

Royal Institute of Public Health and Hygiene

On Dec. 9, 10, and 11, at 4.30 P.M., at the institute, 28, Portland Place, London, W.1, Lord Horder will deliver the Harben lectures. He is to speak on Fifty Years of Medicine.

North of England Otolaryngological Society

The following officers have been appointed for 1953: president, Mr. R. R. Simpson; vice-president, Mr. J. M. Wishart; immediate past president, Mr. G. S. Seed; secretary, Mrs. F. Cavanagh; members of council, Mr. R. Thomas, Mr. J. I. Munro Black, Mr. R. S. Venters, and Mr. J. D. Gray.

Mothercraft Exhibition and Conference

This exhibition and conference which opened at the Central Hall, Westminster, S.W.1, on Oct. 30 will continue until Nov. 12.

Royal Society of Arts

Mr. P. W. Brian, SC.D., of Imperial Chemical Industries, will deliver three Cantor lectures on Mondays, Nov. 17, 24, and Dec. 1, at 6 P.M., at the house of the society, John Adam Street, Adelphi, London, W.C.2. He will speak on Microbiology.

First-aid in Mines

A portable first-aid room, which can be moved forward as the coal face advances, is on trial at Markham no. 1 colliery, near Chesterfield. It is 12 ft. long, 6 ft. high, and 6 ft. wide, and contains a cabinet on wheels, for quick transmission, trestles, stretcher, eye-lamp, two chairs, dressing-bin, freshwater containers, and flasks of tea.

Research into Ageing

The research committee of the International Association of Gerontology consists of an American and a European division. The European division held its meeting at Liège on Sept. 25–27, under the presidency of Prof. L. Brull. The officers of this division are Prof. A. P. Thomson (chairman), Professor Brull, and Dr. V. Korenchevsky (hon. secretary), and those attending from this country included Prof. J. B. Duguid, Prof. Alexander Haddow, Dr. W. H. Lloyd, and Prof. Alexander Kennedy. The committee will hold sessions at the third International Gerontological Congress, which is to be held at Oxford in July, 1954.

Practice Arrangements

At a meeting of London Executive Council on Oct. 23, the general benefits committee reported the case of a practitioner with a list of 3936 health-service patients who is also employed by an industrial company. According to the report, a check had shown that the majority of prescriptions for this practitioner's patients were issued by his assistant. The committee had formed the opinion that the doctor should do at least half of the work of the practice and should attend morning and evening surgeries. The doctor had been given a month to review the position, and had been informed that, if his proposals were unsatisfactory, it might be necessary to ask the medical service committee to investigate the conduct of his practice.

Society of Medical Officers of Health

At the dinner of this society in London on Oct. 23, Mr. Iain Macleod, the Minister of Health, expressed pleasure at being in a gathering "that is almost entirely Scottish." He urged members not to mourn too much the passing of hospitals from their control. He was less happy about the relation of local authorities to the National Health Service; but a solution of this problem might have to await a more rational arrangement of local-authority boundaries—a task that no Government with a small majority would care to undertake. Mr. Macleod had heard that the society was considering a change in its name; and he suggested that "preventive medicine" might be incorporated in the new title. Mr. Macleod then proposed The Society; and in his reply Dr. Andrew Topping, the president, suggested that the achievement of local authorities between the passing of the Local Government Act of 1929 and the start of the National Health Service had not been fully appreciated. He still rued the passing from the M.O.H.'s control of the tuberculosis and infectious-disease hospitals, with their social implications. Dr. Topping also held that general practitioners should have a better status; they could, he thought, work more commonly in hospitals. Dr. C. F. White spoke in kindly terms of The Guests; and Mr. George North, LL.D., and Prof. G. S. Wilson responded.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 1060. The proportion admitted was 92·4%.

The International Congress of Medicine and Military Pharmacy which was to have been held in Montevideo in March, 1953, will not now take place.

Prof. F. Grundy has been appointed a member of the committee set up by the Minister of Food to inquire into the law and the practice of the slaughter of horses.

Surgeons and technicians from seven countries are now attending a two-week training course at Queen Mary's Hospital, Roehampton, on the manufacture and fitting of artificial limbs and the rehabilitation of amputees. The course is sponsored by the World Veterans Federation and the International Society for the Welfare of Cripples, and the Ministry of Pensions has provided facilities and personnel.

Diary of the Week

NOV. 2 TO 8

Monday, 3rd

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.4
3.30 P.M. Mr. T. Holmes Sellors: Surgery of Diseases of the Chest.
5 P.M. Sir Geoffrey Todd: Medical Aspects of Diseases of the Chest.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Prof. N. J. Scorgie, B.SC.: Animal Epidemiology.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5 P.M. Prof. Arnold Sorsby: Streptomycin and other Newer Antibiotics.

Tuesday, 4th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Sir Bryan Matthews, F.R.S.: Life at High Altitudes.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.30 P.M. *Section of Orthopædics.* Mr. J. G. Bonnin, Mr. E. Mervyn Evans, Mr. J. A. McLaughlan, Mr. R. H. Metcalfe: Fractures in the Aged.

SOCIETY OF APOTHECARIES OF LONDON
3.30 P.M. Sir William Gilliatt: Changes in Obstetrics and Gynæcological Practice in Last Fifty Years.
5 P.M. Dr. Kenneth Harris: Pitfalls in Diagnosis of Coronary Thrombosis.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. C. O. Carter: Genetics.

WEST END HOSPITAL FOR NERVOUS DISEASES, 73, Welbeck Street, W.1
5.30 P.M. Dr. C. Worster-Drought: Neurological demonstration.

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Section of Surgery.* Mr. R. C. Brock, Prof. C. G. Rob, Mr. Frank Forty: Reconstructive Arterial Surgery.

SOCIETY OF APOTHECARIES OF LONDON
3.30 P.M. Dr. Robert Forbes: Medicolegal Hazards in General Practice.
5 P.M. Dr. R. Hale-White: Present and Future Trends in General Practice.

ROYAL EYE HOSPITAL
5.30 P.M. Mr. L. H. Savin: Differential Diagnosis of Headache.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. C. H. Andrewes, F.R.S.: Work of World Influenza Centre.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Epitheliomata.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. H. G. Hanley: Urological Problems during Pregnancy.

SOCIETY OF APOTHECARIES OF LONDON
3.30 P.M. Sir Horace Evans: Medical Aspects of Hypertensive Disease.
5 P.M. Mr. A. Dickson Wright: Surgical Management of Hypertension.

MIDLAND MEDICAL SOCIETY
8.15 P.M. (*Birmingham Medical Institute.*) Prof. Melville Arnott, Mr. A. L. D'Abreu: Management of Mitral Stenosis.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (University of Manchester.) *Section of Medicine.* Dr. W. G. Oakley: Diabetes.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons, 18, Nicolson Street.) Dr. J. K. Slater, Dr. Montague Hadley: Coal Gas Poisoning.

Thursday, 6th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Dr. R. R. Bomford: Changing Concepts of Health and Disease, with particular reference to "Psycho-somatic Medicine." (Bradshaw lecture.)

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
4.30 P.M. Dr. C. F. Hadfield: Random Reminiscences of Fifty Years. (Frederic Hewitt lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Group-Captain W. K. Stewart: Physiological Effects of Gravity.

UNIVERSITY OF LONDON
5 P.M. (1, Wimpole Street, W.1.) Prof. Arthur W. Proetz (St. Louis): Clinical Aspects of Respiratory Air Currents. (Semon lecture.)

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
2.15 P.M. (1, Wimpole Street, London, W.1.) Dr. W. Rees Thomas: The Unwilling Patient. (Maudsley lecture.)

ROYAL EYE HOSPITAL
5.30 P.M. Miss J. M. Dollar: Squint.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Haber: Specific and Foreign Body Granulomas.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Co S.W.1
5 P.M. Dr. Denis Williams: Neurological lecture-demonstra

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverp
8 P.M. Mr. John Hamilton: Avoidable Stillbirths and Neo Deaths.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Mr. J. R. Cameron: Melanoma.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. J. Duguid: Cholesterol and Atherosclerosis.

Friday, 7th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Section of Otology.* Air Vice-Marshal E. D. D. Dicks Effects of Intense Sound and Ultra-sound on the Ea (Presidential address.)
2.30 P.M. *Section of Laryngology.* Mr. J. P. Stewart: Use Cortisone in Allergic Rhinitis. (Presidential address.)
5.30 P.M. *Section of Anæsthetics.* Dr. M. D. Nosworthy: Aids Anæsthesia. (Presidential address.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. J. Wallace: Congenital and Developmen Abnormalities.

ROYAL EYE HOSPITAL
5 P.M. Dr. J. Blewett: Diagnostic Value of X rays in Ophthalm Work.

Saturday, 8th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
11.30 A.M. Dr. Proetz: Olfaction.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
NOON. (Hammersmith Hospital, Ducane Road, W.12.) Prof. W. I. C. Morris: Uterine Rupture.

Appointments.

BOLAND, C. R., M.A., M.D., M.SC. Dubl., F.R.C.S.I.: surgeon, S Kevin's Hospital, Dublin.
BOVERI, R. M., M.D., L.R.C.P.E.: asst. chest physician, Herefordsh group of hospitals and Herefordshire county council.
KERTESZ, ANDREW, M.B. Lond., D.C.P., D.T.M. & H.: asst. pathologist, General Hospital, Nottingham.
MACCARTHY, H. M., F.R.C.S.I., M.R.C.P.I., F.A.C.S.: surgeon, S Kevin's Hospital, Dublin.
NORTH, J. F., M.A., M.B. Camb., F.R.C.S.: part-time consultant plastic surgeon, Dudley and Stourbridge group of hospitals.
TILLEY, ROBERT, M.R.C.S., D.P.H.: appointed factory doctor, Ho district, Kent.
WILLIAMS, A. H., M.R.C.S.: appointed factory doctor, Bargo district, Glamorganshire.

East Anglian Regional Hospital Board:

ASCROFT, N. O., M.B. Lpool: medical registrar, Foxhall Hospital
KEYES, MARY, M.B. N.U.I.: medical registrar, Papworth Hospital
PETTIGREW, R. W., M.B. Edin.: senior registrar in chest medicine East Norfolk Chest Clinic.

South-East Metropolitan Regional Hospital Board:

ELWELL, H. V. W., M.A. Camb., L.R.C.P., D.P.M.: asst. psychiatrist Hailsham group of hospitals.
GOLEBIOWSKI, A. K., MED. DIP. Lwow: asst. chest physician, Preston Hall group of hospitals.
MESTER, A. J., M.D. Cracow: asst. physician (geriatrics), Greenwich and Deptford group of hospitals.
ORCHARD, N. P., M.D. Lond.: consultant pathologist, Dartford group of hospitals.
WILSON, K. L., M.A. Camb., F.R.C.S., D.L.O.: consultant E.N.T. surgeon, Greenwich, Deptford, Woolwich and Lewisham group of hospitals.

Colonial Service:

BLAND, R. H., M.D. Dubl., M.R.C.P.I.: D.M.S., eastern region, Nigeria.
BOOKLESS, D. W., M.B. Edin.: M.O., Fiji.
CARROLL, D. S., M.R.C.S.: M.O., Barbados.
CHISWELL, D. A., L.R.C.P.: resident M.O. (interne), Kenya.
FLETCHER, G. H., M.B. Lpool: M.O. (Silicosis Bureau), Northern Rhodesia.
GOLIGHTLY, D. L., M.B. Durh.: M.O., Northern Rhodesia.
HARBEN, E. F., M.B. Madras: M.O., British Honduras.
IRWIN, D. B., M.D. Lond., M.R.C.P.: physician specialist, General Hospital, Barbados.
JAMES, S. T., M.B. Wales: M.O., Federation of Malaya.
JOLLY, T. G., M.B. Belf.: M.O., Fiji.
JONES, S. H. O., M.B. Manc., D.T.M. & H.: D.M.S., Gambia.
KNIGHT, ELLEN, M.R.C.S.: M.O., Tanganyika.
MAYCOCK, HELEN, M.R.C.S., D.C.P.: pathologist, Federation of Malaya.
PRAG, I. I., M.B., D.P.H.: M.O., Jamaica.
REES, W. H., M.R.C.S.: M.O., Fiji.
TARR, L. H., M.B.: M.O., Federation of Malaya.
TERRELL, J. D., M.B. Glasg.: M.O., Federation of Malaya.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

OPPORTUNITY AND THE UNIVERSITIES *

G. W. PICKERING
M.A., M.B. Camb., M.D. Ghent, F.R.C.P.
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF LONDON, AT ST. MARY'S HOSPITAL

IF life is a game—and I believe that those who enjoy ife, and who contribute most to the happiness of their fellows, regard it as such—then an important component of the art of living is the recognition and use of opportunity. For opportunity means that circumstances have arisen which first make a desirable goal attainable. The recognition and use of opportunity are behind every successful enterprise, whether it be the hoeing of weeds, the sailing of a boat, the climbing of a mountain, a business deal, an act of diplomacy, or the winning of a battle. That great experimental scientist, Louis Pasteur, is reputed to have said: "Opportunity comes to the prepared mind." Small men often dismiss a great achievement as a piece of luck, and so it may be; but much more often it is the culmination of hard work and hard thinking, which has prepared the mind for the opportunity presented to it.

CLINICAL SCIENCE

There are, of course, many opportunities presented to the universities in the field of medicine; but, to my mind, the most important and the most timely is the development of the teaching of clinical science. This opportunity has long been evident and was repeatedly emphasised by my teacher and friend, the late Sir Thomas Lewis, who devoted the Huxley lecture given at Birmingham in 1935 to the subject of Clinical Science within the University. During the seventeen years that have since elapsed, the progress of scientific knowledge and the perfection of scientific method on the one hand, and the establishment of the National Health Service on the other, only emphasise the desirability of exploiting this opportunity fully without delay.

Clinical science includes all aspects of the scientific study of disease in man. It must use, and does use, the knowledge and methods of other biological sciences, such as physiology, anatomy, biochemistry, pharmacology, bacteriology, and pathology. But there has been, and is, a body of opinion that considers that these branches of science are alone of importance to the advancement of medicine and that clinical science is an applied science, in that it merely uses knowledge derived from animal experiment and applies it directly to the recognition, understanding, prevention, and treatment of disease in man. It is not my purpose to belittle the importance of these branches of biological science. No-one with any knowledge of the history of medicine or with an elementary sense of justice can deny the importance of the contributions that they have made or will make. They have won their place in the world of science, and in the universities, and their position if it needed defending would find an ardent champion in me. What I want to emphasise is that if we are to see the full fruits of the efforts of science to prevent and cure disease we require an attack all along the line, and that clinical science must win a place in the world of science, and in the universities, equal and not inferior to those of the other branches. For after all, from the point of view of the community, all this expenditure of human effort and of money is justified in so far as it alleviates human suffering. Any work which seeks to elucidate the cause of disease, the mechanism of disease, the cure of disease, or the prevention of disease, must begin and end with observations on man, whatever the intermediate steps may be.

All this, you may say, is obvious enough. What is not so obvious, or at any rate is not so clearly borne out by work that has already been done, or by opinions commonly expressed, is that man is a species that in many respects is quite unlike any species kept in cages and subject to the kinds of experiments that can be made by any discipline other than clinical science. He is more or less omnivorous, and his diet varies widely, from the tapioca, maize, and sweet potatoes of the African native, to the seal-meat of the primitive Eskimo, and the vitamins, carbohydrates, proteins, fats, and antibiotics of the North American civilisation. He becomes addicted to alcohol, tobacco, narcotics, and hypnotics. He is exposed to a variety of industrial poisons and hazards. He is about to expose himself to speeds exceeding that of sound, and perhaps, unless he can be prevented, to radioactive emanations, the effects of which we dimly perceive to be immense. Finally, and above all, man is possessed, to an exceptional degree, of that peculiar property, the mind, with its fears, desires, loves, and hates interwoven with the pattern of conditioned behaviour that is built up from the moment of his birth until the time of his death.

I need not remind a university of the importance of the mind, since it is in its exercise that the justification of a university lies. But I think I should emphasise how little we know still of its inner workings. I can go further and state that we still know practically nothing of the rôle it plays, if any, in the cause of organic disease. There are, of course, ideas abroad, summed up in the term psychosomatic medicine, which suggest that many diseases whose expression is organic are due to diseases of the mind. But with few exceptions the evidence is dangerously thin. May I also remind you that the greatest threat to the future welfare of mankind, war, is an expression of the mind of man, particularly of the behaviour of masses or crowds, and their relationships to individuals. Many people nowadays are alive to the threat which hangs over the whole of mankind. They recognise that man's knowledge of and control of physical agencies has far outstripped his knowledge and control of mankind. This is not surprising when the place of the scientific study of man is still to be fought out in that university course which would seem to have this as its focus—namely, the medical curriculum.

PRESENT LIMITATIONS

The importance of science to the practice of medicine needs no emphasis. The limitations imposed on the practitioner are the limitations of exact knowledge. Since I began the study of medicine, the power to heal and prevent disease that science has placed in the hands of the profession has been enormous. Effective treatment has been introduced for diabetes, for pernicious and other forms of anæmia, and for the infectious diseases with the notable exception of those due to viruses, while vitamin deficiencies have been almost eradicated in this country. Nowadays, the soldier is unlikely to die from typhoid, dysentery, or malaria, scourges that previously killed more troops than the enemy; and blood-transfusion and antibiotics have enormously decreased the death-rate from wounds. These advances have been made by team-work in which all branches of medical science have played a part, and all I wish to claim for clinical science is that it played the leading part in some of these advances, while none could have been made without it. But a review of these contributions of science reveals another important fact—namely, that discovery is not enough; it must be understood and used by the body of the profession if it is to bear fruit. The importance of the scientific attitude of the profession is well illustrated by the Pacific war. A notable factor in the Allied victory was that the Allies were better able to control malaria

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* An address delivered at the inaugural session of the Medical School of the University of Birmingham on Oct. 6, 1952.

and dysentery, although mepacrine used for malaria was a German invention, and the sulphonamides used for dysentery were also of German origin.

Despite these advances, the doctor is still too often powerless, or his power is limited. Cancer, atheroma, hypertension, nephritis, Hodgkin's disease, the leukæmias, rheumatic fever, and rheumatoid arthritis are only some of the many diseases of which we do not know the exact cause or causes, which we cannot prevent, and for which we have no, or relatively ineffective, treatment. It seems unlikely that these diseases will prove to be simple examples of disturbed nutrition or invasion by microbes, and that their prevention and cure will be a simple consequence of a laboratory discovery. It seems almost certain that clinical science must play a major part in the attack, though, as I have emphasised, science must work as a team.

Take for example the problem of cancer. It seems that a number of chemical substances and certain viruses can transform the behaviour of certain cells so that they become cancerous. It seems also that the carcinogenetic agent may have had access to the body some years before the cancer develops. It seems therefore extremely probable that the factors which induce cancer in man will be identified only by scientific inquiry in man.

In the two subjects of great interest to me, animal experiment has helped to define the problem to be solved and to indicate clearly that the solution must come from clinical science. Thus hypertension can be produced in a variety of ways in the animal and it is possible that one of them may be an uncommon cause in man; but the solution of the vital problem, of essential hypertension, must come from man. Peptic ulcer can be produced in animals by inducing excess production of acid in the stomach, or by interfering with its neutralisation; the same mechanism probably holds for duodenal ulcer in man, but the inherited and environmental factors concerned only begin to be determined. Gastric ulcer is not, however, so caused, and here again we must depend on work on man.

Finally, I must mention psychological disturbances, the commonest cause of discharge from the Army in the last war, and a correspondingly large problem in peace. Psychology and its clinical counterpart, psychiatry, are branches of science as yet in their infancy with a meagre equipment of scientific method. These too, should participate in a general advance of clinical science. The body and the mind are not separate phenomena, and no serious scientific investigation on the one can afford to neglect the other.

THE OPPORTUNITY

I hope that these considerations will have convinced you of the importance of the scientific study of disease in man. In this country today we are presented with an opportunity of carrying out this study that would have seemed unbelievable seventeen years ago when Lewis gave his lecture. Most of the universities have established full-time professors with suitable assistants in the clinical subjects, including social medicine and pædiatrics and psychiatry. Moreover, the National Health Service has come into being, with its wealth of full-time hospital posts both senior and junior. Many men and women thus occupy posts with responsibility for the sick but in which remuneration is adequate, duties are limited, and tenure is secure—conditions that are eminently suitable for the pursuit of scientific knowledge, provided that these men and women have the urge, are prepared to use their leisure, and know how.

It is true that the whole-time posts in the health service exist primarily for the treatment of the sick; but it is also true that the man who is merely content to follow routine, and who makes no attempt to improve his own capacity to recognise disease, to understand it and to treat it, is a dull fellow, who is unlikely in the long run to render the best service. In the same way an institution in which no attempts are being made to advance knowledge is a dead, dull place, where the second-rate is all that is sought and attained. Thus even if we demand the efficient treatment of the sick, we are more likely to get it in an institution which seeks to advance knowledge and is, as it were, on its toes.

The catch in all this is that the vast number of men appointed to such posts do not know how to advance their subject, because they have had no training in scientific method as applied to the study of human disease. Let me give you a simple example. Over twenty years ago, severing the splanchnic nerves and removing adjacent sympathetic ganglia was introduced as a means of treatment of hypertension, and since that time many thousands of these operations have been performed. But to this day we cannot fully assess its value, because, although many series of patients subjected to this operation have been published, none have adequate controls. That is to say, no-one has taken a series of patients selected according to certain criteria and operated on some selected at random, leaving the remainder as controls, so that the effects of the operation on the course of the disease could be established once and for all time. This may sound an immoral proceeding, but it is in fact the best way to establish the value of a remedy whose effects are not at once and in all cases curative. To me it would seem a more immoral proceeding to use on a large scale a remedy without establishing whether it benefits or harms the patient. Obviously no-one introduces a remedy without believing it does good, but the history of medicine shows how often these beliefs are false. It is a man's duty to the profession and the community to prove whether his treatment is effective, and it is our duty as educators to see that the methods and standards of proof are known.

TEACHING OF SCIENTIFIC METHOD

For the fact is that the medical curriculum and the medical courses of most universities contain no organised teaching in clinical science, despite six years of intensive work by teachers and students. The first part of the curriculum does of course include examples of the scientific method as applied to the experimental animal and the test-tube, and certain aspects of normal behaviour. But in the second or clinical part of the curriculum the efforts of teachers and students are confined to learning the established discipline of medical practice. A few teachers try to teach scientific method during the clinical course; but the teacher knows and the student knows that his curriculum is overcrowded, and that he will not be examined in scientific method in his final examination. The discipline of medical practice cannot be dispensed with in the medical curriculum, but it is scarcely a sufficient object by itself for university education. As the Dean of Harvard said at a Harvard dinner which I attended: "I tell my students that in ten years' time half of what you are taught will have been shown to be wrong, and the trouble is that neither I nor any of your teachers know which half."

There are some who would say that scientific method is adequately taught in the preclinical curriculum and there is no necessity for it in the second or clinical part, which should be concerned solely with the art of medicine. This would be a just argument if all or even most doctors were going to be physiologists, biochemists, or anatomists, or were going to work in laboratories. But they are dealing with a very different kind of material. In this connection may be quoted a comment from the Cambridge report on "University Education and Business" (1945), the report of a Committee which included Sir Frederick Bartlett:

"The view that a University course should not be closely related to a man's ultimate career, but should be a general education in non-vocational subjects, is open to various interpretations. If it is meant that a University course should not consist merely of specific instruction designed for earning one's living, then no objection can be taken to it. If, on the other hand, the statement is interpreted to mean that a man is best prepared for life by reading subjects wholly unconnected with his career, then a good many objections can be taken to it. Such an interpretation depends ultimately on the assumption that habits of thought are transferable from one subject to another, but there is nothing in experimental psychology to suggest that such transfer will take place automatically. Any subject can be used as a means of training and developing the intelligence, and when intelligence has been developed by exercise it will be a better instrument for studying other subjects. This, however, is not the same as saying that the clarity in thought attained in one subject is directly transferable to another. In order to secure clarity the ideas involved must be easily manipulated, and an early acquaintance with these ideas is a great aid to proficiency. Further, if the subject is one for which the student has special interest he will more readily advance by using his innate ability unchecked by lack of interest in the subject matter."

WHAT, WHEN, AND WHOM

If, then, we are agreed that there should be some university teaching in clinical science, three questions remain, what to teach, when to teach, and whom to teach.

Lewis devoted much attention to the subject matter which he described by the term "theoretical teaching" to distinguish it from the "vocational teaching" of the craft. I dislike the term theoretical since it seems to stress hypothesis, which in another place Lewis described as "the heart which no man of right purpose wears willingly upon his sleeve." I have become more and more impressed with the validity of Karl Pearson's dictum that "the true aim of the teacher should be to impart an appreciation of method rather than a knowledge of facts." Again, to quote Barclay's *Apology*, "He that desireth to acquire any art or science, seeketh first those means by which that art or science is obtained." Disease in man poses problems which require the use of special methods to elicit an answer, and I think that the teacher should lay special stress upon these methods, their usefulness, and their sources of error. It would seem to me extremely probable that the methods expounded by Fisher in his *Design of Experiments* will find special application in the field of clinical science. This has already become clear in the clinical trial of new remedies, a method of therapeutic experiment which has in a brief space of time yielded conclusive and exact evidence of what may be expected of the antibiotics used singly or in combination and in defined dosage in specific types of disease of given severity. It is clear that the whole field of therapeutics needs an overhaul by the use of these methods by which we shall learn which of the old remedies are worth retaining and which should be discarded. But the whole field is vast and the science is young. At this stage methods of inquiry are usually borrowed from other subjects. But in the future, as the science grows, it will develop methods of its own to elucidate its own problems. No doubt different teachers will deal with different aspects. Out of them will come some well-defined course or courses with an accompanying textbook. But that lies in the future.

Lewis had in mind that the teaching of clinical science should form part of the undergraduate curriculum, some teaching being given to all students, and special attention being given to those with unusual ability and interest. I have tried to do something along these lines, but not enough. I have come to doubt whether such teaching reaches the average student, partly because he is not innately interested in discovery and exact knowledge, and partly because the medical curriculum is so overcrowded that he is chiefly obsessed with the task of memorising, and so appreciates the dogmatic teacher who presents him with material which can be reproduced in the form of an answer to an examination question. I think the most profitable step would be to arrange a short course for the abler students who elect to take it in the time which can be spared from the other duties of the undergraduate course. But I think ultimately it will be desirable to arrange a course, with full practical classes leading to an honours degree, for graduate students. Eventually, we might hope that such a course would have been taken by most of the staffs of the university clinical departments, and by the holders of senior posts in the hospital service. Such a course would economise men's time, since it would be given only to those able enough and interested enough to profit by it. That such courses would immensely improve the standard of thought and investigation into human disease is strongly supported by experience. There can be no doubt that physiology and biochemistry would never have made the progress that they have without the second part of the natural sciences tripos at Cambridge, the honours school of physiology at Oxford, and the honours B.SC. courses of other universities. Many universities are suitable for the development of such honours courses, but I can think of few with a staff more suited by virtue of their energy and intellect to carry out such a project successfully than the University of Birmingham.

OBJECTIONS

You may feel that the effect of what I am advocating is more and more research, when already none of us can keep abreast with the periodicals which multiply and divide until our medical libraries can scarcely contain the ever-increasing flood that descends upon them. The volume of publication is due to other causes, mainly the uncritical assessment of men by the weight of papers they have written. A body of men educated in scientific method and standards of criticism would result not in more but in less publication, not in more but in better research. Much of the work now published is badly conceived, badly executed, and inconclusive or misleading. One of the major causes of this is that there has been no serious attempt by our universities to educate men in scientific method and standards of criticism in the field of human disease.

Some feel, too, that scientific work on patients is not in their best interests, and they may doubt whether an improvement in the scientific standard of clinical investigation may not be accompanied by a corresponding fall in the ethical behaviour of the doctor towards his patient. It is perfectly true that the doctor who is interested in scientific proof has an interest and an objective other than what he regards as the best interests of each individual for the time being. And it is therefore important that any courses in clinical science should emphasise the importance of the ethical issues. But the fact is that there is a great deal of muddled thinking on this point. Take for example the treatment of hæmatemesis. Some doctors believe in starving their patients, some in feeding them, some in liberal transfusion, some in limited transfusion, some in operating on all cases, others in operating on selected cases, and yet others in operating on none. Each of these doctors, following his belief, or prejudice, believes when he prescribes his treatment that he is acting in the best interests of his patient. Yet there can be no doubt that some of these treatments have a much higher mortality than others, and that many patients die who should not die if the merits of the rival methods of treatment had been properly established by scientific standards. As I have said before, the chief limitation on the power of the doctor to help his patient is ignorance. The cure for ignorance is experience, and there can be no doubt whatsoever that in the long run the scientific method is by far the most economical use of experience both in terms of human effort and in terms of wastage of life by dangerous or ineffective therapy. Professional standards and scientific standards may seem at times to be in conflict, but in the long run they are but two aspects of the same problem—how the doctor can best help his patient.

OPPORTUNITY—OR UNIFORMITY ?

Finally, I would like to emphasise that a new suggestion for the improvement of medical education carries with it a real danger for the student. Nearly all individuals and committees that have seriously considered the curriculum agree that it is too full, and that the students' load should be lightened. Yet when these recommendations come to be implemented, the reverse happens and the load is increased. We are now witnessing a tragic instance of this kind. The medical faculties of our universities owe their present comfortable circumstances to the recommendations of the Goodenough Committee. Another of the recommendations of this committee was that the duration and content of the medical curriculum should be reduced, and such importance was attached to this recommendation that the committee thought that it might well be made a condition for the increased grants for medical education. Unfortunately, this reduction in the curriculum has never been made, and, where the university courses have been revised, they have been made longer and more rigorous.

Nowadays in some universities a boy entering medicine must look forward to a minimum of six years' undergraduate training, one year's house-appointments, and two years' military training—a total of nine years before he becomes a free agent. Add to that the recommendations of the Royal Colleges of five more years' training, much of it prescribed in detail, before he can become a specialist, and we have a total of fourteen years of training rigorously prescribed for the intending specialist.

Each of these recent additions, or proposed additions, to the compulsory requirements, looks innocent enough by itself: one, the compulsory year of house-appointments, is by general agreement necessary, and one, military service, depends on circumstances outside the control of those responsible for education. But when we look at the total sum we can quickly see how catastrophic the effects will be. If we wished to stereotype medicine, to ensure that we should never again have our James Mackenzies and our Thomas Lewis's I cannot imagine a more effective method. For these fourteen years are the formative years, the years of ideas and initiative in which the individual begins to make his contributions, if he is to make them at all. Real progress comes from the new approach, from the man who in his experience and outlook is different from the majority. We cannot legislate for such men, but we can ensure that never again shall they have the opportunity to acquire that unexpected and unusual outlook and exercise it effectively in medicine; and this is precisely what we seem to be trying to do.

Whenever I consider these increases in compulsory requirements I find myself so astonished that I am tempted to wonder if it is I or those who take the opposite view that are mad. I suspect there are many like myself who are dismayed, but we have allowed, or are allowing, small groups of zealous bigoted men to undermine our position. If we have the interests of medicine and of the student sincerely at heart, we must realise what we are doing and allowing to be done, and try to retrieve the lost ground, both in the undergraduate curriculum and in the postgraduate period. But we must act, for the sands are running out.

I see all this not as the machinations of wicked men, nor necessarily those of stupid men, but as part of a disease of society which might be named compulsory uniformity. It is not a new disease, but it has found an unusually susceptible population, and the organism has acquired exceptional virulence, in this age of reasoned planning. The facts to which I have drawn attention are its manifestations in the domain of medical education. I regard this as a serious disease and one which our society must learn to recognise if it is to eradicate it before it is too late. I would therefore like to end by saying that while I advocate the teaching by our universities of scientific method as applied to human disease, I would not see it added as a compulsory requirement to the undergraduate curriculum, or as a compulsory postgraduate requirement for any post. If in the future I do advocate these things, you will know that I, too, have fallen a victim to this fell disease.

THE EFFECT OF HEXAMETHONIUM BROMIDE ON THE CARDIAC OUTPUT AND PULMONARY CIRCULATION

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WITH the reintroduction of the tetraethylammonium compounds in 1946 by Acheson and Moe, there has been a renewal of interest in drugs that block the autonomic ganglia, and in the last two years the methonium compounds have been used therapeutically as hypotensive agents. The methonium compounds have the advantage, over the tetraethylammonium compounds, of smaller side-effects and longer action. Paton (1951) has demonstrated that they act by "competitive block" of the autonomic ganglia without affecting the release of acetylcholine from the preganglionic nerve-endings. He has also shown that in lowering blood-pressure these compounds act by relaxing autonomic arteriolar tone

TABLE I—RESULTS OF INTRAVENOUS INJECTION OF HEXAMETHONIUM BROMIDE

Case no.	Age (yr.)	Sex	Dose (mg.)	State	Blood-pressure (mm. Hg)	Pulse-rate	Cardiac output (litres per min.)	Right ventricular systolic pressure (mm. Hg)
1	61	M	25	Before*	205/90	68	5·4	31/5
				After†	99/59	58	4·8	8/0
2	30	M	100	Before	196/92	75	5·9	44/6
				After	148/82	88	7·4	29/3
3	54	M	20	Before	255/110	82	5·8	26/4
				After	126/61	83	5·9	20/0
4	57	M	10	Before	259/117	57	5·4	29/2
				After	162/108	64	4·7	19/0

*Before hexamethonium bromide. †After maximum effect.

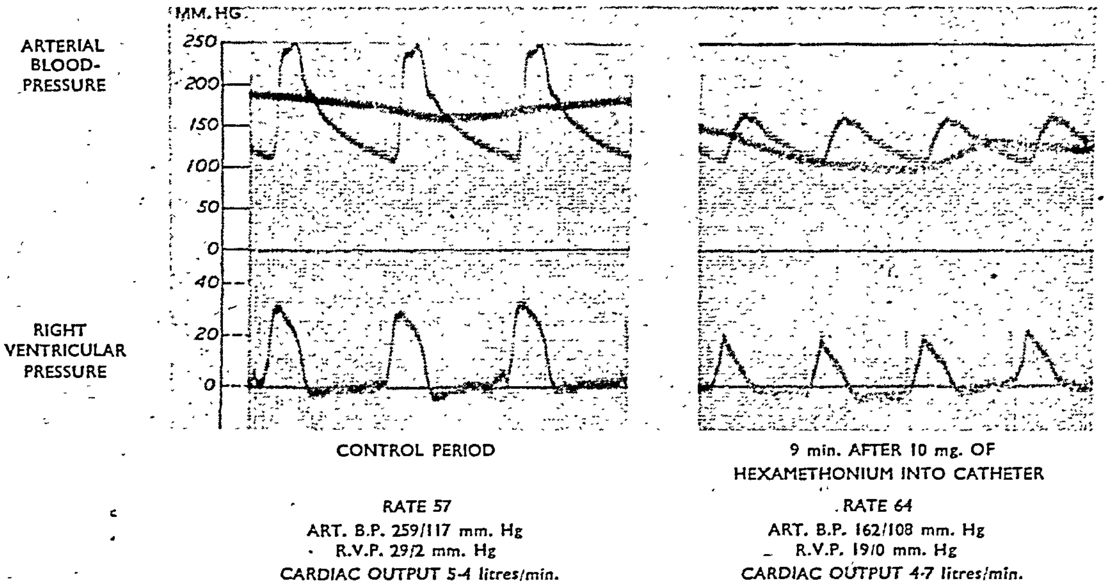

Fig. 1—Effect of hexamethonium on systemic and right ventricular pressures. Arterial and right ventricular pressure tracings obtained with strain gauge before and after injection of hexamethonium bromide. Cardiac output estimated by direct Fick method.

rather than by a direct action on blood-vessels. The value of postural hypotension in the treatment of hypertensive patients with these drugs was described by Restall and Smirk (1950), who recently (1952) demonstrated that this postural or gravitational hypotension was due to "decrease in the capacity of vessel walls of dependent parts to contract and thereby resist gravity-pressure dilatation." They showed that postural hypotension could be overcome by immersing the subject in water up to heart level.

The present investigation was undertaken to determine the effect of hexamethonium bromide on the cardiovascular system, with special reference to the changes in cardiac output and pulmonary circulation.

METHOD

Fourteen patients with severe hypertension from different causes were studied. None was in congestive failure at the time of the investigation, but all had clinical complications of their hypertension indicating a need for hexamethonium therapy (McMichael 1952).

Cardiac outputs were determined by the direct Fick principle with the method described by McMichael and Sharpey-Schafer (1944), mixed venous samples being obtained from the right atrium or ventricle by cardiac catheterisation.

In four patients the effects on cardiac output and right ventricular pressures were observed after the injection of hexamethonium bromide through the cardiac catheter. The dose used was that previously found to produce a satisfactory fall in systemic blood-pressure. Estimations of cardiac output, simultaneous right ventricular tracings (Bayliss et al. 1950), and brachial arterial tracings were obtained during a control period and after the injection of the drug when the blood-pressure had become steady at its new level. The patients were kept in a horizontal position during the period of observation.

In ten patients the hexamethonium bromide was given by subcutaneous injection and the postural effects were studied. Cardiac outputs were estimated from mixed venous samples obtained from the right atrium during a control period in the horizontal position and subsequently with the patient tilted 30°–45° feet downwards. The investigations were repeated 30 minutes after the subcutaneous injection of hexamethonium bromide. The dose used gave a substantial fall in blood-pressure when the patient was in the feet-down position, and was based on the result of a test on the previous day. Auscultatory blood-pressure measurements were taken.

The arterial oxygen saturation was determined with an ear oximeter (Wood 1950), with which the changing concentration of Evans Blue dye passing through the warm ear was recorded by photographing the light spot of the galvanometer on the falling plate of a Cambridge electrocardiographic camera (fig. 3). Dye time-concentration curves were thus obtained after the injection of Evans Blue (1% solution) through the cardiac catheter directly into the right atrium (Gilmore et al.) in the vertical and horizontal positions before and after the injection of hexamethonium bromide. From these curves the mean circulation-time from heart to ear was derived. The cardiac output (simultaneously estimated

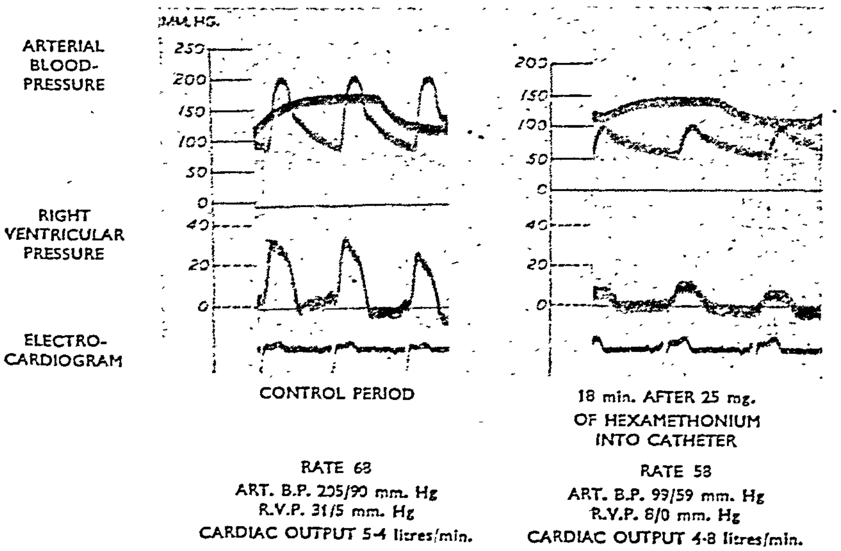

Fig. 2—As fig. 1.

In the tilted position the mean circulation-time was greatly prolonged after hexamethonium, indicating an increase in the cardiopulmonary blood volume.

It is concluded that hexamethonium prevents the normal reduction in the lung vascular capacity which occurs in the feet-down position. This, together with the fall in the pulmonary-artery pressure, implies that the pulmonary vessels have a vasoconstrictor nervous mechanism which is blocked by hexamethonium compounds.

We should like to express our thanks to Dr. M. E. Etheridge, Dr. Brenda Morrison, Dr. L. W. Ritzmann, and Dr. N. J. Selverstone for help in making these observations, and to Dr. R. Steiner for radiological help. Part of the expenses were met by a grant from May & Baker Ltd, who also supplied the drug.

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THE MANAGEMENT OF CŒLIAC DISEASE

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FOR many years there has been controversy over the relative importance of carbohydrate and fat in the production of cœliac disease. In his original description Gee (1888) advised a trial of cream and fresh butter, while recognising that the amount of farinaceous food must be small, and Howland (1921) and Haas (1938) based their dietetic management on the exclusion of starches. In this country Still (1918) and Parsons (1929), although recommending a reduction of starch, held a failure of fat-absorption to be the chief difficulty and advised that both fat and carbohydrate should be severely curtailed, leaving protein as the main source of nourishment. A diet of this type remained in vogue until after the late war, and was reflected in the special rations allowed for cœliac children on production of an analysis showing a high excretion of fat in the fæces. Whatever else it achieved, this type of diet undoubtedly led to an insufficient calorie intake over long periods, and contributed to the long stay in hospital of many of these children, while it was all too common an experience that progress towards recovery was tardy in the extreme.

In recent years fat-balance studies have shown that isolated analyses of fæcal fat give no true indication of the amount of fat that is being absorbed; and that cœliac children can absorb more than half their dietary fat even when the disease is severe. The wisdom of excluding fat from the diet and of thus denying them the opportunity of absorbing any fat at all is therefore open to question. Nutrition depends on what is absorbed rather than what is voided, and to base a dietary régime on stool analysis errs in the direction of treating the stools rather than the patient. It might be more reasonable to argue that, if fat-absorption is below normal, a greater head of fat should be supplied to make good the wastage in the stools.

Since 1947 we have treated 64 children with cœliac disease, and our results form the basis of this communication.

STARCH AND GLUTEN

One of us has reported that the entire exclusion of starchy food from the diet led to a significant increase in fat-absorption (Sheldon 1949), and this led to treatment with a diet in which protein and fat were given in normal amounts but carbohydrate was restricted to simple sugars. The children improved rapidly: not only was there a swift gain in weight and a steady though less spectacular gain in height but their perverse and unhappy behaviour quickly changed to a happy demeanour. The beneficial effect on fat-absorption of withdrawing starch from the diet has since been confirmed by Lowe et al. (1951).

Meanwhile in Holland Dicke (1950) and Weijers and van de Kamer (1950) observed that both wheat flour and rye flour exert a deleterious effect upon fat-absorption in children with cœliac disease, but that this is due to the protein component (gluten) and that, if the gluten of wheat flour is removed, the remainder, consisting of wheat starch, is well tolerated.

We have confirmed this observation at The Hospital for Sick Children, Great Ormond Street, and it has also been confirmed by Anderson et al (1952). These workers correctly point out that the benefit accorded to children with cœliac disease by the exclusion of starch is not so much due to the strict removal of all starch as to the fact that its removal from the diet entails the exclusion of wheat gluten. The precise manner in which gluten operates adversely on children with cœliac disease remains to be elucidated.

The present position concerning our dietetic management of these children may be summed up by saying that the objective is a diet from which gluten is completely excluded but which is in other respects normal. How long a child with cœliac disease should remain on such a diet has not yet been determined, but to base a return to gluten simply on a clinical assessment of well-being is in our experience insufficient. All too often, when gluten is reintroduced the rate of growth promptly slows, although if treatment has persisted for several months the complete picture of cœliac disease does not necessarily reappear. Thus if the child has already reached school age he may continue happily at school, maintain a fair appetite, and perhaps only pass one or two rather bulky motions each day. As at this stage the children are probably attending hospital only three or four times a year, the fact that the return to gluten has checked growth may escape notice for several months. We shall come back to this point later when describing our method of following up these children, with particular attention to recording their heights and weights, from which it is hoped to find a means, more precise than clinical assessment, of deciding when a diet devoid of gluten can be abandoned. Perhaps such a diet should be persisted with throughout the years of growth.

Although the removal of gluten from the diet is essential it would be incorrect to suggest that this is all that need be done for the dietetic management of a young child severely ill with cœliac disease. Several weeks of careful, experienced, and persuasive nursing may be required before the child can accept a full gluten-free diet, the ingredients of which must be gradually added, with many a rebuff, to a diet which at the beginning is much simpler; there may have to be an early phase in which fat is reduced and starchy foods are entirely withheld.

It is also necessary for the physician to become "caloric-conscious" and to know the energy value of the diet he has prescribed. A good diet can easily fail to enable a child with cœliac disease to gain weight unless sufficient food is being ingested daily, and we have been surprised at the high calorie intake that some of our patients have required. As soon as the child has started taking his new diet satisfactorily, the calorie intake should be steadily increased until the weight begins to rise: this can be done either by increasing the amounts at each meal, or, if the child seems already to have reached satiety, the calorie intake can be augmented by the addition of glucose. In some of our cases the intake of glucose has gradually risen to 4 oz. a day. The accompanying table shows the number of calories per pound body-weight that has been needed to get a satisfactory weight gain. We have used not the expected but the actual body-weight, and, as with marasmic infants, the more wasted the patient the higher must be the calorie intake per lb. of body-weight.

Daily calorie intake per lb. body-weight	40–49	50–59	60–69	70–79	80–89	90–99	100 or more
No. of cases ..	4	8	15	12	11	4	2

It will be seen that the great majority of the children needed 60–90 calories per lb. body-weight per day. Such a high calorie intake would be very difficult to achieve if fat, with its high calorie value, were excluded from the diet.

ANÆMIA AND INFECTION

The importance of dealing with anæmia and infection must be pointed out, for otherwise dietetic treatment is bound to be disappointing.

Anæmia is common in children with cœliac disease and is usually hypochromic. If the hæmoglobin is above about 65%, the anæmia can be slowly rectified by adding iron to the diet; but, if the anæmia is more severe, it is better to give a blood-transfusion. We have transfused blood in nearly a quarter of our cases. Occasionally the anæmia is megaloblastic; it will then respond quickly to a fortnight's course of folic acid 5 mg. thrice daily. This type of anæmia occurred in 5 of our cases. Not uncommonly the severely ill child with cœliac disease combines anæmia with œdema, usually in the lower extremities; occasionally ascites is present, and usually such children have a lowered blood-protein level. A blood-transfusion will serve the added purpose of raising the blood-proteins, or this may be accomplished by a transfusion of plasma. It is permissible to hope that, in the future, children suspected of having cœliac disease will be given a trial of a gluten-free diet while their disease is still in its early stage, and will be restored towards health before their condition has sunk so low as to require transfusions of blood or plasma.

Infection.—Cœliac disease uncomplicated by infection is an afebrile illness with a normal erythrocyte-sedimentation rate. Intercurrent infections, usually of the upper respiratory passages, arise easily in these weak children, and almost invariably lead to an exacerbation of the cœliac symptoms, which require prompt recognition and treatment. It is equally essential to recognise and treat any focus of persistent infection, whether in the gums, urine, or throat; otherwise a satisfactory response to dietetic management cannot be expected.

DIET

The following description of our dietetic management begins with a young child—say about two years of age—already severely ill with cœliac disease, greatly wasted, and with an appetite capricious to a degree. To such a child we offer four foods: skimmed milk, 'Prosol,' * glucose, and banana purée. The prosol is
by adding 1 drachm of powder to 1 oz. of wat
prosol and skimmed milk being given togethe
proportions. The mixture is sweetened by
teaspoonful of glucose to every 2 oz. Feeds
every four hours, either five or six feeds in tw
hours, and usually 8 oz. at each feed.

Banana purée is given either separately or m
some of the milk feed, starting with half a ban
and increasing to a whole banana. Not inf
the child dislikes the banana, in which case it i
If the stools remain frequent and watery '
may be used to help consolidate them, 2 or 3
fuls being added to each 8-oz. feed until t
become formed.

Changes from the initial diet begin as soon as
evinces interest and pleasure in feeding.
additions consist of minced chicken, egg cus
biscuits made from soya flour and spread wi
and honey, and these are followed by sieved s
vegetables (such as cabbage, cauliflower, beet
tomato), sieved fruits, and cheese. Each chil
separate study, for one likes what another
only one new food is tried on any one day, a
trials are made with really small helpings-
tablespoonful.

As regards the initial diet, skimming of
continues until the stools are of good consist
down to one or two daily; skimming is then pro
discontinued until whole milk is being given,
this stage may not be completed until chi
custard, and soya biscuits are already part of
Prosol continues, with either skimmed or wl
until the menu has become comprehensive.

The final step is to add starch, but strictly
any gluten-containing foods. We are greatly
to the Energen Foods Co. Ltd. for supplies
starch (wheat flour from which gluten has been
with which bread, cakes, and biscuits can be m
is the first starch to be added. A little later f
do not contain gluten—e.g., potato and rice—
made from oats and maize are introduced.
time the child is on a full diet devoid only
and it is at this stage that the child leaves
to continue at home on a gluten-free diet,
hospital as an outpatient.

From the beginning of treatment vitamins are
vitamin C in the form of a 25 mg. tablet o
acid daily; vitamins A and D as 10 drops
concentrate ('Radiostoleum,' 'Adexolin,' or
liver oil); and, often in the early stages, vita
'tab. Benerva co.' 1 thrice daily.

We have thought that the addition of potat
maize flour sometimes tends to increase the s
abdomen, but they are taken with such relish, a
the diet to become so diversified, that th
qualification has not deterred us from givi
Occasionally their addition has caused d
or mild colic, which has been taken as an
to persevere for three or four weeks longer on
free diet before resuming a very gradual int
of these flours.

From the foregoing description it will be ap
that the build-up of the diet for children wi
disease is a continuous process carried out und
tions of close watchfulness. Attempts have b
by others to divide the dietary into stages,
has not been our practice, for it seems to
unrealistic; nor could the various hospital
departments be expected to reach uniformit
end-points of the various stages.

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* Prosol (Trufood Ltd.) is a dried skimmed milk with added protein. When reconstituted by adding 1 drachm of powder to 1 oz. of water, it has the composition: protein 7·75%, fat 0·125%, and carbohydrate 3·4%.

† Arobon (Nesfoods Ltd.) is prepared from the carol
virtues being due to its lignin, pectin, and heav
content.

When the child leaves hospital, the principles of a gluten-free diet are explained to the mother, and she is given the following instructions, which include a list of the foods that contain gluten and must be avoided, while indicating a few of the foods which are in fact gluten-free but which, we find, are often withheld unless their harmlessness is mentioned:

"Your child may have an entirely normal diet except that nothing may be given which is made from wheat flour or rye flour. As a substitute for flour, pure wheat starch, as supplied by the Energen Foods Co. Ltd., Bridge Road, Willesden, London, N.W.10, may be used in unlimited quantities. It may be found useful to supplement the diet with soya flour and cornflour, which are also harmless. Potatoes may also be given in normal quantities.

"The following are some examples of foods in common use which may NOT be given as they are made from or may contain wheat or rye flour:

Bread
Biscuits
Cakes
Cream of wheat
Doughnuts
Energen rolls
'Grape Nuts'
Ice-cream (commercial)
Macaroni
Malted milk
Noodles
'Ovaltine'
'Procea' bread
'Proferin' rolls
Packet cake and pudding mixture
Packet soups and gravy browning
Pastry mix
Patent foods
'Puffed Wheat'
Paste (fish or meat)
Rusks
'Ry-Vita'
Semolina
Spaghetti
'Shredded Wheat'
Sweets of unknown composition
Sauces (commercial)
Salad cream
Sausages
Tinned soups and meats
Vermicelli
'Vita Wheat'
'Weetabix'

"No breakfast cereal foods other than those specifically recommended should be given. The following, however, are harmless:

'Cornflakes'
'Puffed Rice'
'Rice Krispies'

"Gravies and sauces may be thickened with pure wheat starch or cornflour, but not with ordinary flour. Ordinary household cocoa may be given but not proprietary preparations (such as ovaltine).

"*NOTE.*—Do not give any other foods unless you are quite sure that they are entirely free of wheat or rye flour."

We also supply the mother with the following recipes for the preparation of bread, cakes, and biscuits:

GLUTEN-FREE RECIPES

Wheat-starch Loaf

½ lb. pure wheat starch
2 oz. sugar
2 oz. margarine
4 teaspoonfuls baking-powder
Milk as required

Sieve the dry ingredients into a basin, rub in the margarine, and mix in enough warm milk to make a batter consistency. Mix lightly and pour into a greased tin. Bake in a quick oven for 10 min., then reduce to moderate heat for a further 30 min.

Soya Wheat-starch Loaf

2 oz. soya flour
7 oz. pure wheat starch
2 oz. fat
5 teaspoonfuls baking-powder
1 teaspoonful sugar
½ teaspoonful salt
6 oz. milk
6 oz. water

Method as for wheat-starch loaf

Wheat-starch Cake

½ lb. pure wheat starch
4 oz. sugar
4 oz. margarine
1 teaspoonful salt
3 teaspoonfuls baking-powder
4 oz. milk
1 egg (optional)
Flavour with coconut, dates, or chocolate

Sieve the dry ingredients into a basin, rub in the margarine, and mix in enough milk to make a soft dough. Knead lightly and turn into a well-greased shallow tin. Bake about 30 min. in a hot oven (400°F, Reg. 7)

Small Cakes

6 oz. pure wheat starch
4 oz. margarine
4 oz. sugar
1 egg
1 heaped teaspoonful baking-powder
Grated orange rind

Cream together margarine and sugar, add the egg and orange rind, and then the flour. Cook for about half an hour in a moderate oven (300°F, Reg. 5). Makes eighteen small cakes

Wheat-starch, Soya-flour, and Rice-flour Cake

4 oz. rice flour
4 oz. pure wheat starch
2 oz. soya flour
4 oz. castor sugar
4 oz. margarine
1 egg
6 oz. milk
1 oz. sultanas
4 teaspoonfuls baking-powder

Sieve the dry ingredients into a basin, rub in the margarine, and mix in enough milk to make a soft dough. Knead lightly and turn into a well-greased tin. Put in a quick oven (400°F, Reg. 7) for 5 min., then reduce heat to 300°F (Reg. 5) and bake for a further 55 min.

Soya Wheat-starch Biscuits

3 oz. soya flour
3 oz. pure wheat starch
3 oz. margarine
3 oz. sugar
1 egg
Vanilla or orange flavouring

Cream together margarine and sugar, add the egg, soya flour, and pure wheat starch, and knead into a stiff dough. Roll out ¼ in. thick and bake in a moderate oven for 10 min.

Soya Biscuits

Follow the recipe for soya wheat-starch biscuits, using 6 oz. of soya flour and omitting wheat starch.

RATIONING

The special rations for children with cœliac disease, introduced during the late war reflected the opinion that fat was injurious and that protein should be the main source of energy. In the acute phase of cœliac disease five extra meat rations were allowed, and the fat ration was cancelled: in the "convalescent" stage the fat ration was restored, but only two extra meat rations were allowed.

When, in the design of the gluten-free diet, pure wheat starch was substituted for the gluten-containing flours of the normal dietary, it was found impossible to make a loaf or a cake which would hold together without the use of eggs or fat. This presented no great obstacle to the preparation of such foods while the children were in hospital, but it was soon found that, after discharge on a gluten-free diet, the cœliac in the home was consuming most of the family's slender resources of eggs and fat. The Ministry of Food have therefore authorised the issue, to children undergoing treatment for cœliac disease with a gluten-free diet, of one extra fat ration, and one priority egg allowance, in return for which one of the two extra meat rations hitherto allowed in the "convalescent" stage is surrendered. This alteration in rationing has been found adequate for the use of wheat starch.

PROGNOSIS

There have always been wide divergences in the prognosis of cœliac disease given by different observers.

Gee (1888) wrote "Death is a common end . . . even when it tends slowly to recovery they are left frail and stunted." Cheadle (1903) had seen 1 fatal case only. Still (1918), reporting on 41 cases, observed that 6 of the children had died (1 from pneumonia) and asked: "Is there ever complete recovery in the sense of attaining eventually average height and acquiring normal pubertal growth?" Howland (1921), however, describing a series of 30 cases treated by exclusion of polysaccharide from the diet without a death, observed: "They do not remain semi-invalids. Many become vigorous and strong, some even with no trace of dietary idiosyncrasies, sometimes with a digestion that must be treated with care." The experience of Parsons (1932) was that, in spite of careful treatment, progress towards recovery was always slow and intermittent, and it was his opinion that "Any definite retardation of growth always leaves it mark . . . and . . . the child never reaches normal height."

Andersen (1947) and Haas and Haas (1950) reported a high degree of success with a diet free from cereal starches, and the latter conclude that less than a fifth of the patients need more than two years' dieting. Their criteria of cure, however, do not seem strict enough, nor do they define normal growth.

The prognosis of cœliac disease was, before the late war, discussed clearly only in terms of mortality. Hardwick (1939), reviewing the published series, found an over-all mortality of 15% in 544 cases.

In the present series of 64 cases there has been 1 death from cœliac disease: a severely ill child died in tetany very shortly after admission and before treatment could be effective. Another child, who was doing well on a starch-free diet, was killed in a motor accident. It would seem that, under good conditions of care, mortality is approaching vanishing-point, and a different method of assessing results is required.

No technique of management is completely effective unless it allows the children to regain optimal growth as regards both height and weight. The ideal growth curve would start with a recovery phase in which tissues were being rebuilt and the growth lag was being made good; in this phase the rate of gain in weight would be abnormally high; when the optimal level was reached, the curve would flatten out toward a normal rate of gain.

On the starch-free (and incidentally gluten-free) diet this ideal curve was attained while the children were under our care in hospital, where they gained weight rapidly at gradients of 20–100 lb. a year; but in few cases was this curve continued after the children were discharged to their homes. In most cases a flattening in the gradient, before the optimum had been reached, coincided with discharge from hospital. Despite this lack of growth, however, the children nearly all remained free from symptoms in what passed for normal health, and grew slowly, while their parents were attempting either to maintain a starch-free diet at home or were being allowed to try relaxations of the diet. We suspected that this lack of growth was attributable to the great difficulty, both technical and economic, of giving at home a diet from which both the staple foods, bread and potatoes, were entirely excluded; but there seemed little to be done about it, short of admitting apparently well children to hospital and keeping them there indefinitely. Whenever one of these children became ill and was readmitted, the ideal curve was resumed once more upon the reinstitution of a strict starch-free diet.

The promise which starch-containing gluten-free diets offered of easier dietary maintenance at home led us, toward the end of 1951, to review all cases treated with starch-free diets since 1947. Of the 64 children in the series 2 have died, and we have lost touch with 3. Of the remaining 59, 25 who are now on a normal (gluten-containing) diet are in a state of health regarded by their parents as normal, and would pass without comment in a school environment; but a study of their growth pattern suggests that many would probably benefit from a gluten-free diet. 15, whose development was clearly unsatisfactory, although they too were broadly symptom-free while on a normal or partially starch-free diet, have in the last nine months been put on to a gluten-free diet, and all have since shown an increase in the weight gradient above normal rates of gain. The remaining 19 cases are more recent, and all the children have reached a gluten-free diet as a part of their initial management. In no case has the introduction of starch, free from gluten, interfered with the progress of the weight curve.

Both in children discharged on a gluten-free diet after initial treatment, and in those introduced to a gluten-free diet after a period at home on a "starch-free" or normal diet, there have sometimes been delays in response or periods of lack of growth. In the absence of infection or other intercurrent disease such failures have always been found, if careful enough investigation was made, to be attributable to the inclusion of a gluten-containing food in the diet; and normal growth has been resumed on the exclusion of the offending article. Although we have made no precise experiments to determine the effective threshold toxic dose of wheat gluten, it is within our experience that this is small. We have observed on several occasions that the relaxation of the diet to the extent of allowing one slice of toast a day (containing about 2 g. of gluten) checks growth.

The gluten-free diet is not difficult to give at home, nor is it expensive. The difficulties we have encountered are two:

(1) The presence of small quantities of wheat flour in a wide range of manufactured products not clearly of wheat-flour origin—e.g., ovaltine and 'Horlicks.'

(2) The difficulty of persuading parents that the diet must be rigidly adhered to even if experience shows them that relaxation of the diet brings in its train no dramatic return of symptoms. It must be explained to them that the ill effects may merely consist in a growth failure measurable only over several months.

Our technique of assessing progress, and of deciding in the future when gluten may safely be introduced, is as follows:

Individual weight and height curves are plotted on a chart, upon which are printed means and standard deviations of height and weight from ages 1 to 12 years. Increments in height are regarded as of even greater significance than increases in weight.

The initial rate of gain while the child is "catching up" will be faster than normal, but at some point within the normal range the growth curves will flatten out toward the normal gradient. It is particularly important that the diet should be strictly maintained for some months beyond this point, until the child has continued, from his optimal level, to grow steadily, and has thus provided personal standards of normality whereby his subsequent behaviour can be judged. When this stage has been reached, gluten-containing foods may be experimentally introduced, but it must be recognised that their failure to bring about an immediate clinical relapse is no proof that the sensitivity to gluten has passed. In most cases it will take three or four months for lack of growth, consequent on relaxation of the diet, to show itself.

The more closely we study the long-term growth charts of our patients the longer does it appear necessary to withhold gluten from the diet, but we are not yet in a position to say whether gluten should be excluded throughout the years of growth. There is, however, in our experience nothing incompatible with such a hypothesis. There is certainly no justification now for accepting anything short of optimal growth as evidence of success in treatment.

Many aspects of cœliac disease remain to be studied; but against the background of the conception of cœliac disease as a specific poisoning with certain cereal proteins, there is a rich field for precise metabolic investigation on the one hand, and on the other for therapeutic success with the simplest of weapons.

It is a pleasure to record the generous help we have received from Prof. A. C. Frazer and his department in Birmingham, and from Dr. W. W. Payne at Great Ormond Street throughout our investigations into this disease; to acknowledge the kindness of our colleagues who have made available to us their cœliac patients; to pay tribute to Miss Dillistone, the hospital's dietitian, who has followed so patiently the requirements of a changing technique; and to Sister Parcell for her nursing skill; and to express our thanks to the Ministry of Food for coöperation in making the experimental diet possible before a change in rationing was finally decided.

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RELATIVE NOCTURNAL POLYURIA AS A FACTOR IN ENURESIS*

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This paper is based on the investigation of a consecutive series of 100 children with enuresis but without ascertainable organic disease. This investigation was made in 1950–51 at Whipps Cross Hospital, and its purpose was to lay bare any mechanical factors which might be responsible for the incontinence. The ages of the patients ranged from four to fourteen years: 18 children, fully continent of urine, served as controls.

Ström-Olsen (1950) has suggested that nocturnal enuresis in adults is often associated with hypersomnia; but excessively deep sleep cannot be the chief cause of the wetting in children, since continent children do not wake to pass urine but contain the total volume of urine excreted during the night and void it in one act in the morning. Further, the administration of copious drinks at 8 P.M. to a wardful of continent children has repeatedly produced wet beds in 10% of the occupants. The normal child is dry because the volume of urine he excretes during the night is less than the volume that his bladder will hold.

DIURNAL RHYTHM OF WATER EXCRETION

The first descriptions of the rhythm of excretion of urine were given by Roberts (1860) and Quincke (1877). Roberts stated that $4^1/_2$ times as much water was excreted by day as by night, and of the solid constituents of urine twice as much.

Simpson (1924) studied the rate of excretion of water in more detail, keeping the fluid intake constant. He found that the rate of excretion rose sharply at about 7 A.M. and dropped sharply in the evening at any time between 4 P.M. and 10 P.M. This rhythm, he claimed, was not affected either by darkness or by sleep. Borst and de Vries (1950) have described this rhythm more recently.

METHOD OF INVESTIGATION

The children, both enuretics and controls, were studied in the ward for six days each. The normal ward routine was followed, drinks being offered at meal-times, but further fluid being given if the child desired. The fluid intake was recorded.

During the daytime each child passed urine as desired, and the time, volume, and specific gravity were noted on each occasion. The greatest volume passed in one act, and the mean of all these volumes, served as two measures of the volume of urine that the bladder would comfortably hold.

During the night both the enuretics and the controls were woken every three hours and urged to void urine. A few children, who continued to wet despite this, were woken every two hours, so that all the urine excreted could be measured. The twenty-four hours of each day were divided into two periods of twelve hours each at 8 A.M. and 8 P.M. The mean volume excreted in each of these periods was recorded, and the day to night (D/N) ratio was calculated for each child.

FINDINGS

Controls

In the 18 normal children the volume of urine excreted by day was generally two or three times that excreted by night. The lowest D/N ratio was 1·8, and the ratio was independent of the age of the child. The mean volume in ounces of urine excreted in the twenty-four hours was not greater than twice the age in years plus 18 (or, in millilitres, sixty times the age in years plus 540). The mean volume in ounces passed by a normal child in one act was at least half his age in years (or, in millilitres, fifteen times his age in years). The greatest volume voided by a normal child in these conditions in one act was twice the mean volume.

For example, a normal child aged six years would at each act pass on the average 3 oz. but occasionally 6 oz. (180 ml.). His average excretion in the twenty-four hours would be less than 30 oz. (900 ml.), of which less than a third would be excreted during the night.

Enuretic Children

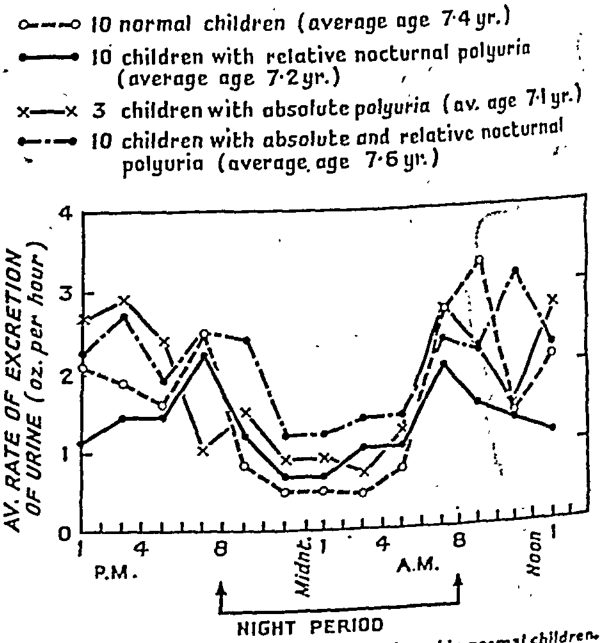
Of the 100 enuretic children, 69 were found to excrete an unduly large proportion of their urine by night, the D/N ratio being less than 1·8. I suggest this condition be called relative nocturnal polyuria. Among these 69 all degrees of severity were found, with D/N ratios varying from 1·8 (the lowest figure compatible with a normal diurnal rhythm) down to 1·0, at which figure there is no appreciable diurnal rhythm at all. In only 2 children was the D/N ratio less than 1·0, indicating a reversal of the diurnal rhythm as described by Batty (1948).

Of these 69 children with relative nocturnal polyuria 11 were found to be passing an abnormally high volume of urine in the twenty-four hours, and a further 5 children with a normal diurnal rhythm passed a similarly excessive amount of urine (absolute polyuria). In none of these children was there any albuminuria or glycosuria, and in all the urinary specific gravity was normal.

Excretory Rhythms Compared

The diurnal excretory rhythms found in normal children and in three groups of enuretic children are shown in the accompanying figure. The curves differ in degree rather than in type. In all of them there is an evening diuresis greatest at 7 P.M., followed by a decrease in excretion to a minimal figure about midnight. There is a morning diuresis starting at 5 A.M. and reaching a peak about 8 A.M. However, the minimal rate of excretion at night was considerably above the normal in all three groups of enuretic children.

The evening and morning peaks of diuresis explain the tendency for nocturnal incontinence to occur shortly after going to bed (Smellie 1949) and shortly before rising in the morning.



Diurnal rhythm of urinary excretion in enuretic and in normal children.

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* Adapted from a thesis submitted to the University of Oxford for the degree of Doctor of Medicine.

SYMPTOMS OF RELATIVE NOCTURNAL POLYURIA

Of the 69 children with relative nocturnal polyuria all were wet at night, and only 14 were also incontinent by day. In these 14 children the nocturnal wetting was the more severe, the diurnal wetting occurring only when precipitancy of micturition prevented the child from reaching the lavatory in time.

Apart from nocturnal enuresis the most common symptoms of children with relative nocturnal polyuria were diurnal frequency, precipitancy of micturition, and excessive thirst. On the other hand, infrequent diurnal micturition was also not uncommon.

Of these 69 children, 37 had diurnal frequency and 27 of these also had precipitancy of micturition. Excessive thirst—i.e., drinking at least once between each two meals in all weathers—was found in 34 children, and of these 20 had diurnal frequency.

In 31 children the bladder held less than the normal amount of urine—a condition attributed by Braithwaite (1950, 1951) to an achalasia of the detrusor muscle of the bladder. Of these 19 had diurnal frequency, while 6 had only precipitancy of micturition.

The parents of all the children with relative nocturnal polyuria and of a consecutive series of non-enuretic outpatients were questioned about the depth of sleep of the child. More of the enuretics than of the continent children were regarded as being deep sleepers, but 12% of the enuretics were described as light sleepers. Deep sleep, therefore, is by no means an essential accompaniment of enuresis with relative nocturnal polyuria. The connection is not so obvious as that noted by Ström-Olsen (1950) in adults.

No association was found between relative nocturnal polyuria and intelligence. Some sufferers were dull and backward, but several had won scholarships.

FAMILY HISTORY IN RELATIVE NOCTURNAL POLYURIA

Of the 69 children with relative nocturnal polyuria 47 had a family history of enuresis. In all, 67 relatives were affected, of whom 38 were near relatives (siblings or parents) and 29 were distant relatives (uncles, aunts, cousins, or grand-relatives). Of these affected persons 10 were still enuretic in adult life, and 5 were still enuretic as children. All the others had recovered, 5 after passing the age of sixteen, and the remainder at ages evenly distributed between four and sixteen years. Spontaneous recovery from wetting is therefore by no means invariable.

In addition, 12 parents of patients were found who had never been bed-wetters but had, from infancy, always risen at least once a night (in some cases two, three, or more times a night) to void urine. In 4 parents who had been bed-wetters in childhood this symptom had been superseded by the symptom of waking in the night to pass water, when the wetting spontaneously ceased. This symptom might, I suggest, be called excessive nocturnal micturition.

Inquiries about the family history of 20 consecutive continent outpatients revealed only 1 known enuretic relative, and his wetting was only occasional. 7 children with psychogenic enuresis, in whom the diurnal excretory rhythm and the ability to hold urine were both normal, had no family history of enuresis or of excessive nocturnal micturition. The frequency with which enuretic children have a family history of enuresis has been mentioned by many writers (e.g., Batty 1948). From the present series it seems that such a family history is especially characteristic of those children in whom relative nocturnal polyuria is the cause of the enuresis.

Excessive nocturnal micturition also occurs among the relatives of children with relative nocturnal polyuria. It may take the place of enuresis as a symptom if the patient is woken by a full bladder. It also represents one of the ways of spontaneous recovery from nocturnal enuresis, sleep becoming less deep as the patient grows older.

The relation of excessive nocturnal micturition to nocturnal enuresis is illustrated by a pair of female twins aged eight years. These girls were so similar in appearance that only close friends could distinguish between them. Both had relative nocturnal polyuria. One twin was a severe nocturnal enuretic, whereas the other woke three times each night to pass water and was quite dry.

SUMMARY AND CONCLUSIONS

Many children with nocturnal enuresis have an abnormal diurnal excretory rhythm, excreting during the night an unduly high proportion of their total urine. It is suggested that this condition be known as relative nocturnal polyuria. It is sometimes associated with diurnal frequency and with precipitancy of micturition. These symptoms may be due either to polyuria from excessive drinking or to a reduced functional capacity of the bladder.

Relative nocturnal polyuria is often familial, occasionally presenting itself in other members of the family as excessive nocturnal micturition. This latter condition may take the place of nocturnal enuresis, when the stimulus of a full bladder becomes sufficient to wake the patient.

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MILONTIN: A NEW DRUG IN THE TREATMENT OF PETIT MAL

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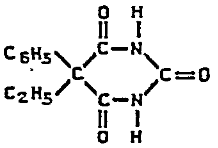
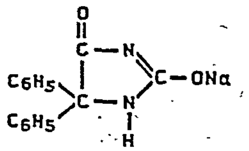
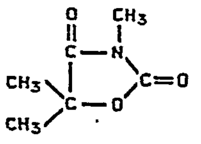
THE relation of 'Milontin' (N-methyl-a-phenyl-succinimide) to other anticonvulsants is shown below:



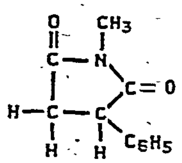
BARBITURATES (*phenobarbitone*)



HYDANTOINS (*phenytoin sodium*)



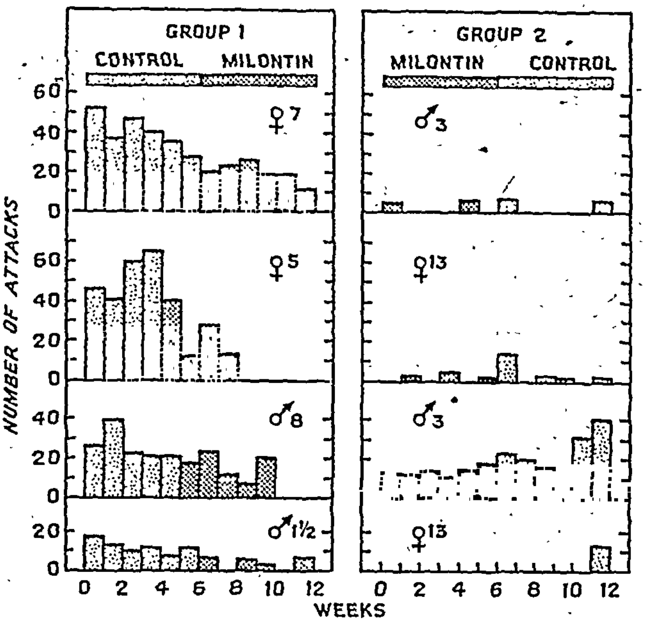
OXAZOLIDINEDIONES (*troxidone or 'Tridione'*)



SUCCINIMIDES (*'Milontin'*)

It was selected for trial in petit mal because of its ability to prevent leptazol convulsions in laboratory animals in non-depressive dosage (Miller and Long 1951). Administered by mouth to mice and dogs it proved relatively non-toxic, and biochemical, hæmatological, and urinary findings remained normal.

Of 20 unselected cases in the present study, which included 17 children, 10 were of pure petit mal (pyknoepilepsy), showing a transient lapse of consciousness, in some cases associated with bilateral rhythmical jerking



Effect of milontin, compared with control capsule, on number of petit-mal seizures.

or twitching of the eyelids but rarely of the head and arms. 5 patients exhibited the akinetic form of petit mal, which includes the salaam spasm of infants and consists of a sudden loss of postural control, with nodding of the head or a fall. This was in some instances accompanied by pykno-epilepsy. In the remaining 5 patients grand mal was combined with one or both of these types of petit mal. One adult with psychomotor and major epilepsy was included in the trial.

Abnormal electro-encephalograms were obtained in 16 patients, of whom 12 gave records pathognomonic, and 3 suggestive, of epilepsy, the classical spike-and-wave complex of petit mal occurring in 6. Since the value of electro-encephalography in diagnosis is limited, cases lacking this confirmation but fulfilling the clinical criteria defined above were not excluded from the trial.

Phenobarbitone had been given previously to 18 patients, of whom 9 also received troxidone and 4 amphetamine. Apart from 1 patient in whom a 75% reduction of attacks was effected after nine months' therapy with troxidone, these drugs had been ineffective or had produced only temporary improvement.

CONTROLLED EXPERIMENT

According to a key retained by the statistician, one of four groups of capsules (A, B, C, and D) was prescribed, of which two contained milontin and two a lactose control. In most cases after six weeks, the alternative capsule (A1, B1, C1, or D1) was substituted and given for an equal period. The parent was provided with a form on which to record the number of seizures each day, and the patient was seen at fortnightly intervals, when the urine and the blood were examined.

TABLE I—EFFECT OF MILONTIN COMPARED WITH CONTROL CAPSULE ON NUMBER OF PETIT-MAL ATTACKS

—	Control		Milontin		Change (%)	Average change (%)
	No. of attacks		No. of attacks			
	Weekly range	Weekly average	Weekly range	Weekly average		
Group 1	27–51(6) 46–64(4) 21–38(5) 7–17(6)	39 52 26 11·8	10–21(6) 12–39(4) 6–23(5) 0–6 (6)	17·0 23·0 15·0 3·8	56 56 42 68	56
Group 2	0–7 (6) 0–13(6) 5–38(6) 0–12(2)	2·17 2·83 21·5 6	0–6 (6) 0–4 (6) 9–17(6) 0 (10)	1·67 1·33 12·70 0	23 53 41 100	54

Length of course in weeks is indicated in parentheses. Patients in group 1 received control capsules first and those in group 2 milontin first.

In the patients who received milontin after a control period the average reduction in the number of petit-mal seizures was 56% (table I); in the patients in whom milontin preceded the control the average increase in the number of attacks was 54%. The efficacy of milontin in the treatment of petit mal is therefore established.

Daily records of the number of attacks were charted for all subsequent patients, and to some of them control capsules were given for the first two or three weeks to obtain for comparison the premedication frequency of attacks. In the 5 patients with both major and minor epilepsy phenobarbitone, alone or with phenytoin sodium ('Epanutin'), was also prescribed. Major attacks were not exacerbated by the introduction of milontin.

RESULTS

The results of treatment were assessed by comparing the average weekly number of seizures during the last five weeks of the milontin course with that of the control or premedication period.

Table II shows that in 5 patients (26%) of the 19 in whom the effect of milontin could be assessed, the attacks were entirely controlled for at least five weeks, the average seizure-free period for the group being nine weeks.

There was a reduction of 80% or more in the number of attacks in 7 patients (37%), and in 4 (21%) the average reduction was 42%. One patient was unaffected, and 2, after temporary improvement, were worse. The effectiveness of milontin was related neither to the type of petit mal nor to the age of the patient. In all the responsive cases the duration and severity of the attacks were much reduced, and in many cases both mental and physical activity was enhanced. These effects were most noticeable in a girl aged 11 who, while taking troxidone, had been introverted and depressed.

TABLE II—EFFECT OF MILONTIN IN 19 UNSELECTED CASES OF PETIT MAL

Petit mal	No. of cases	Average reduction (%)
Entirely controlled	5 (26%)	100
80 % or more reduction	7 (37%)	84
Partial control	4 (21%)	42
Unchanged	1 (5%)	—
Worse	2 (11%)	—

In 1 patient with psychomotor epilepsy, attacks were reduced to 16% of their former number, and their duration was curtailed.

The length of treatment in this preliminary trial ranged from six to twenty-four weeks, with an average of twelve.

TOXIC SIGNS

Of the 21 patients 13 exhibited toxic effects in the following order of frequency (the numbers of cases are indicated in parentheses): abnormal urinary findings (10); drowsiness (5); nausea (4); dream-like state (3); dizziness (2); pyrexia with macular erythematous rash (2); erythema multiforme (1); and vomiting (1).

Minor Side-effects

Nausea, vomiting, pyrexia, and rash occurred with small doses of milontin; but these effects, seen only at the start of medication, were transient and apparently due to idiosyncrasy.

In 1 patient taking milontin 0·9 g. daily erythema multiforme developed within twenty-four hours of

TABLE III—ABNORMAL URINARY CONSTITUENTS AND TOXIC DOSE COMPARED WITH MOST EFFECTIVE DOSE

Case no.	Age (yr.)	Sex	Protein-uria	Micro-scopic hæma-turia	Granu-lar casts	Toxic daily dose (g.)	Most effective daily dose (g.)
1	11	F	+	++	+	2·7	2·7
2	10	F	—	—	+	2·7	1·8
3	8	M	—	++	+	2·7	2·7
4	7	F	+	+++	+	4·8	4·8
5	5	M	—	+	—	2·7	1·5
6	5	F	—	+	—	0·9	0·9
7	4	M	—	—	+	1·8	1·2
8	4	F	—	+	—	0·9	0·9
9	3	F	—	+	—	0·9	0·9
10	2½	F	—	+	—	0·9	0·9

beginning a second course of milontin and necessitated its withdrawal.

Drowsiness, related to the size of the dose and relieved by its reduction, developed only in children. It was apparent in 2 patients, aged eight and eleven years, with a daily dose of 3·6 and 4·8 g. and in 2, aged five years, with 1·8 and 2·4 g. The addition of amphetamine in 1 case neither relieved the drowsiness nor affected the number of seizures. In another, after temporary reduction, the dose of milontin was raised at a slower rate without recurrence of the sign.

Effect on Kidneys and Urine

Evidence of glomerulo-tubular damage, discovered in 10 of 17 children treated, was transient in 7 despite continued medication. In 3 it persisted, and in 1 of these, a child aged seven years taking 4·8 g. daily, its degree necessitated the discontinuance of milontin. For five days her seizures had been completely controlled, and they did not recur when milontin was withdrawn. A week later the urine contained fewer red cells and casts, and subsequent specimens were normal.

As shown in table III, in 3 patients the toxic dose was greater than that producing the best effect, but in 7 these doses were equal. The development of this side-effect was not related to the duration of the treatment.

Increased frequency of micturition occurred in 3 patients, with enuresis in 1.

Against these unfavourable reports in children the following two case-records illustrate a relative lack of toxicity in older patients.

A boy, aged 15, while taking control lactose capsules, developed acute nephritis subsequent to streptococcal tonsillitis. In error milontin was administered during this illness with no deterioration in the urinary findings.

In an attack of automatism a man, aged 39, with psychomotor and major epilepsy, took in a single dose 20 grammes of milontin and 70 grains of phenobarbitone. He was admitted to the *Miller General Hospital*, where, after five days' coma, he recovered. His urine on the third day of coma contained protein 35 mg. per 100 ml., numerous granular casts, and a trace of milontin, but two days later, on his recovering consciousness, no abnormal constituents were found. A blood-count on the fourth day of the illness showed Hb 105%; red cells 5,000,000 per c.mm.; white cells 11,200 per c.mm. (polymorphs 86%, lymphocytes 10%, monocytes 2%, eosinophils 1%); and platelets 200,000 per c.mm. Signs apart from those common to phenobarbitone poisoning were not observed. Milontin being a succinimide derivative, it is worthy of note that sodium succinate has been proposed as an antidote in barbiturate poisoning.

Effect on Blood

Normal cell-counts were obtained in all the patients; but in 1, showing toxic effects with a daily dose of 4·8 g. of milontin, the white cells, which on five occasions had numbered about 9000 per c.mm., fell to 4000 per c.mm., of which 1500 per c.mm. were neutrophils, when hæmaturia and drowsiness were severe. This depression, though not amounting to definite leucopenia, shows the need for caution and repeated blood examinations.

DOSAGE

Milontin was supplied in capsules each containing 0·3 g. To mask the bitter taste, for small children, a suspension of the drug in mucilage was flavoured with syrup of orange.

In all the present cases the initial dosage of 0·3 g. three times a day was increased at intervals of two weeks to 0·6 g., 0·9 g., and 1·2 g. three or four times a day until the greatest effect was secured or toxicity resulted. On this routine, when the most effective dose was exceeded, in some cases the more serious side-effects developed, and it is now considered desirable, provided some improvement is evident, to limit the dose for much longer periods to that suggested in table IV, which shows the average optimum daily dosage and its relation to age.

EXCRETION OF MILONTIN

In part, at least, milontin is excreted in the urine as a glycuronide.

The urine of patients receiving milontin contained a reducing substance on which tests for sugar were negative. On adding it to a solution of benzidine in glacial acetic acid, a pale orange colour resulted which was not obtained with normal urine (Mr. H. F. Weston).

TABLE IV—MOST EFFECTIVE DAILY DOSE ACCORDING TO AGE

Age-group (yr.)	No. of patients	Range of optimal daily dose (g.)	Average optimal daily dose (g.)
1–3	5	0·9–1·2	0·9
3–6	6	0·9–1·8	1·5
6–12	6	0·9–2·7	1·8
Adults	3	1·8–2·7	2·1

Paper chromatography of the urine of 2 patients showed more glycuronide than normal, and on hydrolysis glucuronic acid was released; glucose, in small amount, was also found.

Assessed by its clinical effect in patients with numerous seizures the action of milontin begins within half an hour and lasts about four hours. A cumulative effect was not observed, and on withdrawal, in some cases, there was an exacerbation of seizures.

DISCUSSION

In the initial clinical trial (Zimmerman 1951), based on a study of 50 selected patients with petit mal, milontin equalled or surpassed troxidone in therapeutic efficacy and had the advantage of being relatively non-toxic. Renal damage was not observed, and minor toxic signs appeared in only 11 patients (22%), whose ages were not stated.

The present trial, though corroborating the effectiveness of milontin, was accompanied by a much higher rate of toxicity, and signs of glomerulo-tubular damage, hitherto unreported, were discovered in 10 patients (48%). The large doses used in this series, which consisted mainly of children, could in some cases explain this increased incidence of toxic signs, and a reduction might be effected by using the scheme of smaller dosage suggested. Though the seriousness of renal damage cannot be minimised, in most cases this was transitory, and sequelæ developed in none.

In recommending milontin for further trial the conservatism which stems from caution must be tempered by the urgent need for new and improved therapeutic agents in petit mal.

SUMMARY

The efficacy of milontin in the treatment of petit mal has been established by a controlled experiment. Complete control was obtained in 26% of patients, and attacks were reduced by 80% or more in 37% of patients.

In all the responsive cases the duration and severity of seizures were diminished.

Relief was secured in a patient with psychomotor epilepsy.

In 13 of 21 patients toxic effects were encountered, and signs of glomerulo-tubular damage occurred in 10. The most effective dosage in the present series was related to age, and the more serious toxic effects resulted when this dosage was exceeded.

Further trial is recommended; but, particularly in children, there is need for regular and frequent examination of the urine and the blood.

I am indebted to Dr. Charles F. Harris for his encouragement and permission to carry out this trial in the children's epilepsy clinic. My thanks are also due to Dr. A. White Franklin and Dr. J. Aldren Turner for allowing me to treat their cases; to Mr. M. P. Curwen for statistical advice; to my colleagues in the pathology department, the pharmacists, and lady almoner for their coöperation; to Dr. L. I. Woolf, of the Hospital for Sick Children, for chromatographic investigations; and Dr. Robert Hodgkinson, director of the department of clinical investigation, Parke, Davis & Co., London, for help in the preparation of this paper. Milontin was developed in the research laboratories of Parke, Davis & Co., from whom supplies of the drug were obtained.

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GASTROJEJUNOCOLIC FISTULA FOLLOWING GASTROJEJUNOSTOMY FOR INFANTILE PYLORIC STENOSIS

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A BOY with infantile pyloric stenosis was treated by posterior gastrojejunostomy at the age of 6 weeks. Thirty-seven years later partial gastrectomy was done for a gastrojejunocolic fistula. Examination of the resected specimen showed that the pyloric tumour had persisted.

CASE-RECORD

A married man, aged 37, was referred to me as a case of gastrojejunocolic fistula. At the age of 6 weeks he had been admitted to a hospital for sick children in Glasgow with intractable vomiting, and diagnosed as having infantile hypertrophic pyloric stenosis. After a short course of treatment he had been operated on in September, 1915, a posterior gastrojejunostomy being done under general anæsthesia. He had had a stormy convalescence and been discharged from hospital about two months after the operation. Since childhood he had always complained of digestive troubles, and he could not ingest large meals, whatever their content. From January, 1936, to November, 1951, he had been treated on many occasions for chronic duodenal ulcer. An analysis of his symptoms during this period, however, would have supported a diagnosis of gastrojejunal ulceration, because in addition to recurrent attacks of acute indigestion, to hunger pains relieved by food, alkaline powders, and vomiting, and to bouts of melæna, there were times when he experienced severe pain localised to the left of the umbilicus and backache situated "to the left of the middle of the spine." Barium-meal radiography from time to time in different clinics confirmed the diagnosis of chronic duodenal ulcer, there being a persistent deformity of the cap. The stoma appeared adequate and to be working in a satisfactory manner. In November, 1951, he had a recurrence of tarry stools, with attacks of vomiting and diarrhœa. The vomitus was "like porridge and evil-smelling, and belching of malodorous gases was uncontrollable." He lost weight rapidly owing to nausea, anorexia, and frequent attacks of vomiting and diarrhœa. Barium-meal radiography established the presence of a gastrojejunocolic fistula. He was admitted to a London hospital on Feb. 15, 1952, for further investigation and preoperative treatment.

On examination the patient was thin, emaciated, and anæmic. His blood-pressure was within normal limits, and there was severe secondary anæmia of the hypochromic microcytic type. His abdomen was scaphoid, with an area of rigidity and tenderness localised to the left of the umbilicus.

Preoperative preparation included a light non-residue diet rich in protein; colonic and gastric lavage with physiological saline solution, blood-transfusions, intramuscular injections of vitamins B and C, adequate dosage of penicillin and streptomycin, phenobarbitone gr. $^1/_2$ thrice daily, 'Soneryl' gr. 3 at night, and 'Sulphathalidine' 2 g. eight-hourly for five days.

Operation.—On Feb. 23, under general anæsthesia, the epigastric scar was excised and the abdomen was explored through a lengthy left paramedian incision. After adhesions had been freed and the diagnosis of gastrojejunocolic fistula had been confirmed, the abdominal viscera were explored. The pylorus was found to be enlarged, bulbous, and firm, with the antral mucosa thrown into long folds. The gall-bladder, liver, pancreas, spleen, and small intestine were normal. A portion of the transverse colon was drawn into, and welded in, a mass of scar tissue to the gastro-enteric stoma. A posterior gastrojejunostomy had been done with a short afferent limb; the stoma was contracted and felt like a small fibrotic ring; an extensive gastrojejunal ulcer, adherent to the pancreas, involved a portion of the stoma and the adjacent part of the efferent jejunal limb; the fistulous tract into the colon readily admitted the index finger; and the stomach wall was hypertrophied, dilated, and œdematous. The colon was separated from its broad fistulous attachment to the water-logged efferent limb of jejunum; and after the sclerotic margins of the opening in the large bowel had been trimmed away, the circular defect in the antimesenteric border of the gut was closed transversely with a Connell loop-on-the-mucosa suture of no. 0 medium chromic catgut and reinforced with a series of closely applied interrupted sutures of fine black silk. Through the gaping hole in the jejunum the base or crater of the gastrojejunal ulcer, which was deeply excavating the pancreas, could be seen. The jejunum was cut free from its line of union with the stomach, and the resulting opening in the small gut was closed after the Finney method of gastro-duodenostomy for duodenal ulcer. The stomach was next mobilised and, after the right gastro-epiploic artery had been isolated, ligated, and divided, and the middle colic blood-vessels had been identified and protected, the stomach was cut adrift from its anchorage to the pancreas. At this stage the liberated first part of the duodenum was transected between clamps, and the distal end was securely invaginated. The base and edges of the gastrojejunal ulcer, which formed a large crater in the pancreas, were destroyed with a diathermy button, after which the left gastric artery was secured and two vasa brevia were underrun with strong silk sutures mounted on aneurysm needles, tied off in continuity, and divided close to the greater curvature.

The stomach was now ready for resection and anastomosis. About three-quarters of the stomach was resected, and the operation was completed by the antecolic Polya-Hofmeister technique. The afferent limb of the jejunum was brought over the transverse colon from right to left, buttressed to the "new" lesser curve, and anastomosed to the small gastric pouch. The afferent limb of the jejunum lying superior to the colon was anchored to the capsule of the pancreas with two sutures of fine silk to prevent rotation, kinking, or volvulus. A drainage tube was passed down to the burnt area of the ulcer crater; the wound was closed with interrupted floss-silk sutures, and the skin margins were approximated with 'Mersilk.'

Immediate postoperative treatment followed conventional lines: *intermittent gastric suction* through a Ryle tube, 2 oz. of water by mouth hourly, blood-transfusion, morphine for pain, intramuscular injections of sodium phenobarbitone for restlessness, the *administration* of vitamins B and C, intramuscular injections of large doses of penicillin, and deep-breathing exercises. The patient made a good recovery and was ordered a generous *non-residue* diet on the seventh day after operation. The drainage tube was removed on the third day, and stitches on the sixth; and the patient was discharged from hospital on the twentieth day after operation.

Pathology.—Examination of the resected specimen showed no evidence of duodenal ulcer; *the* pyloric tumour had persisted; the pylorus was enlarged, barrel-shaped, and fibrotic; and the antral mucosa was thickened and thrown into prominent longitudinal folds. Sections of the margins of the gastrojejunal ulcer showed no signs of malignancy.

Follow-up.—After a short holiday in Scotland the patient returned to Trinidad, and on May 20 I received a letter from him in which he stated: "You will be glad to hear that I am back at work as an engineer in an oilfield and that I am quite well. I have gained 15 lb. in weight, and my appetite is good. I have enjoyed all my meals and am ready for more, and I have never felt so fit, eager for work, or so pleased with life as I am at the present time."

DISCUSSION

Gastrojejunal ulceration is a dangerous and common sequel to gastrojejunostomy, and the number of cases in which this complication occurs multiplies steadily as such patients are observed over increasing periods after the operation. The commonest cause of gastrojejunal ulcer is gastrojejunostomy for duodenal ulcer, the incidence being about 20–30%. The majority of marginal ulcers declare themselves within two years of operation. The occurrence-rate of anastomotic ulcer following operations for duodenal ulcer depends on the type of operation. Thus it is common after anterior or posterior gastrojejunostomy, partial gastrectomy after the Roux-Y procedure, antrectomy, Devine's gastric exclusion, gastrectomy combined with entero-anastomosis, and Finsterer's method of antral exclusion combined with gastric resection. It is becoming apparent that the Billroth-I operation for chronic duodenal ulcer is more productive of stomal ulceration than is a well-conducted Polya type of repair, and that vagotomy combined with a short-circuit operation will be followed in at least 5% of cases by marginal ulcers within three years. Gastrojejunal ulceration is rare (about 1 case in 400) after the Billroth-I types of repair and after the Polya operations for *gastric* ulcer. The operation of choice for chronic duodenal ulcer is gastroduodenal resection in which at least 70–80% of the stomach is resected and the operation is completed by the antecolic Polya-Hofmeister technique. If this extensive resection is impracticable, vagotomy combined with gastrojejunostomy should be done. The patient had a gastrojejunostomy done for infantile pyloric stenosis some three years after the publication of Ramstedt's articles in 1912. Before the advent of Ramstedt's operation of pyloromyotomy, numerous procedures were advocated for the cure of this anomaly, including pyloroplasty by the Heinke-Mickulicz method, Fredet's operation, duodenopylorectomy, Loreta's operation, and gastrojejunostomy. Loreta's operation of divulsion of the constricting pyloric tumour was a failure except in the expert hands of Burghard, and the other operations mentioned had a damning mortality of 50–80%.

When was Ramstedt's operation generally accepted as the procedure of choice for infantile pyloric stenosis? This question can only be answered accurately by studying the operation notes of such cases in various hospitals for infants and by recording the surgical methods selected for the cure of this disease during the anxious years of the 1914–18 war. Few patients with infantile pyloric stenosis were subjected to gastrojejunostomy after September, 1915, and the number who survived this operation were even fewer. Armitage and Rhind (1951) reported a case of gastrojejunal ulcer following gastrojejunostomy for infantile pyloric stenosis for which partial gastrectomy was done. Examination of the excised specimen, as in the present case, showed that the pyloric tumour had persisted into adult life.

Some 10–15% of patients with gastrojejunal ulcer develop gastrojejunocolic fistula; but this sinister complication following, as in the present case, an operation for infantile pyloric stenosis which has been obsolete for over thirty years must be extremely rare.

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COMPLEMENTARY ACTIVITY OF THE BLOOD IN ACUTE NEPHRITIS*

WITH SPECIAL REFERENCE TO PROGNOSIS

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SIXTEEN years ago, in a paper published in this journal, attention was called to the fall that takes place in the complementary activity of the blood in acute glomerulonephritis (Kellett 1936a). Such a fall suggested that an antibody-antigen reaction had taken place, and its extent was such that it seemed improbable that such a reaction should have been localised to the kidneys. That same year evidence was published (Kellett 1936b) which suggested that serum disease in man was a manifestation of reversed active anaphylaxis, and it seemed that acute nephritis might prove to be a particular example of this process. This hypothesis was in accord with Masugi's (1934) experimental work in which he produced acute glomerulonephritis in rabbits by injecting specific anti-organ sera, and with the analogy drawn many years before by von Pirquet and Schick (1905) between the specific complications which may follow scarlet fever and those which may follow the administration of serum.

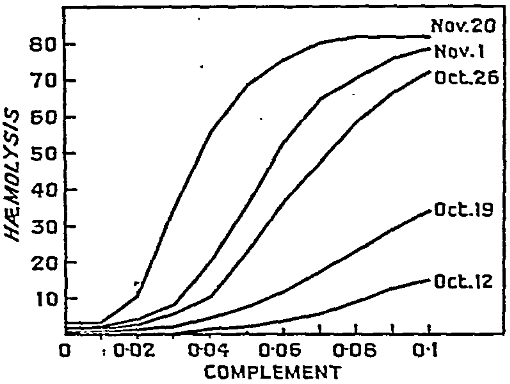

Fig. 1 (case 1)—Rise in complementary activity of blood in six weeks following admission. Activity is measured as the percentage hæmolysis produced by increasing amounts (expressed in ml.) of the patient's serum.

This fall in complementary activity had previously been noted by Gunn (1914–15) and by Weil and Bucholz (1932) and is mentioned in passing by Browning (1912–13). According to Masugi (1939) it was confirmed in Japan by

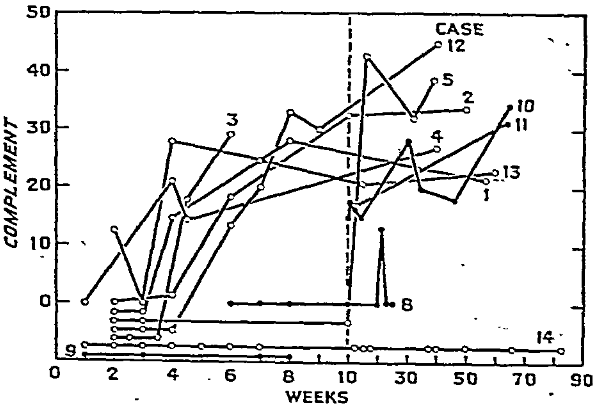

Fig. 2—Changes in complementary activity (expressed in units per ml.), in 12 cases of acute nephritis, from the outset of illness.

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* Based on a communication to the Society of Pathology and Bacteriology, June, 1951.

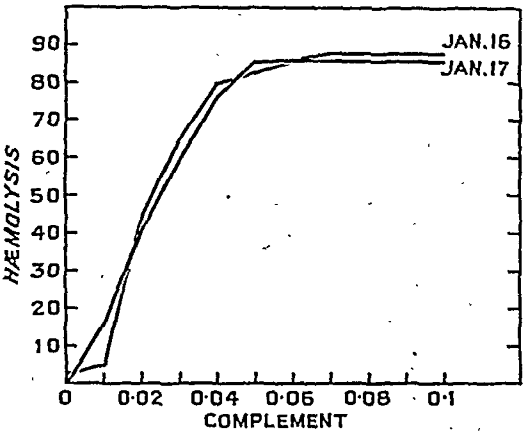

Fig. 3 (case 6)—Eclampsia. Complementary activity unaffected by convulsions. Activity expressed as in fig. 1.

Ogawa and Sato and by Hayashi. In this country it was confirmed by Thomson et al. (1939), who observed that a similar fall did not occur in acute eclampsia. Thomson and I published pathological evidence supporting the belief that this fall takes place in acute glomerulonephritis and not in any other form of Bright's disease (Kellett and Thomson 1939). Recently Reader (1948) has again investigated and reviewed these changes, which have been the subject of a further paper (Lange et al. 1951), published since much of my present article was written.

This paper is concerned not so much with the diagnostic as with the prognostic significance of this change and of the rate of return to normal, and advantage has been taken of the work summarised by Heidelberger and Mayer (1948), the method of estimation adopted being based upon their recommendations. In each estimation use is made of differing dilutions of the serum to be tested, so that the result is expressed as a curve from which one can deduce the least amount of serum—here called a unit—required to bring about 50% hæmolysis in the system.

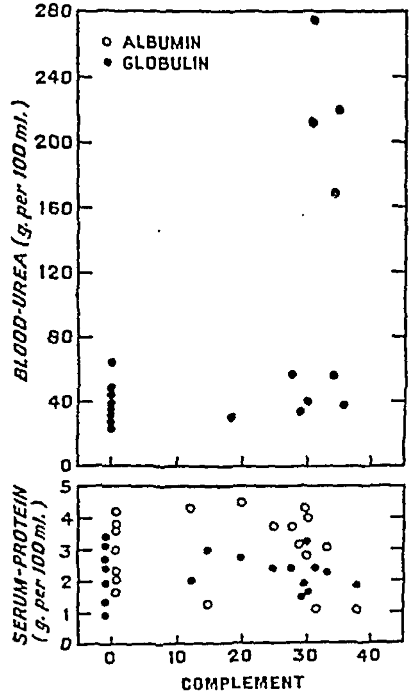

Fig. 4—Readings in cases of acute nephritis showing lack of relation between complementary activity, on the one hand and serum-proteins or blood-urea on the other.

CASES AND COMMENTS

In the following case the findings were not unlike those reported by me previously (Kellett 1936a).

Case 1.—A man, aged 29, was admitted on Oct. 10, 1950, with frontal headache, and swelling of the feet and face for a week. On the day before admission he had vomited three times and on day of admission he had four fits. Blood-pressure (B.P.) 165/100 mm. Hg. The urine contained a large amount of albumin, together with numerous hyaline and granular casts, and the blood-urea was 58 mg. per 100 ml. He was discharged on Oct. 31, and has since remained perfectly fit. When he was last seen a year later his B.P. and urine were normal. The rise in the complementary activity of his blood in the six weeks following admission is shown in fig. 1.

This type of response, in which there is a fairly rapid return of the complementary activity to normal, is that usually encountered in cases of acute nephritis in which apparent recovery takes place. Fig. 2 includes readings recorded in this and four other typical cases of acute nephritis in a boy of 5 (case 2), a man of 43 (case 3), a boy of 8 (case 4), and a boy of $4^{1}/_{2}$ (case 5). In cases 2–5 the onset was less dramatic than in case 1; but in our experience the apparent severity of the onset bears no relation to the degree of the fall in complementary activity or to the ultimate prognosis. The complementary activity remains remarkably unaffected even by repeated convulsions, such as are met with in acute eclampsia:

Case 6.—A woman, aged 24, nearly at term, was admitted on Jan. 15, 1952, to the Richard Murray Hospital under the care of Mr. W. Hunter, suffering from acute eclampsia. She had had five fits before admission and shortly afterwards she had a further two. When seen she was cyanosed, her features were thickened and in many ways suggestive of pituitary upset, and she was drowsy and roused with difficulty. Her urine contained large quantities of albumin. Her B.P. was 180/120. She was sedated with morphine, chloral, and bromide. She had a further six major fits during the night, but was then delivered of a normal healthy child, and made an uninterrupted recovery. A week after admission her B.P. was 135/90. Fig. 3 shows the complementary activity of two samples of blood, the first taken after the first seven eclamptic fits and the second after she had had a further six fits and been delivered of her child.

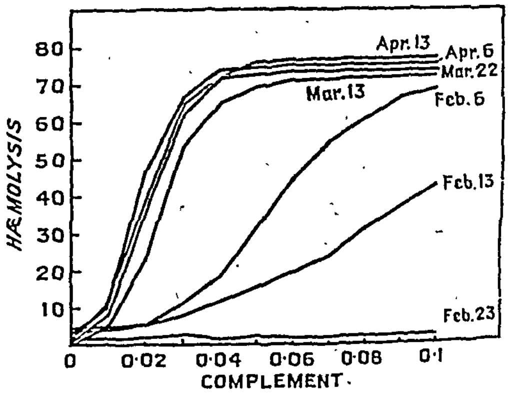

Fig. 5 (case 7)—Complementary activity returns to normal with improvement in renal condition, despite congestive heart-failure which proved fatal. Activity expressed as in fig. 1.

The mode of onset seems to depend on the particular tissues affected and on the temperament of the patient rather than on the degree of renal damage sustained. This is also true of the initial fall in complementary activity, which is not related directly to renal damage. In the terminal stage of nephritis and pyelonephritis, when the renal damage may be extreme, the complement remains at normal level.

This lack of any clear-cut relation between the level of the complementary activity of the blood-serum on the one hand, and the serum-proteins or blood-urea on the other, is clearly shown in fig. 4, which summarises my experience in different cases.

On the other hand, the rate of return of the complementary activity of the blood has often seemed to be closely related to the ultimate prognosis of the renal condition—though not necessarily to the disease process as a whole.

Case 7.—A man, aged 21, was already very ill when he came into hospital on Feb. 1, 1951, and recovery seemed unlikely. He had had rheumatic fever at the age of 6 and since then had had frequent colds and sore throats, but had remained fairly fit until an attack of influenza two days before Christmas. He then became pale and breathless, with swelling of feet and ankles. On admission his temperature was about 101°F, his pulse-rate 112, and his B.P. 140/70. There was loud apical systolic murmur and *Streptococcus viridans* was isolated from his blood. His urine contained a considerable amount of albumin and his blood-urea was 84 mg. per 100 ml. He was given a long course of penicillin, having in all nearly 160,000,000 units, and at first his general condition improved and he became afebrile. His blood-urea dropped to 30 mg., but his pulse-rate became more rapid and he began to fibrillate and developed signs of congestive failure. These were brought temporarily under control with digitalis, mercurial diuretics, and a low-salt diet; but he gradually ceased to respond to treatment and he died of congestive heart-failure three months after his admission, a final blood-urea having risen to 100 mg. Despite this his complementary activity, after an initial depression, had steadily returned to normal (fig. 5).

In this case the complement returned to normal as the nephritis subsided, despite the ultimate death of the patient from cardiac failure, whereas in case 8, in which the nephritis caused death several months after its onset, the complementary activity of the blood remained impaired.

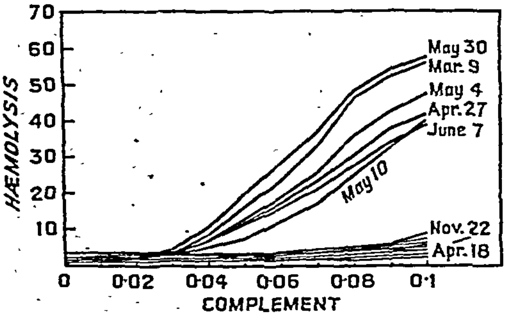

Fig. 6 (case 8)—Complementary activity during seven months of glomerulonephritis ending in death on June 8. Activity expressed as in fig. 1.

Case 8.—A man, aged 39, was admitted on Nov. 21, 1950. He had had a cold three weeks previously. Two weeks later his ankles had become swollen and his face puffy and he was becoming short of breath and had severe headaches. His B.P. was 130/75, and his urine contained much albumin and a few red cells and white cells. He steadily went downhill, being readmitted on Jan. 17, 1951, and remaining in the ward until his death on June 8.

In this case death seemed to have been caused by the progressive impairment of renal function, and the complementary activity of the blood was reduced throughout the illness, though at times it showed a slight improvement (fig. 6). This was in striking contrast with the findings reported in my first paper (Kellett 1936a) (which dealt, however, with only 3 patients with acute nephritis, all of whom recovered) and with the majority of our results during the past few months. Moreover, the following case suggests that these continued low readings were the expression, not so much of the persistence of the initial infection, but of the persistence of certain reactions of the body following infection.

Case 12.—A man, aged 40, was admitted on Feb. 5, 1951, as a case of acute nephritis. He had been quite well until ten days previously, when he developed influenza and a sore throat. Five days later his face had become puffy, also his hands and feet, and this was followed by headaches and vomiting four or five times a day. His urine had become dark and he was passing very little. His B.P. on admission was 155/95. His urine contained large amounts of albumin, and red and white cells, and his blood-urea was 156 mg. per 100 ml.

He seemed to have a classical acute nephritis, but in addition he gave a history of about 20 shivering attacks, lasting a few minutes each, six days before admission. He had cellulitis of the right side of the face together with redness and tenderness behind the left ear, with some local pitting œdema. Accordingly he was given aureomycin and penicillin, having in all 30 g. of aureomycin and approximately 20,000,000 units of penicillin. His temperature dropped at once, and his face returned to normal within a week. But a week after the penicillin was discontinued, his face became swollen again, the temperature rose, and he had repeated shivering attacks. Penicillin was administered over the next seventeen days, once more in large quantities, and he was kept under observation for a further two months. When seen in October, 1951, he seemed perfectly fit and his urine was normal.

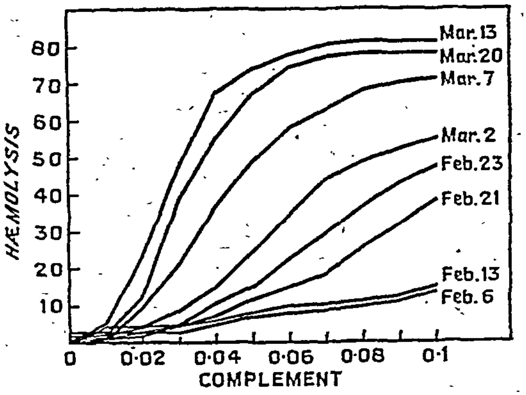

Fig. 7 (case 12)—Complementary activity unaffected by recurrence of cellulitis of face between Feb. 26 and March 2. Activity expressed as in fig. 1.

In this case of acute nephritis a recurrence of the severe and striking initial infection produced neither an exacerbation of the nephritis, nor a change in the rate of return of the complement (fig. 7).

A persistently low level of complementary activity does not, however, invariably imply progressive renal damage.

Case 14.—A woman of 20 was admitted on June 23, 1950. Eight weeks previously she had been delivered of a healthy child and five weeks after this she developed a sore throat. Ten days later her legs, hands, and face had become œdematous. On admission her B.P. was 150/100, and there was pitting œdema of the legs up to the thighs. The urine contained albumin +++ and an excess of leucocytes, red cells, and hyaline and granular casts. The serum-proteins were 3 g. per 100 ml. and the blood-urea was 64 mg. per 100 ml. Her

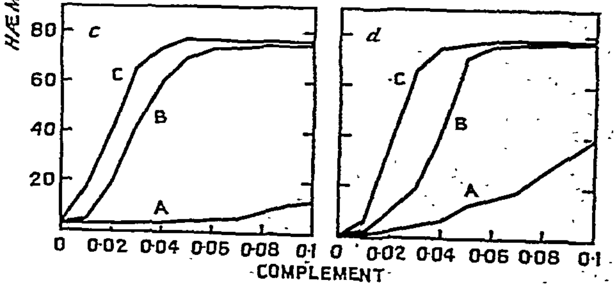

Fig. 8—Failure of serum fractions from nephritis patients to neutralise complementary activity of normal serum. Activity expressed as in fig. 1.

(*a*) A = Serum from case 14
B = Complement from normal person
C = A + B

(*b*) A = Serum from case 12
B = Serum from case of hypochromic anæmia in which complement is low.
C = A + B

(*c*) A = Serum from case 8
B = Complement from normal person
C = A + B

(*d*) A = Serum from case 12
B = Serum from normal person
C = A + B

condition slowly improved until her discharge on Aug. 22: the serum-proteins were 7 g. per 100 ml. and the urine contained albumin +, a few red and white cells and no casts. Since then she has appeared to enjoy excellent health. In January, 1951, the total proteins were 6 g. per 100 ml. and the urine contained albumin and a few white cells. In October, 1951, though she felt well, there was still a trace of albumin in her urine and her B.P. at 142/95 was still a little raised, while the blood complement remained low (fig. 3).

Though in this case recovery has not yet taken place, the renal changes have seemed *relatively slight.*

We seem, nevertheless, to be dealing with a real impairment in the complementary activity of the blood rather than with an active neutralisation by some substance of an anticomplementary nature; for, as is shown in fig. 8, the addition of similar fractions of serum from these cases to those of other cases in which the complementary activity was almost normal or normal, does not bring about any obvious inhibition, the final curve being in each case higher.

In 3 other patients (cases 9, 10, and 11) a delay in the return of the complementary activity to normal did seem to be associated with delay in their recovery though in one (case 10), a child aged 14 who died of subacute nephritis, this had been reached at the time of her death. Again, in case 13, the fall noted in the second estimation and shown in fig. 2 did coincide with the reappearance of red blood-cells in the urine and a rise in blood-pressure lasting two or three days.

Despite the difficulties inherent in case 10, and in the fact that similar falls in the level of complementary activity have been seen in certain other conditions, some of which do not appear to be directly related to nephritis, it is possible that this delay in returning to normal is in some way linked with the persistence of the underlying disease process. If that is so, it would seem as though, in type-II nephritis, in which the complement is normal, this particular process has finished some time before the terminal changes have begun in the kidneys and thus called attention to the condition. This also applies to many cases of type-I nephritis in the terminal stages, which again would appear to have been brought about as a result of the damage sustained by the kidneys, rather than as a result of the persistence of the original disease process. Apparently the initial damage to the kidneys may be so severe, or spread over so long a time, that it causes irreversible changes; and if, as I think probable, these changes are associated with a low complementary activity, this test will be most likely to aid prognosis during the first three months or so after the onset of the condition.

SUMMARY

The fall in the complementary activity of the blood which has been described in acute nephritis has been confirmed. However, a similar fall can occur in certain diseases not directly related to acute nephritis. While a delay in the return of the complementary activity to normal is usually associated with progressive renal deterioration, in one case at least the complement remained low for over a year without any obvious deterioration. It seems probable that reduced complementary activity in the early stages of a nephritis indicates acute glomerulonephritis, and that a considerable delay in the return to normal implies a relatively poor prognosis.

It is a pleasure to have this opportunity of thanking Miss G. Partington, B.SC., my technical assistant, who carried out the complementary estimations; my colleagues, for their ready coöperation; and the Newcastle upon Tyne Regional Hospital Board for the research grant which made this work possible.

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Preliminary Communications

EXPERIMENTAL COOLING OF THE BLOOD-STREAM

IN a number of centres research into the physiological effects of cold has been receiving increased attention. This preliminary communication deals with the results obtained during the past two years by a method which I have developed in the Wilkie Surgical Research Laboratory. By this method the animal is cooled by circulating its blood through a refrigerating system outside the body. The physiological response differs fundamentally from that with previous methods, by which cold is applied to the surface of the body.

The apparatus that has proved most suitable is a double-coil glass condenser of 850 sq. cm. cooling-surface, through which arterial blood is diverted to lower its temperature by 10°–20°C before it is returned to the body through a peripheral vein. All surfaces in contact with blood are coated with a baked silicone film. The coolant is ice-water recirculated by a small pump through the double coils of the condenser. In addition a weak heparin-procaine solution in isotonic glucose is given slowly into the arterial cannula during the time that the blood is circulating through the apparatus. When intrathoracic procedures are planned, quinidine sulphate (50 mg. per kg. body-weight, intramuscularly) is given. Artificial respiration is always necessary early in the cooling process.

TABLE I—ANALYSIS OF DEATHS

No. of animals	Cause of death
1	Delayed infarction of bowel due to accidental rise of body-temperature from 25° to 30°C during occlusion of visceral arteries.
1	Acute cardiac dilatation and failure due to too rapid intra-arterial replacement of blood following prolonged exsanguination.
1	Hæmothorax 20 hours postoperatively due to over-heparinisation and extensive dissection of mediastinum.
1	Ventricular fibrillation following extreme cooling (22°C) in absence of procaine and quinidine.

TABLE II—EXPERIMENTS INVOLVING LOCAL ISCHÆMIA, WITH SURVIVAL

Procedure	Duration of test	Effect at normal body-temperature	No. of experiments
Bilateral renal ischæmia	4 hr.	Lethal after 4 hr.	1
Visceral ischæmia (ligation of cœliac, superior and inferior mesenteric arteries, and hepatic artery)	3 hr.	Lethal after 3 hr.	1
Partial cerebral ischæmia (tourniquet)	10 min.	?	1
Complete cerebral ischæmia (ligation of both brachiocephalic arteries)	20 min.	?	2
Myocardial ischæmia (ligation of main descending branch of left coronary artery)	5 min.	Lethal after 2½–5 min.	2

RESULTS

At first some difficulties were encountered in establishing the rate and degree of cooling of the blood which would result in uniform reduction of tissue temperature without undesirable side-effects, but the intense reac-

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tionary responses associated with surface cooling (neuromuscular, vascular, and humoral) were not seen; thus the difficulties and dangers of cooling were reduced. The thermal gradients within the body which result from surface cooling have been shown to initiate dangerous cardiac irregularities.[1] Hypothalamic heat-regulating responses including shivering, as well as thyroid and adrenal calorigenic effects, are restricted by the rapidity of the deep cooling when the blood-stream is directly cooled.

In 33 consecutive experiments, unselected mongrel dogs under pentobarbitone anæsthesia, were cooled rapidly (0·5°C per minute) to body-temperatures between 22° and 26°C, and then subjected to various procedures that would have brought about the death of a normal animal. 4 deaths followed, all at least partly attributable to technical faults (table I).

In the remaining 29 animals, 35 separate procedures were carried out at body-temperatures of 24°–26°C. After body-temperature was restored to normal, uncomplicated recovery ensued in all animals without any sign of neurological or other defect (tables II–IV). In one experiment in which cardiac arrest occurred when the body-temperature reached 22°C, regular and effective heart action was maintained by a bipolar electrode passed down the jugular vein into the right auricle. Spontaneous cardiac activity returned with a rise in body-temperature. This suggests a means of producing temporary quiescence of the heart, which is very desirable in certain forms of cardiac surgery.[2]

TABLE III—EXPERIMENTS INVOLVING GENERAL ISCHÆMIA, WITH SURVIVAL

Procedure	Duration of test	Effect at normal body-temperature	No. of experiments
"Lethal" hæmorrhagic shock (B.P. 40 mm. Hg or less)	4–5 hr.	Average survival-time 4 hr.	3
Occlusion of venous return to heart	20 min.	Survival-time $4^1/_2$–18 min.	4
Occlusion of venous return to heart plus occlusion of ascending aorta	Venous 10 min., arterial 5 min.	?	1
Arterial exsanguination	1–$2^1/_2$ hr.	Survival-time 3–4 min.	12
Exsanguination and occlusion of venous return, followed by cardiotomy with exposure of interior of right ventricle and exploration of pulmonary artery	1 hr. (ventricle open for 20 min.)	Immediate death	2

These results do not indicate the maximal resistance of cooled animals to each procedure. The various tests were designed to exceed the degree of injury known or estimated to be lethal to animals at normal body-temperature. It would appear that at this level of cooling functional rather than pathological changes take place, and that under certain forms of stress these changes may be of advantage to the organism. No histological damage has been found in any tissue following cooling and the functional changes are completely reversible.

Bigelow et al.[3] showed that when dogs are subjected to surface cooling an oxygen debt does not develop; during this period oxygen supply is therefore at least adequate to meet oxygen requirements. From my experiments it would appear that not only is this true but that also during cooling reduction in oxygen demand is much greater than reduction in oxygen availability, and a relative oxygen surplus exists at the capillary level. Thus tissues partly or entirely deprived of their blood-supply for periods considerably exceeding the lethal period at normal temperatures can, at these lower temperatures, survive without evidence of transient or permanent injury.

TABLE IV—MISCELLANEOUS EXPERIMENTS, WITH SURVIVAL

Procedure	Duration of test	Effect at normal body-temperature	No. of experiments
Asphyxia (clamping intratracheal catheter)	10 min.	Survival-time 4–6 min.	2
Prolonged cooling at 25°C for 24 hr. using electrophrenic respiration	24 hr.	?	1
Cooling without rewarming	Return of voluntary respiration and normal body-temperature after 24 hr.	—	1
"Lethal" tourniquet shock (bilateral tourniquets on hind-limbs)	5 hr.	Lethal after 5 hr.	1
Artificial control of action of cooled heart by intracardiac stimulation	50 min.	?	1

The effect of cooling in preventing the usual sequence of late events in oligæmic shock (capillary paralysis with increasing vascular capacity) may be due not only to the reduced oxygen demand of the tissue-cells but also to depression of harmful enzyme activity which occurs when the cell is injured by anoxia; for example, it is significant that the limbs did not swell after five hours of tourniquet-ischæmia.

These findings raise the hope that controlled hypotension in surgery may be employed more safely and more intensively in conjunction with cooling of the blood-stream. "Cold" surgery may extend the dry field enjoyed by the orthopædic surgeon to the brain, the heart, and the abdominal viscera, and even in the surgery of the extremities may eliminate the danger of ischæmic damage. There may be special indications for "cold" surgery in operations for congenital heart defects and when surgical emergencies arise in the presence of acute fevers.

SUMMARY

Cooling of the blood-stream appears to be a practicable method for lowering the respiratory activity of the cell without depressing the function of essential tissues below a level compatible with life. At 25°C body-temperature dogs can survive drastic and prolonged reductions in blood volume as well as suspension of blood-flow, both locally and systemically. Cooling brings about what might be termed temporary degradation of the more delicate higher organism to the level of the more resistant lower organism, and in so doing enables it to withstand otherwise lethal ischæmia.

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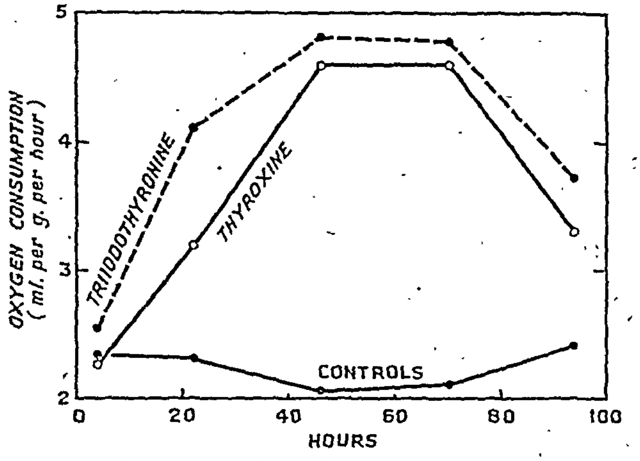
EFFECT OF 3:5:3′-L-TRIIODOTHYRONINE AND CERTAIN ANTI-THYROXINE SUBSTANCES ON THE OXYGEN CONSUMPTION OF MICE

IN view of recent work on the isolation, preparation, and properties of 3:5:3′-L-triiodothyronine (Gross and Pitt-Rivers 1952a and b, Roche et al. 1952), we considered the effect of this substance upon the oxygen consumption of mice to be of interest. Of six groups of 8 mice, two were treated with sodium L-thyroxine (1 mg. per kg. body-weight) by subcutaneous injection, two with an approximately equimolar dose of triiodothyronine (0·84 mg. per kg.), and two were injected with 0·1% W/V Na_2CO_3 to serve as controls. The oxygen consumption of each group was measured by the method of Maclagan and Sheahan (1950). The results are shown in the accompanying figure. It will be observed that triiodothyronine pro-



Effect of triiodothyronine and thyroxine on oxygen consumption of mice.

duced a somewhat greater increase of oxygen consumption than thyroxine. The latent period was about the same as that of thyroxine, whilst the duration of the effect was similar. Statistical analysis showed that the difference between the two groups was highly significant at four and twenty-two hours ($P<0·01$). This general trend obviously continues, although there is more overlap between individual readings at the later times.

Further experiments were performed to determine whether the antithyroxine drug, *n*-butyl 3 : 5-diiodo-4-hydroxybenzoate (B.D.H.B.) (Sheahan, Wilkinson, and Maclagan 1951), and the analogous *n*-butyl 3-iodo-4-hydroxybenzoate (B.I.H.B.), were capable of inhibiting the triiodothyronine. Some typical results appear in the table.

Contrary to expectation, in acute experiments, B.D.H.B. produced a slight but significant *increase* in oxygen consumption, and in chronic experiments both B.D.H.B. and B.I.H.B. produced a similar increase. In the latter experiments this increase was all the more striking because of the considerable depression of metabolism produced by both substances when given alone. These results with triiodothyronine are, of course, entirely different from the marked *decrease* produced by B.D.H.B. in the metabolism of mice treated with thyroxine, which has previously been reported (Sheahan et al. 1951, Maclagan, Wilkinson, and Sprott 1952).

THE EFFECT OF B.D.H.B. AND B.I.H.B. ON THE RESPONSE OF GROUPS OF 16 MICE TO 3:5:3′-L-TRIIODOTHYRONINE

Compound	Mode of administration	Mean oxygen consumption as percentage of controls ±SE	Significance (Student's t test)
Triiodothyronine	0·84 mg./kg. subcutaneously	192 ±5·5	P <0·01
Triiodothyronine + B.D.H.B.	0·84 mg./kg. subcutaneously + 2×200 mg./kg. subcutaneously	224 ±3·3	
Triiodothyronine	0·25 mg./kg. subcutaneously	165 ±2·3	Not significant
Triiodothyronine + B.I.H.B.	0·25 mg./kg. subcutaneously + 2×200 mg./kg. subcutaneously	170 ±4·2	
Triiodothyronine	0·5 µg./g. dry diet for 2 days 0·1 µg./g. dry diet for 6 days	135 ±4·2	P <0·001
Triiodothyronine + B.D.H.B.	As above 0·3% of dry diet	154 ±2·2	
B.D.H.B.	0·3% of dry diet	78 ±3·1	
Triiodothyronine	0·5 µg./g. dry diet for 2 days 0·1 µg./g. dry diet for 6 days	135 ±4·2	P <0·01
Triiodothyronine + B.I.H.B.	As above 0·3% of dry diet	153 ±2·8	
B.I.H.B.	0·3% of dry diet	68 ±2·3	

This result appears to be of interest in relation to the nature of the normal thyroid hormone, at least in the mouse. Since B.D.H.B. and B.I.H.B. profoundly depress the metabolism of normal animals in spite of their inability to antagonise triiodothyronine, the main circulating thyroid secretion seems more likely to be thyroxine than triiodothyronine. Our findings are nevertheless consistent with the suggestion (Gross and Pitt-Rivers 1952b), that thyroxine may require conversion to triiodothyronine in the tissues before becoming physiologically active. In this event these inhibitory compounds might owe their activity to interference with this preliminary deiodination, the inhibitor exercising some form of competition with thyroxine in the enzyme systems concerned. The synergistic effect of the "inhibitor" with triiodothyronine could be explained on a similar basis, if it is assumed that the normal mode of destruction of triiodothyronine involves dehalogenation, which is again restrained by the B.D.H.B.

Our views on the mode of action of anti-thyroxine compounds (Sheahan et al. 1951) require some extension in the light of these experiments. While these substances certainly antagonise the metabolic effects of thyroxine, if the view advanced above is correct this antagonism might be of a somewhat less specific nature than was previously envisaged, the inhibitor merely exercising a restraint on certain deiodinating processes. Experiments designed to test this hypothesis are being carried out.

EXPERIMENTAL

3-Iodo-4-hydroxybenzoic Acid. *p*-Hydroxybenzoic acid (13·8 g.) was iodinated with iodine (25·4 g.) in ammonia solution (100 ml., s.g. 0·88) by the method of Datta and Prosad (1917). When iodination was complete the mixture was adjusted to pH 4 to precipitate a small amount (1·2 g.) of the diiodo acid. After filtration, the filtrate was acidified to pH 2, when the required acid (20·2 g., 77%) separated. After recrystallisation from water it had m.p. 176–178°. Brenans and Prost (1923) report m.p. 173° (mol. wt. by titration: 270. Calc. for $C_7H_5O_3I$: 264).

The *n*-butyl ester was prepared by refluxing a mixture of the acid (5·28 g.), *n*-butanol (50 ml.), benzene (50 ml.), and sulphuric acid (1 g.) for five hours, during which time the water produced in the reaction was removed by means of a McIntyre still-head. The acid was neutralised and the organic solvents removed by steam distillation. On cooling, the required *n-butyl 3-iodo-4-hydroxybenzoate* solidified (5·37 g., 84%). After recrystallisation from 95% methanol it formed colourless needles, m.p. 100–101°. (Found : C, 41·3 ; H, 3·9 ; I, 39·8%. $C_{11}H_{13}O_3I$ requires C, 41·3 ; H, 4·1 ; I, 39·7%).

The work was aided by a grant from the Medical Research Council to one of us (N. F. M.). The 3:5:3′-L-triiodothyronine and L-thyroxine used were kindly provided by Glaxo Laboratories Ltd.

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Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION

THE annual meeting of the British Orthopædic ssociation was held in Sheffield on Oct. 24 and 25, nder the presidency of Sir REGINALD WATSON-JONES.

THE WATER CONTENT OF THE NUCLEUS PULPOSUS

Mr. A. NAYLOR (Bradford) had studied experimentally he changes in pressure within the isolated intervertebral isc, excised with the bony endplates. Normal discs mmersed in water showed an initial slight fall of pressure ascribed to swelling of the annulus fibrosus), followed y a substantial increase caused by swelling of the ucleus, which reached its maximum size after fifteen ours. Immersion in normal saline usually caused less welling. These pressure changes were not observed in egenerate discs. Further experiments suggested that he swelling was due to osmotic changes, fluid entering hrough the endplates, which behaved much like a emipermeable membrane. Mr. Naylor believed that hanges in the water content of the nucleus pulposus night play an important part in the causation of back ain, and that when the annulus fibrosus was thin or lamaged, swelling of the nucleus due to an increase in ts water content might precipitate herniation.

THE LUMBAR DISC-LESION SYNDROME

Mr. J. R. ARMSTRONG (London) recalled that one of he cardinal features of the symptoms of protruded ntervertebral discs was their episodicity, the symptoms ubsiding and recurring, sometimes repeatedly, at varying ntervals. He discussed the pathological and mechanical actors in the disc and disc-root relationship that might ccount for these periodic variations. He had found evidence of at least twelve such factors, any one of which might operate in an individual case :

(1) final rupture of the annulus might occur suddenly from mechanical forces, and cause marked exacerbation of symptoms ;

(2) a nuclear fragment might become impacted and cause "locking" of the joint ;

(3) the size of a nuclear protrusion sometimes varied during movements and changes of position of the spinal column ;

(4) an existing tear of the annulus might extend, or might heal ;

(5) œdema added to the size of a nuclear protrusion in its early stages ; subsidence of this œdema would lead to decrease of symptoms (œdema might also affect the nerve-root) ;

(6) gradual shrinkage of a protruded nucleus led to spontaneous decrease of symptoms ;

(7) a nerve-root might become adapted to stretching ;

(8) the relationship between nerve-root and protrusion might vary ;

(9) a nerve-root might become elongated ;

(10) a nerve-root often became adherent, with consequent pain when the nerve was stretched by changes of posture ;

(11) permanent pathological changes might occur gradually within the nerve-root itself ;

(12) in the stage of degenerative arthritis, sudden exacerbations resulted from irritability of the intervertebral joint.

TREATMENT OF LUMBAR INTERVERTEBRAL DERANGEMENTS BY TRACTION

Dr. E. J. CRISP (London) said that although some years ago he was sceptical of manipulation in the treatment of intervertebral derangements, he had found that many patients were relieved, often dramatically, by sustained traction. He had designed an apparatus to exert traction on the lumbar spine without pulling upon the thorax or limbs. Traction up to 120 lb. was applied, without anæsthesia, usually for fifteen minutes. Careful measurements had shown that distraction of the spine did, in fact, occur. In a series of over 200 patients treated in this way the results had been good : 15 out of 17 patients with acute lumbago, 9 out of 12 with acute sciatica, and 2 out of 6 with pain after laminectomy were completely relieved ; and 50% of women with chronic back pain were improved. Experience had led him to believe that by no means all back pain or sciatica was due to prolapsed intervertebral disc. In many cases changes in the posterior joints, such as nipping of synovium between the facets, might be responsible. These were the cases that might be expected to respond well to non-operative treatment.

Sir REGINALD WATSON-JONES said that these three papers were particularly interesting because they represented respectively the experimental, the clinical, and the empirical approach. He questioned the significance of experiments in which the intervertebral discs were immersed in water rather than in physiological saline.

Mr. PHILIP WILES (London) said that he had practised manipulation in the treatment of patients with back pain and sciatica, at first with, but more recently without, anæsthesia. He thought that the dangers had been exaggerated. In only two cases had he precipitated an attack of acute sciatica—in each case, he thought, by hyperextension, which he now omitted from his routine. He agreed with Dr. Crisp that in many cases of back pain the underlying pathology was not directly concerned with the intervertebral disc.

Prof. B. L. MCFARLAND (Liverpool) thought that both forced flexion and forced extension were dangerous, and should be avoided. Traction might relieve about 25% of patients with clinically doubtful disc lesions.

Mr. JOHN CHARNLEY (Manchester) drew attention to the unique structure of intervertebral discs. The nucleus consisted almost entirely of acellular matter, which behaved almost like a chemical substance ; thus, it could be dried and subsequently restored almost to normal by immersion. He believed that many pains in the back might be due to temporary pressure changes in discs. Further research on this aspect of the problem was required.

DIRECT SKIN FLAPS AND TUBE PEDICLES

Mr. WILFRED HYNES (Sheffield) described the management of three difficulties that were commonly experienced in skin-grafting by flaps and tube pedicles. One important difficulty was the length of time taken up by the various stages of transferring a flap—often about three months in all. By a special test which indicated the degree of vascularisation at the pedicle of the flap, he had found it possible to reduce the waiting time between stages, sometimes to less than half the time previously thought necessary. In this test atropine (gr. $^{1}/_{25}$) was injected into the flap after clamping the pedicle to be divided. If the effects of atropinisation (tachycardia and dry mouth) were observed within forty minutes, the pedicle could be divided safely. Another difficulty was to decide how much additional time should be allowed for revascularisation when part of the inset was lost by necrosis. Here again the atropine test gave a good indication of the viability of the flap, and it had shown that the blood-flow through a pedicle might be surprisingly good, despite necrosis of a considerable part of its area. A third serious difficulty was the "blue flap," a condition in which, within a few minutes of the operation, cyanosis began to appear around the inset of a flap, and was followed by necrosis which gradually spread and might involve loss of the whole flap. This complication was due to thrombosis of vessels in the flap, the capillary pressure being sufficient to drive blood in, but not to expel it. He had found that if the blood was kept moving in and out of the flap, thrombosis might be prevented or minimised. This could be achieved in some cases by altering the posture of the patient every ten minutes so that blood flowed in and out of the flap by gravity ; or by intermittent venous occlusion by a pneumatic cuff applied to the limb proximal to the flap.

EARLY TREATMENT OF THE BLADDER IN PARAPLEGIA

Dr. A. G. HARDY (Sheffield) emphasised that the problems of paraplegia must be regarded as a whole rather than individually. Thus, successful management of the bladder was closely related to the efficient prevention of sores, sepsis, and prolonged immobility, all of which reacted unfavourably upon the urinary system. Exceptional care in nursing was essential, and the diet should include a high fluid intake. *Management* of the bladder should be designed not only to prevent complications, but also to encourage coördinated reflex activity, which often took a long time to develop and was dependent upon an intact lower segment of the cord. The method favoured was constant drainage through a urethral catheter, changed weekly by a strict aseptic technique. The urine drained continuously into a bottle beneath the bed, except for periods when the tube was clipped for retraining reflex activity. Irrigation was carried out by the closed method. Antibiotics were used as required, but infection was gauged more by clinical than bacteriological evidence. The residual urine was carefully observed, and each week the catheter was left out for a trial period to assess the progress of reflex activity. The duration of catheter drainage varied, being longest after complete transection in the lumbar region; it had never been required for more than thirty-two weeks.

SURGICAL TREATMENT OF DUPUYTREN'S CONTRACTURE

Mr. H. J. RICHARDS (Oswestry) described the surgical treatment of Dupuytren's contracture. He recommended excision of the whole palmar fascia through incisions in the skin creases, with mid-lateral extensions in the fingers. In the typical Dupuytren's contracture there was no actual loss of skin, but simply shrinkage secondary to contracture of the underlying fascia. Once the fascia was removed the skin would stretch again if given time. Skin-grafts were unnecessary. After operation a firm massive pressure dressing was applied to the palm, and the hand put at rest in a posterior plaster shell, no attempt being made at that stage to overcome the original deformity. The sutures were removed on the fourteenth day, and when the wound was fully healed active extension of the fingers began. Correction of the deformity was a gradual process sometimes occupying many weeks or months.

Mr. J. I. P. JAMES (London) confirmed, from his series of 90 cases of Dupuytren's contracture treated by a similar operation, that there was no need at all for skin-grafting. If the operation *and the after-treatment* were correctly done "there was nowhere to put the skin." Nearly all patients regained full movement of the fingers.

SUPRACONDYLAR "Y" FRACTURES OF THE HUMERUS

Mr. E. MERVYN EVANS (Swansea) recalled that in this fracture the olecranon was forced upwards between the humeral condyles. The injury was usually one of adolescents or young adults. Full operative reduction and internal fixation had given disappointing results with consequent elbow stiffness. Mr. Evans suggested a simpler operation in which the fracture was converted into an ordinary supracondylar fracture, which was relatively simple to manage. His method was to fix the medial and lateral condyles rigidly together by a transverse screw, with minimal disturbance of the muscles and joint capsule. Thereafter the supracondylar fracture was reduced by manipulation and immobilised in plaster in the usual way.

PRIMARY INTERNAL FIXATION OF COMPOUND FRACTURES

Mr. F. R. ZADIK (Wigan) said that in closed fractures that were unstable the value of internal fixation was accepted, but that the principle of primary internal fixation of compound fractures was controversial. He believed that many advantages accrued from primary internal fixation, provided the wound did not break down. Wound breakdown was caused either by infection or by tension; infection could be prevented by careful and radical excision of non-viable tissues, and by the use of antibiotics. He had used primary internal fixation in 24 open fractures in which the fragments appeared unstable (tibia and fibula 13, ankle 3, radius and ulna 8): 19 wounds, healed by first intention; 4 broke down (3 from tension, 1 from infection); and 1 wound was not closed completely. His results showed that union occurred in an average time which was not significantly longer than that for simple fractures.

Mr. NORMAN ROBERTS (Liverpool) said that he did not accept the necessity for internal fixation of tibial fractures even in closed injuries. If it was accepted for simple fractures, he saw no objection to extending it to open fractures.

Mr. C. H. CULLEN (Wigan) accepted the advantages of internal fixation for tibial fractures, and thought that Mr. Zadik had shown it to be safe in open fractures.

Mr. H. OSMOND-CLARKE (London) deplored the routine use of internal fixation for all fractures, and thought that every fracture should be treated on its merits. Many unfortunate results of internal fixation of open fractures had been seen during the war.

Mr. WILES emphasised the danger to the limb if aseptic precautions were unsuccessful and the wound broke down.

Mr. T. J. FAIRBANK (Cambridge) thought that the problem rested on the outlook for healing of the wound, as judged from the surgeon's experience. If it seemed certain that primary healing could be obtained, internal fixation was justified.

Mr. J. N. WILSON (Cardiff) and Sir HARRY PLATT (Manchester) thought that the method was justified in certain selected cases.

Mr. J. C. SCOTT (Oxford) agreed that much depended upon the likelihood of healing of the wound, which was the matter for prime consideration. Only exceptionally was internal fixation justified at the stage when the wound was open.

Mr. O. J. VAUGHAN-JACKSON (London) suggested that the practice might become more hazardous in the future because of the increasing incidence of resistant organisms.

Sir REGINALD WATSON-JONES, summing up the discussion thought that the wisdom of internal fixation depended upon the nature of the wound and of the fracture. If the wound was grossly contaminated, the addition of further foreign material was quite unjustified. On the other hand, if the wound was such that primary healing, with suitable management, seemed certain, there could be no harm in internal fixation of the fracture when such a step was advisable on mechanical grounds.

THE DISLOCATED HIP WITH FRACTURED ACETABULUM

Mr. E. A. NICOLL (Mansfield) reported observations on 144 cases of dislocation of the hip-joint, contributed by a number of surgeons forming a clinical research group of the association. A fracture of the acetabulum, complicating traumatic dislocation of the hip, might have three effects:

(1) it might cause instability of reduction;
(2) a fragment of bone might be included within the joint;
(3) the incidence of late osteo-arthritis and of sciatic-nerve lesions was increased.

Instability was likely only when a large segment of the acetabulum was displaced. Treatment should be by immediate operative reduction and fixation by a screw. Inclusion of a fragment within the joint was exceptional, and occurred only with small fragments. Sciatic palsy was three times as common after fracture-dislocation as it was after simple dislocation. In 4 out of 5 cases the nerve lesion was incomplete, affecting almost invariably the peroneal fibres; the lesion was always in continuity, but the prognosis for recovery was poor (5 out of 13 in the series studied).

Sir **REGINALD WATSON-JONES** emphasised the importance of immediate reduction of displaced acetabular fragments in cases of sciatic-nerve palsy; the nerve was usually stretched over the sharp margin of the tilted bone, and recovery was jeopardised by delay in reduction.

BIOCHEMISTRY OF BONE

Prof. **H. A. KREBS**, F.R.S. (Sheffield), said that whereas early studies of bone had been concerned with its composition, more recent work had dealt with its activity. Experiments in which radioactive isotopes were introduced into the body had shown that bone, in common with other living tissues, was in a dynamic state—i.e., the material of which it was made was constantly being changed. In normal circumstances removal and resynthesis proceeded at the same rate, so that there was no apparent change in structural composition. The rate of the exchange varied with different tissues, being relatively rapid in those with high metabolism: thus, in the liver some constituents had been shown to be replaced completely within a matter of days, whereas in bone the process was much slower.

TUBERCULOSIS OF THE ELBOW-JOINT

Mr. **J. N. WILSON** (Cardiff) reviewed 31 cases of tuberculosis of the elbow joint. The disease was commonest between the ages of ten and thirty. He recognised 4 types: synovial, extra-articular, coronoid, and massive; and the massive type was the most common. Sinuses and tuberculous lesions elsewhere were common complications. Conservative treatment by immobilisation in plaster for an average of eighteen months was the standard treatment. Streptomycin had been available for only 4 cases, in which it seemed to help resolution. When the disease was quiescent the elbow was suitable for light exercise without support, but if heavy work was necessary a block leather splint was provided. Arthrodesis had been performed in 3 cases in which there had been persistent pain or recurrent flares. Three other elbow-joints, all with sinuses, underwent spontaneous bony fusion.

SPASTIC EQUINUS DEFORMITY

Mr. **G. A. POLLOCK** (Edinburgh) said that in cases of spastic diplegia the commonest deformity requiring operative correction was equinus, and he described the operation of lengthening the gastrocnemius tendon. Recurrence after operation was frequent, and might be due to inadequate lengthening of the tendon, to lengthening of the whole tendon when the contraction was confined to the gastrocnemius component, or to inadequate splintage after operation. When only the gastrocnemius component of the calf group was contracted, as determined by the knee-flexion test, lengthening of the affected tendon alone was satisfactory; it had the advantage of attacking the trouble at its primary site, of preserving the strength of the calf muscles, and of avoiding the risk of later calcaneus deformity. He illustrated the technique of the operation by a film.

FRACTURE-DISLOCATION OF THE THORACOLUMBAR SPINE

Mr. **F. W. HOLDSWORTH** and Dr. **A. G. HARDY** (Sheffield) described and demonstrated in detail their routine examination of patients with fracture-dislocation of the thoracolumbar spine complicated by paraplegia. They showed how, from simple clinical tests and radiographs, the upper limit of the lesion, the condition of the nerve-roots, and the condition of the distal segment of the cord could be accurately analysed. They emphasised the importance of certain reflexes, especially the bulbocavernosus and the anal skin reflex, in indicating activity in the distal part of the cord. The technique of nursing, by which 50 patients had been successfully treated without a pressure-sore developing, was also demonstrated; after such operative stabilisation of the spine as was required, the patient was nursed on pillows and was turned methodically every two hours. Patients were shown with fracture-dislocations at the D12 to L2 level illustrating:

(1) complete cord lesion and complete root lesion;
(2) complete cord lesion with partial root escape;
(3) complete cord lesion with total root escape.

The function and gait that could be hoped for in each group of patients was shown. The impressive results emphasised the importance of treating paraplegic patients in centres specially equipped and staffed for their care.

Reviews of Books

Diseases of the Ear, Nose, and Throat

Editor: W. G. SCOTT-BROWN, C.V.O., M.D., F.R.C.S., ear, nose, and throat surgeon, Royal Free Hospital, London. London: Butterworth. 1952. Vol. 1. Pp. 756. Vol. 2. Pp. 639. 8 guineas per set.

THE demand for a comprehensive British textbook of otolaryngology will be largely satisfied by the inclusion in this new work of an up-to-date and authoritative account of diseases of the ear. The task of authorship has been shared by 32 contributors, and the personal views of many leading specialists have been supplemented by an extensive review of recent literature. The sections on anatomy are written by anatomists, those on physiology by physiologists—an experiment well justified by the results. The authors of the chapters on allergy, pharyngitis, perceptive deafness, and deafness in children present their difficult subjects particularly clearly. Operative technique is well described; and such related subjects as plastic surgery (by a plastic surgeon), anæsthesia (by an anæsthetist), diseases of the lacrimal apparatus, and the pharyngeal manifestations of general disease, each get a separate chapter. There is too little information for the specialist, however, on some important topics, such as nasal polypi. Divergences of opinion are remarkably few, but where they exist they make for stimulating reading. With a few notable exceptions the reproduction of skiagrams is poor, but the illustrations of clinical material and pathological specimens and sections are very good. The chapter on speech defects is confusing and has no bibliography, and there are inaccuracies in the chapter on nervous diseases of the larynx. But this is a book that fulfils its purpose well, and should be much used.

History of the Royal Medical Society

JAMES GRAY, M.A., F.R.S.E. Editor: DOUGLAS GUTHRIE, M.D., F.R.C.S.E., lecturer in history of medicine, University of Edinburgh. Edinburgh: University Press. 1952. Pp. 355. 42*s*.

To anyone who does not know the Edinburgh Medical School this may seem at first a puzzling book. The title of the society, the royal warrant, the frontispiece of an elderly doctor, the early illustration of the society's house, all suggest a postgraduate body similar to the Royal Society of Medicine or the Liverpool Medical Institution. But it was founded by six students, and was (and is) essentially a student society, though it caters also for young graduates, from whom the presidents have usually been derived. It must be almost unique for a student body to own its own house and obtain a royal warrant; and its meetings and discussions must have had immense influence in teaching students to speak in public and think quickly in debate: indeed, Sir Robert Hutchison tells us that it was one of the most formative influences of his undergraduate days.

In the main the book is concerned with the distinguished men who have been members, most of whom are accorded short biographies which interfere somewhat with the story of the society's development. Cullen, Syme, Liston, and Lister are good examples, and there were others who earned fame away from medicine—Oliver Goldsmith, Sidney Smith, Charles Darwin, and Jean Paul Marat among them. Indeed, the astonishing feature is the very large number of famous men who in their youth were members of this flourishing body. Osler said in 1907: "Looking over the list of members since 1737 I was prepared of course to find the names of many of the great men of the profession, but I did not expect to find a list of such extraordinary distinction. I doubt if there is any other society in the world, except perhaps the Royal Society of London, with such a roll of honour." This book adds great prestige to a unique society.

Statistics for Medical and other Biological Students

L. BERNSTEIN, B.SC., M.R.C.S., senior lecturer in physiology, London Hospital Medical College; M. WEATHERALL, M.A., D.M., B.SC., senior lecturer in pharmacology, London Hospital Medical College. Edinburgh: E. & S. Livingstone. 1952. Pp. 180. 18*s*.

Elementary Medical Statistics

DONALD MAINLAND, M.B., D.SC., F.R.S.E., F.R.S.C., professor of medical statistics, division of medical statistics, the Department of Preventive Medicine, New York University College of Medicine. Philadelphia and London: W. B. Saunders. 1952. Pp. 327. 25*s*.

TEXTBOOKS which seek to introduce the medical student to statistics are becoming infinite in their variety. Authors have to steer between the Scylla of the statistical "cook-book," which merely gives arithmetical recipes for the various technical tests of significance with no attempt at their logical justification, and the Charybdis of a too rigorous approach to their mathematical background. Dr. Bernstein and Dr. Weatherall have veered towards the latter, and the ordinary clinician may be daunted by four pages of mathematical symbols and their definition in the introductory part of the book. The younger student, fresh from the school bench, may be able to assimilate these, and, fortified by a clear discussion of the logic of scientific method, may proceed to a detailed study of the laws of probability and the various descriptive measures of frequency distributions.

An orthodox development of regression and correlation with lucidly worked examples leads to a helpful discussion of the use of transformations in dealing with non-normal distributions. Such distributions often occur in practice but need modification before they can be handled by the usual techniques. Probit analysis, which is becoming increasingly important in the standardisation of biological medicaments, is briefly discussed, and the last five chapters are devoted to an account of the commoner difficulties and fallacies in the design of experiments and the interpretation of their results. Throughout, the practical applications are kept in view, although occasionally obscured by a presentation which is too formal for the ordinary medical student and yet too imprecise for the mathematically sophisticated.

For the complete novice an even simpler introduction is required, but the book may well be useful to initiates who want a fuller description of statistical methods applied to laboratory and clinical work, particularly in pharmacology.

Dr. Mainland's text is less ambitious and in some ways more successful.

Much more space is given to the systematic appraisal of evidence, with emphasis on the interpretation of differences in frequency of events. The concept of the confidence limits of a percentage, and of the differences between percentages, forms the basis for an elementary account of the principles of the clinical trial. Despite some apparent contradictions in the sections dealing with pairing and the calculation of the numbers required to confirm preliminary results, this section should prove helpful to the experimentally minded clinician. These ideas are then translated into tests of significance in measurement. The t-test for the difference between means leads naturally to the analysis of variance and measures of concomitant variation, but the latter subject is treated only cursorily. A most valuable discussion of the clinical relevance of statistical ideas indicates the importance of variability between individuals in the assessment of "normality" and between technicians in the reliability of blood-counts. Dr. Mainland's enthusiasm for Fisherian developments in the field of small-sample technique and experimental design makes him perhaps less than fair to the value of the methods used and results obtained by workers in public-health statistics; indeed his description of the life-table suggests a certain unfamiliarity with this aspect of statistical studies. At every stage, understanding is tested and enhanced by stimulating questions and answers.

No elementary text could be expected to cover the wide field of statistical methods, but the selection of topics discussed and the simple manner of their discussion make this book a useful primer in the numerical approach to clinical medicine.

The Threshold of the Abnormal

A Basic Study of Psychopathology. WERNER WOLFF. London: Medical Publications Ltd. 1952. Pp. 473. 30*s*.

THIS book contains a vast amount of information, and copious erudite references, but hardly a chapter which suggests a fresh outlook on familiar territory. In fact it has the usual faults of a compilation which make one regret that it has been allowed to absorb the energies of an able and original mind. If no-one had written a textbook of abnormal psychology before, this would be a treasure-house, an invaluable repertory: but at this time of day its appeal must be to the author's students and the many porous people who soak up anything psychiatric. Apart from these serfs and sponges, the readers to whom the book will be useful are those who want to find or check references, and are therefore able to draw sustenance even from such a sentence as "Many theories have been proposed to explain the phenomenon of emotion. 7, 11, 12, 24, 25, 45, 109, 111, 115, 143, 198." Such sentences abound, but unfortunately the numbers are not always easily decipherable without a loupe.

The Specialties in General Practice

Editor: RUSSELL L. CECIL, M.D., professor of clinical medicine, emeritus, Cornell University Medical College, New York. Philadelphia and London: W. B. Saunders. 1951. Pp. 818. 75*s*.

THIS book, written by 14 specialists of professorial rank in various North American universities, sets out to supply the general practitioner with a guide to the specialties. "In . . . cases," says the editor, "which come within the field of a definite specialty the practitioner is expected to make at least a tentative diagnosis, to indicate without delay the best course of therapeutic procedure or to refer the patient to a specialist." It is the implied aim of the book to help him to do these things.

The chapters are, naturally enough, of unequal value. In some the author succeeds in seeing his specialty through the family doctor's eyes and gives him the information he genuinely needs; in others he sees it through his own eyes, displays a predilection for the rare, and describes and illustrates elaborate techniques outside the practitioner's range. In many sections there is little discrimination between the rare and the common. The numerous illustrations, from photographs, X-ray films, and diagrams, are uniformly good, but the same cannot be said of the writing. The words spent in avoiding the simple imperative must number thousands in the course of the volume. Transcription of these passages into terse and lucid English would make room for at least one new section.

Handwriting: a Personality Projection (Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 149. 27*s*. 6*d*.).—Few doubt that so individual a characteristic as a man's handwriting gives indications of his personality, and that some people are more skilled than others at the process of divination. Lucid statements of the method, scope, and reliability of "graphology" are, however, very rare. This book by Mr. Frank Victor, PH.D., is a serious attempt to provide the necessary information in a brief form, with references to published work, especially the copious German output of the 1930s. Unfortunately it does not succeed; since, in spite of his just emphasis on release, tension, and energy, Dr. Victor cannot validate the relations he asserts between spatial movements and their symbolism. Failing to provide this, he remains a moderate apologist for the intuitive procedure in the use of which, it may fairly be assumed, he and some other graphologists are highly gifted.

THE LANCET

LONDON: SATURDAY, NOV. 8, 1952

Prematurity and the Obstetrician

THE wastage of fœtal and infant life by stillbirths and neonatal deaths has never attracted as much attention as deaths beyond early infancy. Yet in England and Wales during 1949 there were 31,053 such deaths, compared with 727 maternal deaths and 3789 deaths on the roads. Among the causes of this loss of fœtal and infant life, prematurity is paramount. CROSSE[1] found in Birmingham that in almost half the stillbirths and over half the neonatal deaths the birth weight was under 5½ lb. BAIRD[2] showed that the death-rate among premature infants was ten times that among infants of mature weight; and the Registrar-General's reports make it clear that in England and Wales prematurity accounts for some 40% of neonatal deaths.

For the premature child the first forty-eight hours of life are the most critical; 65% of neonatal deaths take place in this period. Any substantial reduction in the rate of stillbirths and early neonatal deaths among premature infants will depend on either preventing premature birth or reducing the hazards of delivery. Unfortunately, our knowledge of the causes of prematurity is incomplete; and often no satisfactory explanation can be found. CROSSE[1] showed that "cause unknown" accounted for 36% of the large series which she investigated, and BAIRD[2] found that in one group this figure was as high as 52%. Among the conditions known to be associated with premature birth the two most prominent are toxæmia of pregnancy and twins. Other causes—for example, syphilis, diabetes, fœtal abnormality, and the induction of labour for reasons other than toxæmia—are much less common. Work in Australia[3] has shown that careful antenatal supervision can go far towards preventing eclampsia and reducing pre-eclampsia. The Women's Hospital, Crown Street, Sydney, had an average of 9 eclamptics per year in booked cases until 1947; but in 1950–51 there was not a single instance of this complication in such cases. This success has been achieved by an elaborate check of all antenatal patients to ensure regular attendance; by paying close attention to early warning signs of toxæmia, such as increased weight-gain and finger œdema; by controlling weight with a high-protein, high-vitamin, low-carbohydrate diet; by giving daily advice and lectures on diet to new patients; and by more frequent attendance and early admission to hospital of all suspect cases. With eclampsia completely prevented and serious pre-eclampsia uncommon, the induction of premature labour has been correspondingly reduced. There is evidence, too, from other sources that improvement in the diet and nutrition of the pregnant woman not only helps to prevent prematurity from toxæmia, but also reduces the number of unexplained premature births. BAIRD[2] has shown these to be more common in the lower-income groups where diet is poor than in the better-to-do patients. Other nutritional surveys have revealed that the number of unexplained premature births falls when poor diets are brought up to the required standard. Much improvement in this aspect of antenatal care is still possible. In many clinics patients are commonly given extra iron and vitamins—the Ministry of Health encourages this practice by supplying cod-liver oil and orange juice for the expectant mother—but they rarely receive any instruction on how to correct their diets in order to combat anæmia and vitamin deficiency. If these abnormalities are attacked early in pregnancy by proper advice, the iron pills need not be prescribed (even when they are prescribed they are not always swallowed), nor will the urgent intravenous-iron therapy or blood-transfusion be so often needed in late pregnancy. Could not instruction on diet be as regular a feature of antenatal care as that on relaxation? In industrial areas anæmia and ill health are more of a problem than failure to relax during labour. Again, could not some of the time spent in palpating the patient's abdomen be better used in talking to her about matters of health? We would do well to pay no less attention to the mother during pregnancy than to the presentation and position of the fœtus.

Whatever the improvements in antenatal care, however, there will still be some premature births; and in these special treatment is necessary. The respiratory centre of the premature child is particularly vulnerable to depressant drugs, and its fragile skull gives poor protection against intracranial damage. The drugs ordinarily used to relieve the pain of childbirth may delay respiration or prevent it from being fully established. Undoubtedly the safest method is local infiltration of the perineum with, say, 1% procaine, which may be combined with analgesia by inhalation of trichlorethylene just as the child is being delivered. Caudal and spinal analgesia are also said to be excellent in this type of case; but they carry a greater risk to the mother. Even more serious is the risk of fatal intracranial hæmorrhage; resistance to the head from a normal perineum, for instance, may cause a tentorial tear—a danger that has led to prophylactic episiotomy. RUSSELL and BETTS[4] have analysed the effect of this operation in premature delivery, and have shown that it lowers mortality significantly. Their findings also suggest that mortality may be further reduced by applying low forceps, which may protect the child from damage, especially when this procedure is combined with wide episiotomy. Formerly most obstetricians held that in premature delivery forceps should not be applied.

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1. Crosse, V. M. The Premature Baby. London, 1945.
2. Baird, D. *J. Obstet. Gynæc.* 1945, 52, 217, 339.
3. Hamlin, R. H. J. *Lancet*, 1952, i, 64.
4. Russell, G. R., Betts, W. A. *J. Pediat.* 1952, 40, 722.

Epidemiological Attack on Tuberculosis

BECAUSE of advances in chemotherapy and thoracic surgery the main emphasis in tuberculosis has centred lately on treatment of the established case. The epidemiology of the disease has not been neglected, but more thought might have been given to new methods of prevention and control if advances in treatment had been less striking. The value of supervising family contacts is fully recognised[1]; but with few exceptions the epidemiology outside the household has not been studied with an eye to prevention. Exceptions are the "mass" methods of photofluorography and, on a trial basis, inoculation with B.C.G. The study of a complete community in a South Wales mining valley[2] should in a few years increase our knowledge of the epidemiology of tuberculosis in a wider field; and STEWART's[3] studies of infection in factories, and occasional investigations of tuberculin sensitivity in school entrants to indicate sources of infection, are other instances of epidemiological methods extended beyond the household.

GEDDE-DAHL[4] has made an environmental study by the method of "tuberculin matriculation," by which he means the continuous tuberculin testing of the whole population. This is divided at the start into tuberculin-positive and tuberculin-negative groups; the tuberculin-negative group is periodically retested with tuberculin, while the positives and converters are kept under radiological observation "until the risk of disease is minimal." He has applied this technique to a rural community of 6500 on the west coast of Norway where he held the post of public medical officer and was in charge of the tuberculosis diagnostic centre, as well as doing most of the general practice. The percentage tuberculin-positive in each age-group was much lower than that found in this country by the Medical Research Council.[5] At age 15–19, 20% were positive in completely rural areas, and 30% in a small town, compared with over 50% in this country. The proportion positive reached a maximum of 70–90% at age 45–54, and the level fell somewhat in older age-groups. In this context GEDDE-DAHL possibly underestimates the importance of reversion—i.e., the change from the tuberculin-positive to the tuberculin-negative state. The annual reversion-rate may be quite low, but the majority of adults are positive, and a low conversion-rate may thus balance an appreciably higher conversion-rate in a small proportion of the population. Thus in a group, 90% of whom are tuberculin-positive, an annual reversion-rate of 1% will exactly balance an annual conversion-rate of 9%. The conversion-rates observed by GEDDE-DAHL ranged from 1% for the age-group 7–10 years to 5% at 20–24 years, falling to about 4% in older age-groups.

Anyone who underwent tuberculin-conversion was closely observed, and the source of infection was also diligently sought. Because the community was scattered and isolated the chain of infection could often be traced with fair certainty. During the study 274 conversions are known to have taken place. Even in children the infection was intradomiciliary in only half the cases; at age 15–19 only 1 infection in 5 was intradomiciliary, more than half were from known extradomiciliary sources, and just over 1 in 4 from unknown sources. As GEDDE-DAHL points out, when there are many sources of infection a high proportion of children will be infected at home; but as the number of sources of infection falls, infection is postponed until the age of increasing social and work contacts. GEDDE-DAHL also found a connection between the source of infection and the likelihood of tuberculous disease in its widest sense. Of all converters 48% showed some evidence of tuberculous disease; the percentage was 76 for those with intradomiciliary exposure, 41 for those with known extradomiciliary exposure, and 31 for those in whom the source of infection was unknown. The report does not mention the possible influence of genetic relationship with an infectious case, though from a table it appears that over 70% of those infected within the household were related to the infector. GEDDE-DAHL also concludes that patients with uncomplicated primary tuberculosis rarely infect others, though gastric washings may show tubercle bacilli. The type of case mainly responsible for infecting others was the well-established one which perhaps had been recognised elsewhere but had not remained under supervision. Such situations are by no means unknown in this country, and GEDDE-DAHL's plea for more complete notification and greater continuity in control of tuberculosis should find an echo here. The "good chronic" with occasionally positive sputum was a less important source of infection, even of household associates, than might be expected. At the other extreme was a heavily sputum-positive young man who infected 12 or 15 tuberculin-negative people in the course of one evening's singing and dancing at a Christmas party in a crowded schoolroom; even here, however, a much larger number of tuberculin-negative people were present but were not infected. In this survey the *epidemiological incubation period*—i.e., the interval between first infection of a person and his being a source of infection to others—was unknown in 15 cases, at least 1–4 years in 8 cases, at least 5–9 years in 12 cases, and more than 9 years in 7 cases. The close supervision of converters, with treatment when necessary, no doubt helped to postpone the chances of infection being spread.

GEDDE-DAHL recognises that tuberculin matriculation is not feasible in urban communities with high infection-rates—there would be too many untraced infections. Under such conditions mass radiography and preventive inoculation must be the main methods of epidemiological control. There is, however, every reason to agree with GEDDE-DAHL that, as tuberculosis decreases, a point is reached at which mass radiography is wasteful because so many of those examined in this way have never been infected. Similarly in regard to preventive inoculation, a point is reached at which the risk is so slight that mass inoculation is not justified, especially as it spoils the field for epidemiological control by tuberculin matriculation. In this country such ideas may seem utopian; but our methods of investigating and controlling outbreaks of acute infectious diseases, such as typhoid fever and smallpox, would have seemed equally utopian in the

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[1] Aspin, J. *Lancet*, 1952, i, 502.

[2] Cochrane, A. L., Cox, J. Glyn, Jarman, T. F. *Brit. med. J.* 1952, ii, 843.

[3] Stewart, A., Hughes, J. P. W. *Ibid*, 1951, i, 899.

[4] Gedde-Dahl, T. *Amer. J. Hyg.* 1952, 56, 139.

[5] *Lancet*, 1952, i, 775.

19th century. We must be prepared to supplement our efforts to control the disease in the patient and his household by really effective control of the infection in the community.

Identification of Blood Sera

The differentiation of the blood sera of animals of various species is sometimes important for incriminating (or even exculpating) both human criminals and insect vectors of disease. The distinctive constituents of serum which differ from one species to another are the proteins; but, whereas simple chemical compounds can be distinguished with relative ease by chemical and physical methods, the giant protein molecules are very difficult to identify. The various blood-serum proteins all have very much the same chemical composition; they are all built up from the same amino-acids, and many of their physical properties are almost identical. Nevertheless the biological properties of separated protein fractions differ widely; for example, antibody proteins occur in the globulin fractions of serum and never in the albumin. Electrophoretic methods of separation, developed largely by the use of the Tiselius[1] apparatus, make use of slight differences in the distribution of basic and acidic groups in the side chains of the protein molecule, and by this means at least eight different serum-protein fractions have been prepared. Even this method does not yield chemically homogeneous preparations, and Hewitt[2] has shown that the albumin fraction can be further separated into seroglycoid, a protein containing a high proportion of polysaccharide, and crystalbumin, which unlike the other serum-proteins is carbohydrate-free. During the late war large quantities of human plasma were available from blood banks, and this enabled Cohn[3] and his colleagues to develop carefully controlled protein-fractionation methods using organic solvents at low temperature. As a result of this work, gamma-globulin and albumin fractions are now made on a commercial scale, but even so these advances in our knowledge of the chemistry and physics of proteins have not yet made it possible to differentiate between the serum-proteins of different species of animals. On the other hand, immunological methods of differentiating them have been available for fifty years. When an animal is injected with a foreign protein, antibodies appear in the blood, and if the animal's serum is mixed with a solution of the foreign protein a precipitate is formed. Bordet[4] in 1899 found that the blood serum of one species of animal acts as a foreign protein when injected into another species and it gives rise to precipitin formation. This phenomenon was applied to the study of the relation between zoological species by Nuttall[5] in 1904, and his work has remained of fundamental importance. He found that, when the immune serum was mixed with different foreign sera, the amount of precipitate formed was greatest when the foreign serum was of the same species as the serum used for immunisation; less precipitate was formed with sera of different but closely related species; and least of all when the sera of distantly related species were tested. Thus the serum of a rabbit immunised with human serum gave most precipitation when mixed with human serum, less with anthropoid ape serum, still less with that of a monkey, and least with dog and cat serum.

As the test can be carried out with very small amounts of material, it is used in medicolegal work for the identification of blood stains, when it will indicate the animal species from which the blood came. The precipitin technique has also been used in tracing insect vectors of disease. In order to trace and control the spread of diseases transmitted by blood-sucking insects it is necessary to know what are the principal and supplementary hosts whose blood the insects suck, and hence the animal species concerned in the infection.[6] To identify the blood which the suspected insects feed on, the precipitin technique has been used for the past thirty years as a means of examining the contents of the insect's stomach and crop. The experimental difficulties are considerable, for the insects themselves and their alimentary canals are small, the visceral contents are minute, the blood may have been largely digested before the insect is caught, and the original meal of blood is often small. The task of recognising the origin of bloods when the insect has fed on animals of several species is so difficult that every possible perfection of technique must be explored, as Weitz,[7] working under the auspices of the Colonial Research Committee, has lately done. It is perhaps surprising to find how comparatively little present-day technique differs from that used in the original work of Nuttall. Some of the criticisms made by Landsteiner[8] about the early work remain valid. Although blood serum consists of at least eight different protein fractions, the antigen used for preparing the specific sera is still whole serum, which gives rise to a multiplicity of antibodies in the immune serum. Though the work of Dean and Webb[9] on the optimum proportions of antigen and antibody, and the quantitative technique developed by Heidelberger and Kendall,[10] carried matters forward, the methods of the early workers are still in common use today, and it is a tribute to their acumen that their conclusions have stood the test so well.

Changes in General Practice

The Ministry of Health announces that the new arrangements, proposed by the Working Party,[11] for distributing the central pool to general practitioners in the National Health Service will come into operation early next year, probably during the quarter beginning April 1. The reduced limits to be set on the size of practitioners' lists will apply from the same time, but doctors who have more patients than the limits allow will be able to adjust their lists gradually over a period of a year up to April 1, 1954. The Ministry points out that practitioners who now employ assistants may like to gain the advantage of the new basis of payment for partnerships by taking them as partners before April 1, 1953. Under the revised limits, a member of a partnership will be allowed 4500 patients, provided the average for the practice is not greater than 3500; and for a permanent assistant the maximum will be 2000.

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[1] Tiselius, A. *Trans. Faraday Soc.* 1937, 33, 524.
[2] Hewitt, L. F. *Biochem. J.* 1936, 31, 1534.
[3] Cohn, E. J. *Chem. Rev.* 1941, 28, 395.
[4] Bordet, J. *Ann. Inst. Pasteur*, 1899, 13, 225.
[5] Nuttall, G. H. F. Blood Immunity and Blood Relationships. Cambridge, 1904.
[6] Buxton, P. A. Trypanosomiasis in East Africa. H.M. Stationery Office, 1948.
[7] Weitz, B. *J. Hyg., Camb.* 1952, 50, 275.
[8] Landsteiner, K. The Specificity of Serological Reactions. Cambridge, Mass., 1947.
[9] Dean, H. R., Webb, R. A. *J. Path. Bact.* 1926, 31, 89.
[10] Heidelberger, M., Kendall, F. E. *J. exp. Med.* 1929, 50, 809.
[11] See *Lancet*, 1952, i, 1155.

Annotations

SCHOOL DENTISTRY IN SCOTLAND

AN official report from Scotland[1] comments trenchantly on the failure of the school dental service to measure up to its task:[2]

> "At the present time the service is quite incapable of coping with the amount of dental disease in school children and the immense amount of treatment necessary cannot be overtaken. Only about one-sixth of the total school population receives treatment in a given year and much of this treatment is the extraction of aching teeth, leaving other teeth in a diseased condition."

In 1950 only 227,776 children of 785,380 on the school registers were inspected, and of those inspected no more than 115,085 received dental treatment of any kind.

> "It is clear that the ravages of dental decay are outstripping the meagre forces attempting to hold them in check. There is a further factor which accentuates the evil effects of insufficient dental care and that is, that whereas during the war years the incidence of dental decay was steadily declining, there has been a strong tendency in the reverse direction in recent years. Children's teeth now require more attention of a reparative nature than they did some years ago."

The report refers to a memorandum submitted by the subcommittee after it had considered the report of the United Kingdom dental mission on New Zealand school dental nurses.[3] It was then estimated that 500 dentists would be required for an efficient preventive dental service for children and expectant and nursing mothers in Scotland. In view of the impossibility of recruiting so many dentists, the subcommittee had then recommended the use of dental ancillaries similar to the New Zealand dental nurses. The present report reiterates this recommendation as an essential step in building up a preventive dental service in Scotland, and suggests that probably 200 dentists and 600 ancillaries would be required for the complete staffing of such a service. This suggestion, by a committee of dentists, may be set against some of the objections to dental ancillaries which are raised in our correspondence columns this week.

The report also recommends that the preventive services should make every effort to impress on mothers and school-children the importance of oral hygiene and sound nutrition.

BRONCHITIS

IN a survey of illnesses encountered in general practice in Sheffield, Pemberton[4] found that bronchitis was the commonest condition for which patients sought advice, and, as he remarked, "although the diagnosis of 'bronchitis' is not always precise, the condition or group of conditions to which it refers is clearly of great medical and social importance. . . ." Moreover, the treatment of chronic bronchitis is so unsatisfactory that any information which might help to prevent it would be welcome. In a search for such information Pemberton[5] has made a study of the Registrar-General's statistical reviews. Men are at all ages more vulnerable than women, but particularly after the age of 40. The first year of life is one of peculiar danger to both sexes, but again males predominate. The importance of social conditions is shown by the fact that the standardised mortality-ratio for bronchitis is five times greater among the unskilled workers of the Registrar-General's class v than among the professional and managerial members of class I; and when infants alone are considered the difference is even greater. It is rather surprising to find that outside the large industrial towns, people in the south of England seem no less prone to serious bronchitis than those in the north. It is hard to distinguish the effects of climate on bronchitis from those of other environmental conditions, but temperature alone may not be as important as is commonly believed; and Waddy[6] has recently argued convincingly that, in epidemic respiratory infections at any rate, a low absolute humidity may be of greater significance. Among adults the brunt of the disease falls on men in the second half of life who live in the industrial towns. The countryman is relatively immune. The greatest dangers to the town-dweller seem to lie in overcrowded houses, factories, buses, and trains, but atmospheric pollution and specific occupational hazards must also play a part. The figures on which Pemberton bases his assessment of the occupations carrying a special risk of bronchitis are twenty years old and may not apply today, but they show that respiratory illness is (or was) outstandingly common among potters and cotton strippers, probably because they are exposed to a great deal of dust, and among foundry furnacemen, probably because they are subjected to extreme changes of temperature and humidity.

Clearly, a variety of social and industrial conditions are aggravating, if not causing, bronchitis, and this extremely troublesome disease is one of several that we may reasonably hope to subdue, or at least to modify, by further improvements in living conditions both at home and in the workshop.

INSULIN SUPPLY

ARRAIGNED, if that word be not too violent, before the Monopolies Commission, the manufacturers of insulin leave the court without a stain upon their characters. Oversimplified into the form of question and answer, the commission's report[7] would run somewhat as follows.

Was there a case for inquiry?—Yes, because the four firms of B.I.M. (British Insulin Manufacturers) act in collaboration and because one of them, Burroughs Wellcome & Co., produces more than a third of the insulin supplied in the United Kingdom, thus attracting section 2 of the Monopolies and Restrictive Practices (Inquiry and Control) Act, 1948.

Does this collaboration do harm?—No, the coöperation promotes technical efficiency and has been associated with an increase in insulin yields, improvements in formulation, packing, and presentation, and extensive research.

Is the product satisfactory?—Well, the opinion of a number of authorities is "commendatory almost without qualification."

Is the price too high?—Apparently not. Most insulin is supplied under the National Health Service, so that the retail price is now charged only upon a small proportion of retain sales; but insulin prices in the United Kingdom "are now the lowest in the world with the possible exception of those charged in Scandinavian countries."

What is the import position?—It seems that there have been no commercial imports since the war; the commission suggest that the level of the B.I.M. prices may have made the market unattractive to overseas suppliers.

Do, in the words of the Act, the conditions investigated "operate or may be expected to operate against the public interest"?—If the gland supply arrangements are altered, some change in the present system of allocating pancreas supplies may be desirable, and the Ministry of Health and the purchasing departments should watch prices and profits and exercise supervision if need be. Apart from those two cautionary qualifications, the arrangements made for the supply and distribution of insulin neither operate nor are expected to operate to the public disadvantage.

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1. Preventive Dental Services: a report by the subcommittee of the Standing Dental Advisory Committee of the Scottish Health Services Council adopted by the advisory committee on 11th February, 1952. *H.M. Stationery Office.* 1952. Pp. 33. 1s. 3*d.*
2. See *Lancet*, Oct. 25, 1952, p. 814.
3. New Zealand School Dental Nurses: Report of United Kingdom Dental Mission. H.M. Stationery Office, 1950. See *Lancet*, 1950, ii, 491.
4. Pemberton, J. *Brit. med. J.* 1949, i, 306.
5. Pemberton, J. *Med. Offr*, 1952, 88, 39.
6. Waddy, B. B. *Lancet*, Oct. 4, 1952, p. 674.
7. H.M. Stationery Office, 1952. 1s. 6d.

Those concerned in insulin production have thus escaped the criticisms made in previous reports by the commission, for example those on dental goods where elements of exclusive dealing and collective boycott were brought to notice.

Monopoly is a word of some emotional content; the Left may employ it against Big Business in private enterprise, the Right against nationalised industries. Whatever the political implications of the matter, the report is of general interest. The testimony upon which it is based includes evidence from 16 selected hospitals with diabetic clinics. The survey which section 7 of the Act requires the commission to undertake describes the strength and kinds of insulin and the processes of production. We are given a brief history of the discovery of the drug, its introduction into the United Kingdom, and its supply during the separate periods of 1923–27, 1928–40, and 1941–50. As diabetes mellitus is not a notifiable disease, no exact statistics are available, but the report estimates that there are 200,000 diabetic patients in the United Kingdom and that 60–70% of them receive insulin. Retail chemists distribute 80% and hospitals 20%. There is a short history of the legislation on the subject, mentioning the Therapeutic Substances Act, 1925, and its regulations, the Poisons Rules made under the Pharmacy and Poisons Act, 1933, and the Finance Act, 1934, when Neville Chamberlain freed imported insulin from duty. Naturally, however, the most material finding of the commission is their reassuring declaration that the present arrangements do not operate against the public interest and their refusal to recommend that they be discontinued.

INFLUENZA-VIRUS MUCINASE

In his early descriptions of agglutination of red blood-cells by influenza virus, Hirst[1] divided the reaction into two stages—first, adsorption of virus to red cells and, secondly, elution of virus from the cells. The adsorption appeared to be predominantly physicochemical, but Hirst noted that the elution bore many of the marks of an enzymic reaction. Detailed studies, notably by Burnet and his colleagues in Melbourne, have supported Hirst's original observations; and influenza virus has been found to act in enzymic fashion on soluble inhibitors of virus agglutination.[2] In 1949 Gottschalk and Lind[3] showed that interaction of influenza virus with soluble inhibitor produced a dialysable split product, which Gottschalk[4] later characterised as an N-substituted fructosamine.

Early work on the soluble inhibitors was carried out with materials, such as ovarian-cyst mucoid or ovomucin, which are not always to be had in large enough amounts to satisfy the avid requirements of the biochemist. Tamm and Horsfall[5] showed, however, that human urine contains a potent inhibitor of influenza-virus agglutination; and Gottschalk[6] and Odin[7] have analysed this inhibitor. Gottschalk[6] found that after hydrolysis galactose, mannose, and fucose were present along with a hexosamine base, which on chromatographic evidence seemed to be a mixture of glucosamine and galactosamine. The smallest carbohydrate unit in the mucoprotein was estimated to have a molecular weight of (2500)n, where n is not more than 3 or 4. This carbohydrate unit is regarded as a prosthetic group conjugated to protein; about two hundred such groups attached to each protein molecule make a mucoprotein molecule. In addition to the sugars already mentioned, "sialic acid" was detected in the urinary inhibitor.[7] This monobasic reducing acid, whose structure is still unknown, is found in many inhibitory substances, although in pure form it has no inhibitory activity. "Sialic acid" has similar properties to Gottschalk's[4] split product and is probably an important clue to the chemistry of these inhibitors.

The viruses belonging to the influenza/mumps/Newcastle disease/fowl-plague group, which all show mucinase activity, are the only ones where an intrinsic enzymic reaction has been clearly proved. Yet a mystery remains to trouble the biologist: of what use is this enzyme to the virus? Is it a micro-bulldozer which helps the virus to dig its way through the cell wall? Fazekas de St. Groth[8] cast strong doubt on this possibility when he showed that virus particles were taken into cells under conditions where there was no virus enzymic activity. Does the enzyme help the virus to overcome the effects of the host's normal inhibitors, as some have suggested? This sounds the most attractive hypothesis; but although mucoids inhibit agglutination, they rarely inhibit virus infectivity to any great extent; and the virulence of a virus is unrelated to its enzymic activity. Has the enzyme some intracellular function in virus multiplication; or is it a vestigial organ, a virusiform appendix, which may have had some useful function at an earlier stage in virus evolution? At present the facts allow of little more than idle speculation—a pleasant but often fruitless occupation.

STANDARD FOR SEDIMENTATION-RATE

The British Standards Institution has now turned its attention to tubes for estimating the sedimentation-rate of red blood-cells. This attention is timely since at present the results of different workers are often not comparable. The standard textbooks list up to six methods of estimating sedimentation-rate. The proposed standard adopts only two methods: (1) the Westergren, both normal and a micro modification, and (2) the Wintrobe. This limitation is certainly sensible in this country, where most laboratories use one or the other of these two techniques. The tuberculosis departments and sanatoria tend to rely on the Westergren method, while the clinical laboratories of general hospitals on the whole prefer the Wintrobe method.

The Wintrobe technique was originally designed so that the packed red-cell volume—or hæmatocrit—could be determined on the sample of blood that had first been used for determining the sedimentation-rate; and Wintrobe used the hæmatocrit value to "correct" for anæmia, which increases the sedimentation-rate. Of late years the validity of this correction has been challenged; but the technique remains a useful and simple one. By the original Westergren method the tube had a graduated length of 200 mm. and a bore of about 2·45 mm. Such a tube needs about 1·5 ml. of blood to fill it, which in adults is easily obtained by venepuncture. In children, however, venepuncture may not be convenient or desirable, and the institute's technical committee has therefore recommended in addition a smaller tube of Westergren type. Experiments showed that the bore of the tube must be at least 1·5 mm.; so the committee proposes the adoption of a tube with a graduated length of 100 mm. and a bore of 1·65 ± 0·15 mm., which can be filled with only 0·25 ml. of blood.

The standard specifications seem unexceptionable—except for the micro Westergren tube they correspond to types already in use—and they ensure minimal variation of tube-length, tube-bore, and, in the Westergren tubes, size of the lower orifice. Truly comparable results should therefore be obtained with these tubes.

The committee, recognising the importance of proper stands, propose patterns for the three types of tube. They also give valuable instructions for cleaning the

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1. Hirst, G. K. *J. exp. Med.* 1942, 76, 195.
2. Anderson, S. G. *Aust. J. exp. Biol. med. Sci.* 1948, 26, 347.
3. Gottschalk, A., Lind, P. E. *Nature, Lond.* 1949, 164, 232.
4. Gottschalk, A. *Ibid*, 1951, 167, 845.
5. Tamm, I., Horsfall, F. L. jun. *Proc. Soc. exp. Biol., N.Y.* 1950, 74, 108.
6. Gottschalk, A. *Nature, Lond.* 1952, 170, 662.
7. Odin, L. *Ibid*, p. 663.
8. Fazekas de St. Groth, S. *Ibid*, 1948, 162, 294.

tubes. The British Standards Institution asks that comments on this draft standard should reach its offices at 24, Victoria Street, London, S.W.1, not later than Nov. 27.

DICKENS AND THE DOCTORS

FEW real doctors have ever achieved the stature of those concocted by Charles Dickens—though Lord Webb-Johnson, after hearing the Lloyd-Roberts lecture at the Royal Society of Medicine on Oct. 29, tried to make out a case for Lloyd-Roberts himself. The meeting had just had the felicity of hearing Mr. Bernard Darwin on "Dickens's Doctors"; and if they had not known their luck from the start they would have been brought to a proper sense of it by a reminder from Dr. F. M. R. Walshe, F.R.S., the president, that the first three Lloyd-Roberts lectures were on defects of man's structure, racial degeneration, and criminal law and insanity.

Mr. Darwin was somewhat hampered by the richness of his material: we can almost fancy the vast company of doctors on the Dickensian Medical Register a-cocking their medical eyes in an attempt to catch his. Dickens knew more about medicine than the average layman, though a trifle weak on spontaneous combustion. He laughed at doctors, but he liked them too; as we may be sure, Mr. Darwin thinks, from the fact that he had no murderers among them—despite the fact that Dr. William Palmer was at the height of his poisoning practice at about the time he was writing. Many of his doctors are anonymous; and some are spurious, like Doctor Marigold (who was christened after the physician who produced him), or unqualified, like Mr. Alfred Jingle (who asserted that he had saved the life of a female, who had taken prussic acid, by means of a stomach-pump which he happened to have in his portmanteau); and one was a marionette who had trouble with his wires, and delivered his opinions into the air. But among the regular practitioners Dickens had a splendid range, from Sir Tumley Snuffin and Sir Parker Peps (the only two doctors he ever knighted), to poor Mr. Chillip who preferred darkness and draughts to the formidable company of Miss Trotwood, when David Copperfield was on the way. That dull dog Allan Woodcourt in *Bleak House* reminded Mr. Darwin of a don whom he had once asked for an opinion of a dead colleague: "He replied with incredible venom, 'Oh you couldn't possibly *dislike* him.'" Then there was that splendid humbug Mr. Jobling, M.R.C.S., who examined patients for the Anglo-Bengalee Insurance Company, and had a way of smacking his lips and saying "Ah!" Dr. Manette in *A Tale of Two Cities*, with his compulsive reversions to shoemaking, is perhaps more interesting as a patient than as a doctor; and the doctor in Sam Weller's story of the patient who died on principle is mainly notable, Mr. Darwin thinks, for his courageous readiness to admit he did not know how many crumpets would prove fatal. But the doctors whose company he particularly favours are Bob Sawyer of Guy's and Jack Hopkins (who told the story of the rattling fine child who swallowed the necklace) of Barts. Dickens was so fertile, and so uncertain whether he had written enough words to fill an instalment, that he often threw off a new character just to stop a gap. Perhaps Bob Sawyer arrived in this way—certainly Sam Weller's laconic announcement "There's a couple of sawbones downstairs" does not prepare us for this "great creature" (as Chesterton described him). Some find Mr. Sawyer noisy and vulgar, but Mr. Darwin defended him as though he were a favourite younger brother. He smoked in the street: but today who does not? He drank too much: and so did Mr. Pickwick. He called waiters by their Christian names: but Mr. Darwin knew of respectable institutions where distinguished members of our profession call waitresses by their Christian names. Perhaps his habit of sending his boy round to leave bottles of medicine at the wrong houses, and of getting himself called out of church as though to an urgent case, might be regarded as infamous conduct in a professional respect; but then he was so ready to be helpful—to bleed all and sundry on the slightest pretext—and so sound on the curative properties of hot punch. Much must be forgiven Bob, and Dickens clearly forgave him, for he left him—however unbelievably—trying the effects of a little abstinence. Parting wistfully from his noble and but half-explored theme Mr. Darwin exhorted readers of Dickens in the words of Mr. Toots to his wife: "Do, do endeavour to remember the medical man. If you can't, it's of no consequence . . ."

BAROTRAUMA

BAROTRAUMA is by no means a new condition, but its importance increases as more and more people fly in civil and military aircraft. The ears, paranasal sinuses and teeth can all be affected by changes of pressure; and the three types of barotrauma are described by Box[1] in a recent paper.

Otitic barotrauma is a condition in which the ear is damaged when a difference in pressure exists between the middle ear and the surrounding atmosphere. It occurs in aircraft or in caissons, usually when the atmospheric pressure rises during descent, for the normal eustachian tube opens spontaneously during ascent, but not during descent. The tensor muscles of the palate must contract to allow air to enter the tympanic cavity, and this can be done by swallowing, yawning, or auto-inflation by Valsalva's method; but there comes a point at which the pressure difference is so great that the compressible portion of the tube becomes squeezed by the external pressure, and when muscular action is no longer capable of opening it. One or both ears may be affected, and the symptoms produced are pain (which may be very severe), deafness (usually conductive in type), tinnitus (sometimes of alarming intensity) and occasionally vertigo. The changes in the tympanic membrane vary from a slight indrawing, through a stage of congestion and interstitial hæmorrhage, to actual rupture. Effusions of clear fluid or blood into the middle ear may give the appearance of bubbles or of a blue bulging drumhead. The ear may be damaged in this way if the tube fails to open because the passenger does not know what to do, because he is asleep, or because of congestion in his upper respiratory tract. Other causes are hypertrophy of the lymphoid tissue in the tube and malocclusion of the teeth. Ideally flying should be avoided during a severe upper respiratory infection. Treatment of the established condition consists of introducing air into the middle ear either through the eustachian tube or the tympanic membrane. Box mentions only the first of these, and states that politzerisation or catheterisation may be required; but Bateman[2] recommends simple paracentesis of the drumhead as a better method. It can be performed without an anæsthetic and affords immediate relief of pain. The small incision heals very rapidly, and is rarely, if ever, followed by secondary infection of the middle ear. Recurrent attacks of otitic barotrauma may be due to hypertrophy of the lymphoid tissue of the tube. Irradiation, applied either by external or local means, has been used in such cases, but the results are equivocal and the method is not generally accepted.

The pain of sinus barotrauma is also more pronounced during descent, and nasal congestion may lead to the "vacuum" type of headache caused by a blocked ostium. Dental barotrauma, on the other hand, usually occurs during ascent. Molars are particularly affected, and the pain is felt most often in recently filled teeth.

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1. Box, N. E. H. *Med. J. Aust.* 1952, i, 538.
2. Bateman, G. H. *In* British Surgical Practice, London, 1948; vol. III, p. 282.

Public Health

TUBERCULIN SENSITIVITY OF CHILDREN IN THE EAST END OF LONDON

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THIS paper reports the results of Mantoux tests done on 579 children at the Queen Elizabeth Hospital for Children between November, 1950, and November, 1951. It also gives the results obtained in 262 of these children on whom concurrent tests were performed with tuberculin jelly (1) in the ordinary way and (2) on flourpapered skin. The 579 children were either inpatients or attending the outpatient or casualty departments of the hospital, and the vast majority of them were not suspected of, or receiving treatment for, tuberculosis.

METHOD OF MANTOUX TEST

To ensure uniformity all the tests were made and read by the same observer. Each child received an initial injection of 0·1 ml. of 1 : 10,000 Old Tuberculin into the skin of the flexor aspect of the left forearm and an equal volume of control material in the right forearm. Subsequent injections of equal volumes of 1 : 1000 and 1 : 100 Old Tuberculin were given if there was no reaction in the preceding injection. All the results were read 72–96 hours after the injection, the criteria for a positive result being the appearance of an area of erythema or erythematous infiltration at the injection site whose greatest diameter equalled or exceeded 5 mm. in the absence of similar change in the control area. Separate syringes were used for each strength of Old Tuberculin and for the control, a clean needle being used for each injection.

METHOD OF PERCUTANEOUS TESTING

The interscapular area was first cleaned with acetone, and a strip of skin to the right of the midline was gently stroked five times with flourpaper (this was cut into convenient strips 1 in. wide by $1^1/_2$ in. long, a fresh piece being used for each child). Allen & Hanburys' 60% tuberculin jelly was applied to an oval area on each side of the midline and control jelly to similar areas below. The jellies were covered with adhesive plaster for 48 hours, instructions being given for the plasters to be kept dry during this period. The results were read 72–96 hours after the test, a positive result being inferred from the appearance of five or more vesicles or papules within the site of application of the jelly, provided there was no similar change in the control-jelly area. A note was also taken of the presence or absence of erythema.

TABLE I—RESULTS OF MANTOUX TESTS ON 579 CHILDREN

Age (yr.)	Clinically tuberculous				Clinically non-tuberculous					
	Home contact		No contact		Home contact				No contact	
	Open				Open		Closed			
	M +	M −	M +	M −	M +	M −	M +	M −	M +	M −
0–1	..	..	..	..	..	2	..	3	..	46
1–2	3	..	1	..	2	4	..	..	..	64
2–3	..	..	..	..	..	..	..	..	2	47
3–4	1	..	2	..	2	2	..	..	2	59
4–5	..	..	1	..	..	2	..	4	10	53
5–6	..	..	..	..	..	..	..	..	7	60
6–7	..	..	..	..	2	..	..	..	2	37
7–8	..	..	..	..	..	..	..	..	2	47
8–9	..	..	1	..	..	..	..	..	4	35
9–10	..	..	..	..	..	..	..	..	4	16
10 or more	..	..	..	..	..	..	..	..	9	41
Total	4	..	5	..	6	10	..	7	42	505

RESULTS OF MANTOUX TESTS

A questionnaire was completed for all the children tested. This contained clinical, family, and social details as well as a classification of the child as regards active tuberculosis, presence or absence of home contact with tuberculosis, and the results of intradermal and percutaneous tests. An analysis of these results is presented in table I. 579 children were Mantoux-tested, of whom 57 were Mantoux-positive.

DISCUSSION

An accurate assessment of the value of the tuberculin reaction in the diagnosis of tuberculous infection in any age-group depends directly on a knowledge of the percentage of positive reactors among clinically non-tuberculous persons in that age-group. D'Arcy Hart (1932) has pointed out that it is also important for the number of home contacts in the series not to be unduly high. Since the number of home contacts in any collection of children is necessarily fortuitous, it seems to be important, in assessing the diagnostic value of the tuberculin reaction, to exclude them along with all cases of proven tuberculosis.

TABLE II—PERCENTAGES OF MANTOUX-POSITIVE AND CLINICALLY NON-TUBERCULOUS CHILDREN WITHOUT HOME CONTACT IN 1929, 1931, AND 1950–51

Survey	Age-group (yr.)			
	0–2	2–5	5–10	10–15
1929 (Hart 1932)	4·5	15	27	59
1931 (Dow and Lloyd 1932)	13·6		31·2	54·4
1950–51 (present report) ..	4·94		9	18

All children with proven tuberculosis gave positive Mantoux reactions. Of the clinically non-tuberculous children 37·5% of those with open home contact, and none of those with closed home contact, gave positive Mantoux reactions. 7·68% of clinically non-tuberculous children without home contact were Mantoux-positive. None of the infants aged less than 1 year were Mantoux-positive.

The last published series of Mantoux tests on London children were made in 1929 (Hart 1932) and 1931 (Dow and Lloyd 1932). In the last twenty years a great many factors may have conspired to modify the incidence of tuberculous infection in London children, and most authorities suggest that it has fallen. Table II shows clearly that the percentage incidence of Mantoux positivity is in fact very much less in 1950–51 than in 1929 and 1931.

In very general terms the percentage incidence of Mantoux-positive children in each age-group in 1950–51 was about a third of those in 1929 and 1931. Roughly speaking, one in every twenty between 0 and 5 years is Mantoux-positive, one in every ten between 5 and 10, and one in every five between 10 and 15. These results seem to indicate that the determination of tuberculin reactivity is a useful diagnostic measure even up to the age of 15. However, the number of children over 10 who were tested was relatively so small (only 50) that much weight should not be placed on the percentage figures for this group.

TABLE III—MANTOUX REACTIONS IN CHILDREN GROUPED ACCORDING TO NUMBER OF ROOMS OCCUPIED PER HEAD IN FAMILY

No. of rooms per head	Mantoux-positive	Mantoux-negative
Up to $^1/_4$ ..	3 (*5·5%*)	16 (*3·2%*)
$^1/_4$–$^1/_2$ ..	5 (*9·1%*)	66 (*12·7%*)
$^1/_2$–$^3/_4$ ..	24 (*43·6%*)	167 (*32·6%*)
$^3/_4$–1 ..	16 (*29·1%*)	162 (*31·7%*)
1–$1^1/_2$ ..	7 (*12·7%*)	75 (*14·7%*)
$1^1/_2$–2 ..	..	22 (*4·3%*)
More than 2 ..	..	4 (*0·8%*)

It was thought possible that the war-time evacuation of children from London might have had an influence in *preventing or in promoting tuberculous infection.* A note was made in the case of all children who were born before Jan. 1, 1945, to say whether or not they had been evacuated. Of 199 such children 63 had been evacuated. Of the 199 children 24 were Mantoux-positive, and 9 of these had been evacuated; 175 were Mantoux-negative, and 54 of these had been evacuated. Hence, of the Mantoux-positive children 37·5%, and of the Mantoux-negative 30·9%, were ex-evacuees. The difference between these two figures is too small to infer that evacuation raised the chances of becoming Mantoux-positive.

More interesting deductions can be made from a consideration of the details of housing and family income in relation to the percentage incidence of tuberculin sensitivity. Table III shows the numbers of Mantoux-positive and Mantoux-negative children grouped according to the number of rooms per head in the family. The percentage figures relate to the total number Mantoux-positive and Mantoux-negative, and these are presented graphically in fig. 1. From the figure and the table 12 children were omitted because they came from institutions or had been in hospital for a long time.

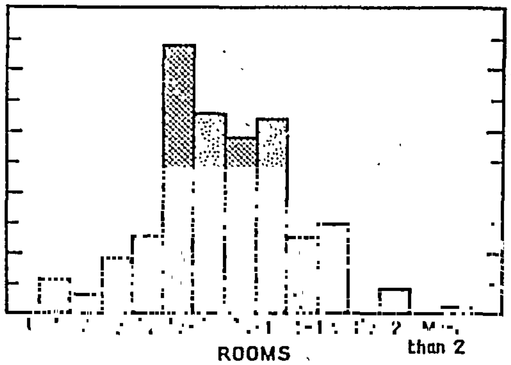

Fig. 1—Percentages of Mantoux-positive and Mantoux-negative children grouped according to number of rooms per head in family: hatched, Mantoux-positive; stippled, Mantoux-negative.

From these figures it will be seen that more than 58% of the Mantoux-positive children came from families with $^3/_4$ of a room per head or less, and none from those with $1^1/_2$ or more rooms per head. About 81% of all the children lived in families with 1 or less room per head, and nearly 50% with $^3/_4$ or less room per head.

Table IV and fig. 2 are similarly arranged to show the influence of the amount of housekeeping money available per head in the family per week. Here the most striking features are the relatively large number of positive reactors from families with less than 10*s.* per head devoted to housekeeping expenses; nearly 30% of positive reactors are from families with up to 20*s.* per head in the family. The figure and the table also show that the bulk of these East End families spend between 15*s.* and 35*s.* per head on food, clothing, and shelte 16 children were omitted: 12 were from institutions o had been in hospital a long time, and for 4 others th details of *housekeeping money were not known.*

RESULTS OF PERCUTANEOUS TESTING

A comparison was made of the ordinary tuberculi jelly test and the flourpaper technique. 262 childre were tested, and results are detailed in tables V and VI.

DISCUSSION

In 1946 Deane described a new way of performin the percutaneous tuberculin-jelly test which he claimed enhanced its reliability. This consisted in gentl stroking of the selected skin area with an abrasive afte preliminary cleansing with acetone. Deane used cabinet-maker's sandpaper no. 0, lightly abrading the skin with five or six gentle strokes before applying the jelly. 40 children, positive to Mantoux 1 : 1000, were tested with the ordinary jelly technique and his modified method. The former gave 35 positive results (87·5% agreement with the Mantoux test) and the modified method gave 40 positive results (100% agreement).

TABLE IV—MANTOUX REACTIONS IN CHILDREN GROUPED ACCORDING TO WEEKLY AMOUNT OF MONEY SPENT ON FOOD, CLOTHING, AND RENT PER HEAD IN FAMILY

Housekeeping money per head per week (*s.*)	Mantoux-positive	Mantoux-negative
Up to 10	4 (*7·3%*)	1 (*0·2%*)
10–15	..	13 (*2·5%*)
15–20	13 (*23·6%*)	85 (*16·7%*)
20–25	6 (*11·0%*)	138 (*27·1%*)
25–30	12 (*21·8%*)	112 (*22·0%*)
30–35	12 (*21·8%*)	89 (*17·5%*)
35–40	5 (*9·0%*)	30 (*6·0%*)
More than 40 ..	3 (*5·5%*)	40 (*8·0%*)

Dick (1950) asserted that sandpaper no. 0 was too coarse, and advocated the use of a finer paper known *in* the trade as cabinet-maker's flourpaper. In his investigations he gave six gentle strokes with the flourpaper after cleansing the skin with acetone. Plaster was applied over the jelly for 48 hours, and the results were read 24–48 hours after its removal. Erythema was ignored, but four or more vesicles at the site of *application* of the jelly were regarded as a positive result. By this technique Dick claimed that, with a jelly of Old Tuberculin 60%, results approximated to those of an intradermal Mantoux test of 1 : 1000.

In a large series of tests on subjects aged 5–20 he found "two apparently false positives by intradermal standards among a total of 224 positive to the modified jelly test—that is, rather less than 0·9%. In a comparative test of the flourpaper method properly executed and grossly over-used there was no evidence of an increased incidence of false positive reactions. Dick also compared the relative efficiency of three jellies: 0·2% P.P.D. jelly (designed approximately to equal the tuberculoprotein content of undiluted O.T.); 60% Old Tuberculin jelly; and 85% Old Tuberculin jelly. The 0·2% P.P.D. jelly was definitely inferior to 60% Old Tuberculin

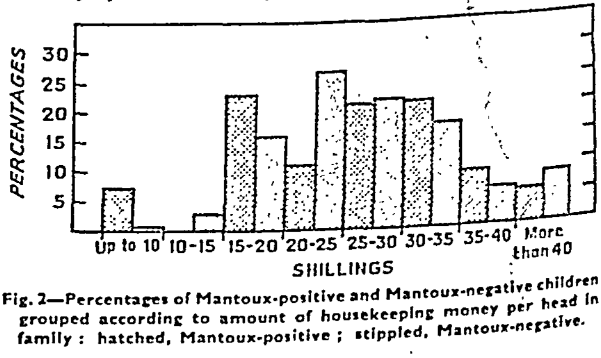

Fig. 2—Percentages of Mantoux-positive and Mantoux-negative children grouped according to amount of housekeeping money per head in family: hatched, Mantoux-positive; stippled, Mantoux-negative.

TABLE V—RESULTS OF MANTOUX AND PERCUTANEOUS TESTS IN 262 CHILDREN

Percutaneous tests	Mantoux-positive (24)			Mantoux-negative 1 : 100 (238)
	1 : 10,000	1 : 1000	1 : 100	
Jelly test } + Flourpaper }	14	..	..	2
Jelly test } − Flourpaper }	..	1	3	192
Jelly test + Flourpaper −	1	..	..	..
Jelly test − Flourpaper +	..	3	2	44
Total	15	4	5	238

jelly, and the 85% Old Tuberculin jelly had no advantage over that of 60%.

Lendrum (1951) reported his results on a large series of Portsmouth children and young adults. He found that Old Tuberculin jelly applied by the flourpaper technique gave 98·4% agreement with 10 tuberculin units (0·1 mg.) of Old Tuberculin intradermally. He also used a 60% P.P.D. jelly but found it to be inferior to Old Tuberculin jelly.

Clark (1951) reported a series of 1499 children who were Mantoux-tested and also had Old Tuberculin jelly applied to skin previously rubbed vigorously with ether. There were identical results in 1440 cases (96·06%).

TABLE VI—RESULTS IN TABLE V DIVIDED INTO AGE-GROUPS

Percutaneous tests	Age-group (yr.)											
	0–5 (137)				5–10 (102)				10–15 (23)			
	Mantoux +			M −	Mantoux +			M −	Mantoux +			M −
	1 : 10,000	1 : 1000	1 : 100		1 : 10,000	1 : 1000	1 : 100		1 : 10,000	1 : 1000	1 : 100	
JT } + FP }	7	..	..	..	4	..	..	..	3	..	..	2
JT } − FP }	..	1	..	101	..	..	3	74	..	..	..	17
JT + FP −	..	..	..	..	..	..	..	..	1	..	..	..
JT − FP +	..	1	1	26	..	2	1	18	..	..	..	..
Total	7	2	1	127	4	2	4	92	4	..	..	19

Tables V and VI show the results obtained in concurrent tests with tuberculin jelly by the ordinary method and with flourpaper, compared with the Mantoux reaction. 262 children aged 0–15 were tested. Of these 24 were Mantoux-positive (9·16%). Congruous results were obtained in 206 (78·62%) and incongruous in 56 (21·37%). These incongruous results, further analysed, show that the jelly test and the flourpaper test both disagreed with the Mantoux test in 6 instances; the jelly test disagreed with the flourpaper test and the Mantoux test in 5 instances; and the flourpaper test disagreed with the jelly test and the Mantoux test in 45 instances.

The ordinary jelly test disagreed with the Mantoux test in 11 cases (4·2%). Of these, 9 jelly tests were negative with positive Mantoux reactions, and 2 jelly tests positive with negative Mantoux reactions.

The flourpaper test disagreed with the Mantoux test in 51 cases (19·5%). Of these, 5 flourpaper tests were negative with positive Mantoux reactions, and 46 (17·5%) were positive with negative Mantoux reactions. In this series the flourpaper test gave 23 times as many false positive readings as did the ordinary jelly test, and missed giving a reaction in 5 cases as opposed to 9 cases with the jelly test. These 5 misses represent an error of 1·9% of the total.

Table VI shows the results in three 5-year age-groups.

In 137 children aged 0–5 years tested there were 108 congruous results and 29 incongruous results (21·17% disagreement). Of these children 7·3% were Mantoux-positive; 5·1% had positive ordinary jelly tests; and 25·5% had positive flourpaper tests. The 102 children aged 5–10 years gave 78 congruous and 24 incongruous results (23·5% disagreement). Of these children 9·8% were Mantoux-positive; 3·04% had positive jelly tests; and 24·5% had positive flourpaper tests. The 23 children aged 10–15 gave 20 congruous and 3 incongruous results (13·04% disagreement); 17·4% were Mantoux-positive; 26·1% were jelly-positive; 21·7% were flourpaper-positive.

These results do not suggest that false positive reactions are much commoner in infants and young children under 5 with the flourpaper technique than in older children. In all infants under 1 there were no reactions with intradermal or percutaneous tests. In the age-group 0–5 there were 26 false positives with the flourpaper test (19%) against 18 aged 5–10 years (17·6%).

The flourpaper tuberculin-jelly test seems to be superior to the ordinary tuberculin-jelly test as an indicator of tuberculin insensitivity, but is apt to give rise to a high percentage of false positive reactions; hence positive results require checking by intradermal tests. Possibly the aberrant reactions with tuberculin jelly applied to the flourpapered skin are due to one or more of the proteins other than tuberculoprotein present in Old Tuberculin.

SUMMARY

The results are presented of a Mantoux survey of 579 children from the East End of London.

None of the infants aged less than 1 year were Mantoux-positive. 547 children were clinically without tuberculous infection and gave no history of home contact. Of these, 42 were Mantoux-positive (7·68%). The incidence of these children in three 5-year age-groups was:

0– 5 years	.. ..	4·94%
5–10 years	.. ..	9%
10–15 years	.. ..	18%

These percentages are roughly a third of those for comparable groups reported by D'Arcy Hart (1932) and Dow and Lloyd (1932). Broadly speaking, one in every twenty aged less than 5 years, one in every ten aged 5–10, and one in every five aged 10–15 is Mantoux-positive.

More Mantoux-positive children came from families with the smallest amount of living space in the home, and from families with the smallest incomes.

Comparative surveys of the ordinary tuberculin-jelly test and the flourpaper technique with intradermal control are reported. 262 children were tested. The ordinary jelly test disagreed with the Mantoux test in 11 cases (4·2%), of which 2 were false positives. The flourpaper jelly test disagreed with the Mantoux test in 51 cases (19·5%), of which 46 were false positives.

I wish to thank the research committee of the Queen Elizabeth Hospital for Children for permission to make these tests; the physicians and surgeons of the hospital for allowing me to make them on their patients; and Dr. H. M. M. Mackay and Dr. R. H. Dobbs for their encouragement and advice.

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Lead Poisoning from Nursery Cot

An 11-month-old boy, whose death from lead poisoning was the subject of an inquest at Maesteg,[1] was poisoned when he chewed the paint off his cot. The cot was originally painted by the manufacturers with a harmless paint, but a lead-containing paint was used by the parents to redecorate it. A recent article in our columns[2] pointed out that lead paint in the nursery is the commonest cause of lead poisoning in children in this country.

Training in Mothercraft

The London County Council have decided that the rehabilitation of mothers whose "home circumstances and ill health are such that they have no control over their children and little understanding of how to bring up the family" may reasonably be considered to be included in the duties assigned to local authorities by the National Health Service Act, 1946. As an experiment the council therefore propose next year to provide training in mothercraft for ten women during 1952–53. The health visitors of the council will continue to help many of these women in their own homes, but where this is not possible the council plan to send expectant or nursing mothers and mothers with children below school age to recuperative centres for training and reablement. The children may, where suitable, accompany their mothers to the centre.

Infectious Diseases in England and Wales

Disease	Week ended October			
	4	11	18	25*
Diphtheria	25	21	29	[illegible]
Dysentery	192	160	181	255
Encephalitis :				
Infective	1	3	2	[illegible]
Postinfectious	—	—	—	1
Food-poisoning	117	162	114	61
Measles, excluding rubella	4696	5721	7787	9175
Meningococcal infection	29	40	30	21
Ophthalmia neonatorum	32	28	29	23
Paratyphoid fever	23	25	15	8
Pneumonia, primary or influenzal..	371	416	440	519
Poliomyelitis :				
Paralytic	101	92	86	75
Non-paralytic	54	17	33	26
Puerperal pyrexia and fever ..	219	256	254	251
Scarlet fever	1284	1617	1761	1934
Smallpox	—	—	—	—
Typhoid fever	4	2	6	8
Whooping-cough	1126	1078	1076	1206

*Not including late returns.

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[1] *Sheffield Telegraph*, Oct. 23, 1952.

[2] Millichap, J. G., Llewellin, K. R., Roxburgh, R. C. *Lancet*, Aug. 23, 1952, p. 360.

Special Articles

THE CHILD UNDER THE N.H.S.

Discussion by Medical Women's Federation

ONE of the main events of the Medical Women's Federation meeting in London last Saturday was a discussion on The Care of the Child in the National Health Service. Dr. DORIS ODLUM, president of the federation, presided. The chief arguments put before the large audience were (1) that responsibility for the child's medical care is now divided among too many distinct clinics and individuals; (2) that the general practitioner must be given a larger share of the work and become a true family doctor; and (3) that the rivalry between doctors and health visitors, which exists in some regions, must end. The evils were thought to be largely those of inadequate exchange of information and lack of the right education.

Dr. URSULA SHELLEY (London) opened by pointing out that the infant-mortality rate had dropped from 153 in 1900 to 30 in 1950, while such diseases as diphtheria and rickets had almost vanished. This was the fruit of a whole series of measures such as the start of school medical inspections in 1908 and the Maternal and Child Welfare Act of 1918, and the present very high standard of child health in this country was not the work of the N.H.S., though the provision of free medical attention and free hospital treatment for all since 1948 was undoubtedly a valuable additional measure.

The trouble now was not too little medical attention, but too much—of a fragmentary kind. The child was born in hospital; after ten days he went home with his mother, and the health visitor called to see him: later he attended the infant-welfare clinic, which might refer him direct to hospital if he were ill. Alternatively he might be seen for the first time by the family doctor, but in a little while he would come within the purview of the school medical officer, who might refer him to the nutrition clinic, the enuretic clinic, or a whole host of others. When finally he emerged from his school-days he came back to the general practitioner, without a written word of his medical history in spite of all the records which had been compiled by the different services. Mostly each clinic tended to keep its discoveries to itself, and each saw only a part of the child. But the child was not an isolated unit but a member of a family. An uncle's tuberculosis, a father's nasal trouble, a mother's insufficient love, and poverty and overcrowding in the home were all important factors in his existence. The one person who was fitted to know all these factors and assess them, and to follow continuously the child's medical history, was the family doctor. He must be given more opportunity to do work now performed by local-authority clinics. He should do all the immunising and vaccinating of his patients—which should be made compulsory again. He should visit his child patients in hospital and interpret to the parents the hospital specialist's advice. In London a child referred by the school medical officer to the psychiatric clinic might have to wait six months for a diagnostic interview, when a family doctor who knew the full home background could have settled the problem almost at once. Child pyschiatry was a field the general practitioner ought to enter, but he often suffered from lack of confidence or knowledge. He needed refresher courses in pædiatrics, and contact with specialist clinics to guide him, as well as health centres to ensure that he could get an X-ray and laboratory service directly. The training of the medical student needed to be more practical, with less emphasis on rare diseases and special treatments and more about the various clinics and auxiliary workers who existed in the world of practice. There should be some financial inducement to the practitioner to undertake a greater share of child-health work, because it had to be recognised that a child gave much more work than an adult. A man with a family of his own to support could not be expected to occupy his time with this extra work when the capitation fee was the same for child and adult.

Dr. Shelley also pointed out that there was a lack of sufficient long-stay accommodation for children, for instance for those with tuberculosis, physical handicap, or mental defect. This sometimes blocked beds in acute hospitals. It also meant the children were not getting the special rehabilitation they should.

Dr. CHARLOTTE NAISH (York) described how she was dissatisfied with the division of medical responsibility even before the N.H.S., and in 1942 she set aside a surgery afternoon to run her own independent infant-welfare clinic. Although she charged fees for attendance, the mothers came because they preferred the continuity of care by one person, and appreciated the opportunity to have their postnatal examination at the time they brought their children for weighing. She organised a mothers' club and a fathers' club in conjunction with her welfare clinic and found she could thus do very valuable educative work, creating a closer relationship with patients, and also reducing the number of night calls by allaying fears. Since 1950 the local authority had allowed her the services free of a health visitor paid from the rates, which showed how there could be fruitful coöperation between practitioner and public-health worker. Though a practitioner might not know much about preventive medicine he could quickly pick it up. Running his own clinic need not be time-consuming, and the education thus given could help parents to nurse their children at home and so reduce hospital admissions. The home help could do the shopping, and the district nurse might tender useful advice, but only the mother could nurse the child.

Dr. Elspeth Warwick (Nottingham) defended the maternity and child-welfare and school medical services against some of their critics. The work these services did was laid down by law, and some of the comments arose from lack of detailed knowledge of their capabilities and functions. Since 1948 local-authority antenatal clinics had been used less, and more practitioners were giving their patients antenatal advice. This was a pity since the health and mothercraft teaching at the local-authority clinic was a very valuable part of its work, and it was useful for the mother to get to know her health visitor before her baby was born. A way must be found of merging the work of practitioner and local-authority clinic, either by inviting the doctor to see his patients at the clinic premises or by providing him with a local-authority midwife and health visitor. Local authorities ought to invite doctors to periodic conferences, and doctors ought to feel they must attend. Special efforts should be made to bring doctors and health visitors to know one another personally.

Dr. Sylvia Guthrie (Manchester) put in a plea for the maintenance of the special children's hospitals, both because of the special needs of children—for instance in schooling and physiotherapy—and because the sick children's nurse was much better trained there than in the small children's ward of a general hospital. She thought hospitals should invite health visitors on ward rounds, and bring together general practitioner, clinic worker, and specialist in discussion groups.

Dr. Margaret Reed (Cambridge) said she had run an infant-welfare surgery for fifteen years. She felt there was some danger of doctor and health visitor being rivals in the care of the child. As medical officer to the Perse School for Girls she always referred girls to their own doctor. Some of the commonest troubles, however, were postural and could be treated by the physical training mistress. More should be done for the children of problem families, and more provision made for mentally handicapped children.

Dr. Catherine Crane (M.O.H., York) thought the extent to which coöperation between the different parts of the health service already took place had been rather minimised. Many local-authority health committees had coöpted general practitioners, and medical officers of health were on local medical committees. Midwives, district nurses, tuberculosis visitors, and so on, all got on well with practitioners. It was only the health visitor who was shunned, though one practitioner in eight in her area holds regular discussions with a health visitor. But only Dr. Naish had wanted a health visitor at her clinic.

Dr. Margeret Methven (Edinburgh) thought that prevention and early treatment of behaviour problems and neurosis should be the family doctor's province, but he needed more knowledge of the subject, as did the health visitor, while hospital obstetric services ought to be more practically aware of the importance of the mother-child relationship.

In further discussion Dr. Dorothy Taylor (Ministry of Health) said the Ministry had been worried by the opposition to health visitors. They were qualified nurses, who could help with feeding difficulties and the ailing child where lengthy guidance and supervision of the mother was needed. Dr. Mary Crosse (Birmingham) also emphasised their value in educating mothers, and thus doing preventive work. Dr. Audrey Gardham (London) wanted the school medical officer to send a summary of the school-leaver's health record to his family doctor. Dr. Annis Gillie (London) pointed out that many general practitioners did part-time clinic work, which was valuable experience and gave them a foot in both camps.

Dr. Georgie Brodie (lately Ministry of Health) summed up the conference, and praised the work being done at York under a woman medical officer of health. Interchange of information was lacking between one branch of the N.H.S. and another; there was ignorance among the members of the health team of each other's responsibilities and work, and ways must be found of improving this situation. All the same, Britain was the Mecca of the world's child-health workers.

THE JOHN RYLE HEALTH CENTRE

An Experiment at Nottingham

The new health centre at Clifton, Nottingham, was opened by Miss Enid Russell-Smith, an under-secretary of the Ministry of Health, on Oct. 17. The centre has been named after the late John Ryle, first professor of social medicine in the University of Oxford.

The centre is a block of four terraced houses (fig. 1) which were modified during building by providing through communication between all the houses on the ground floor and between two houses on the upper floor. The ground floor is taken up by 4 general practitioners' surgeries, and the upper floor by a small maternity and child-health centre, and two self-contained flats for a resident nurse-secretary and a caretaker. The centre will serve a housing estate which has been going up for the past year. The population at the moment is only 2000, but there will be 22,000–23,000 people living there when the work is finished in four years' time.

The circumstances seem particularly favourable for the successful development of a health centre. The estate is entirely new, it lies about five miles from the centre of Nottingham, and it is separated from the city by a green belt more than a mile wide. The only other dwellings within a mile or so are in a hamlet of about 50 houses, and the nearest existing medical services are two miles away.

The plans in figs. 2 and 3 show the way in which the accommodation is set out.

Ground Floor

Each surgery occupies the ground floor of one house, and has a separate entrance. The surgery has been planned to allow a rapid circulation of patients. The front door opens into a small hall, leading to a waiting-room which comfortably accommodates 15 people. The waiting-room leads in turn to a consulting-room which is the living-room of the ordinary house, the only extra fixture being a washbasin. The examination-room, which would have been the kitchen, is little smaller than the consulting-room, and contains a couch and facilities for sterilisation and urine-testing. A door leads from the examination-room back to the hall.

Communicating doors for the doctors lead from waiting-room to waiting-room. The central "tunnel" which normally goes through to the back of the terrace has been bricked up, and its floor made level with that of the two adjacent rooms. Besides providing a connection between the middle two surgeries, the "tunnel" also acts as a store.

Space and water heating throughout the building is by electricity.

There is a small external store for each house. These are used in various ways—e.g., one store contains an electric incinerator.

The forecourt of the building is paved, and at the back there is a paved area for the parking of cars and prams.

Upper Floor

The accommodation in the local-health-authority centre is small, but it provides useful temporary facilities for the

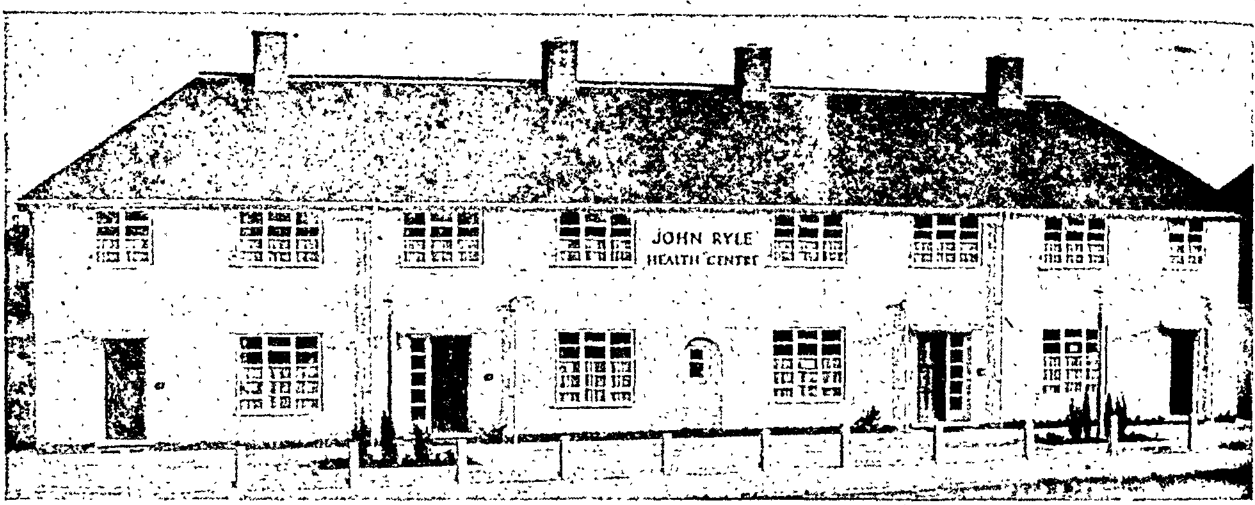

Fig. 1—The John Ryle health centre.

care of mothers and children among the population at the moment, and it will probably cater for a population of about double the present figure.

The two flats for the nurse-secretary and caretaker are reached through the halls of two of the surgeries. Each flat contains a living-room, a bedroom, a kitchen, and a bathroom.

Working Arrangements and Administration

The doctors who use the centre belong to four firms, each having its own surgery, and they began work in the surgeries on Oct. 20.

Records will be kept by the individual doctors. The telephone in each surgery is linked with a switchboard in the office of the centre, which will be staffed between the hours of 9 A.M. and 5.30 P.M. At other times the telephone extensions will be put through to the individual doctors' consulting-rooms or, on rota, to the flat of the caretaker or the nurse-secretary.

An agreement on the lines of the model contract prepared by the British Medical Association, the Ministry of Health, and the London County Council has been completed between the City of Nottingham Corporation and the Nottingham County and City Executive Council, while a suitable agreement of a similar kind has been concluded between the individual firms of doctors and the executive council.

The rental to be paid under these arrangements includes accommodation, telephone facilities, and lighting and heating, but not secretarial and nursing assistance. However, a home nurse lives in a nearby house, and will be able to carry out duties in the doctors' surgeries which she would normally do in the home—a policy already adopted elsewhere in the city.

This kind of centre differs in many ways from those already in use in other parts of the country.[1] The surgeries are entirely separate and self-contained units, and will not be used for any other purpose. The records will not be kept in a central office.

The type of building and accommodation is not very different from that to which most patients are now accustomed. The small suites, including the separate examination-room, provide adequate facilities for all the work of general practice.

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[1] See *Lancet*, 1952, i, 253; *Ibid*, p. 1297; *Ibid*, Oct. 18, 1952, p. 772.

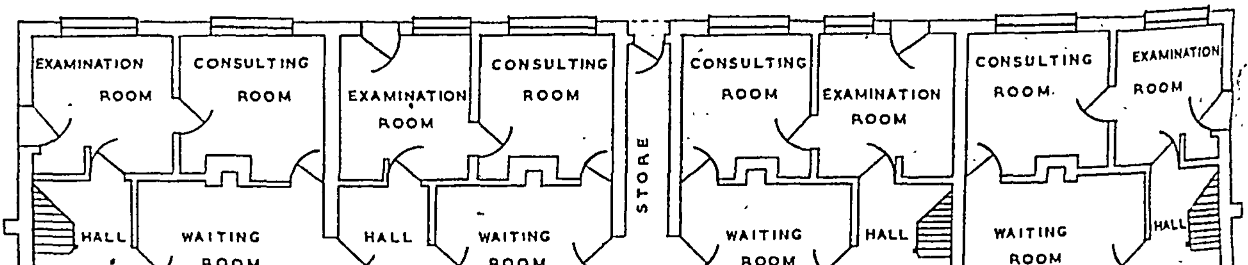

Fig. 2—Plan of ground floor.

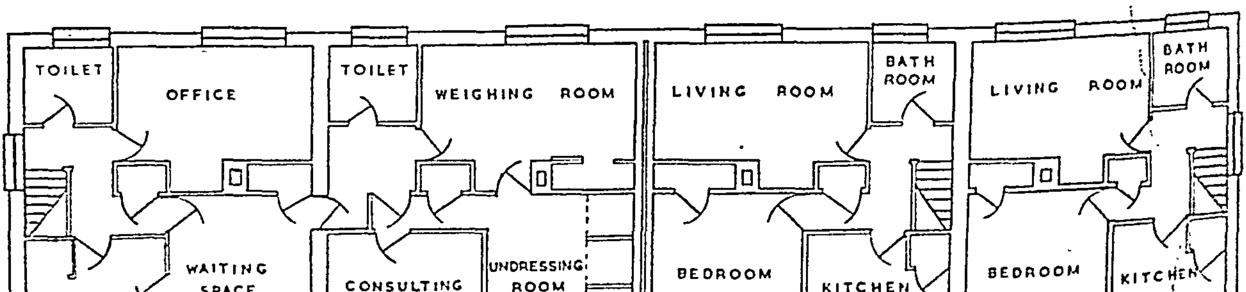

Fig. 3—Plan of upper floor.

In England Now

A Running Commentary by Peripatetic Correspondents

HERE in the Falkland Islands we lead a country life—even in the Colony's capital, Port Stanley, which has about 1100 inhabitants. The main occupation is keeping sheep, of which there are some 650,000. The climate requires them to be hardy, with thick fleeces; and they are bred for wool, not for mutton. In former years sealing played a big part in the island life; but what remains of it is now confined to the West Falkland, where a limited number of sea-lions are killed annually; and in the Colony's coat-of-arms the seal has been replaced by a sheep. The old device, however, remains the same: *Desire the Right!* This sounds very well, but its meaning is not so plain as one would think. Only the other day I came across a pamphlet (commemorating the Colony's centenary in 1933) which explains that "desire" derives from the ship *Desire* in which John Davis discovered the Falklands in 1592, and "right" stands for the Right Whale, a now rare whalebone species which was in the old days plentiful and important for the Falklands.

In other parts of the Southern Hemisphere sheep-farming is impaired by heat-waves, sandstorms, and droughts; but here a long cold spring, with snow showers and blizzards, brings danger to lambing. According to the meteorological records, we have the same amount of annual sunshine as Kew Gardens; but we find it hard to agree with these statistics, for we have to burn a peat fire throughout the year. Living in the Antipodes means, of course, that the sunny side of a house faces north, that the waxing moon here is the waning moon at home, and that I get my hay-fever in January. At the end of one's life one goes "h' East" in the Falklands instead of "going West," as in England.

I found it difficult at first to follow the peculiarity of pronunciation which the "Kelpers" (i.e., Falklanders, from kelp, a seaweed) share with the Cockneys. I know now, of course, what a "hitching heczema" means; yet the other day I felt flabbergasted. One of our workmen at the hospital asked me about his "hydrops." What an educated chap, I thought, and was about to indulge in a lengthy and suitable explanation of this unpleasant condition, when the local sister came to my linguistic rescue.

* * *

A murrain on your metric system and a plague on all these infuriating international units. Why can't we prescribers emulate the electrophysicists with their amperes, volts, and watts? How satisfying to be able to order a hench of cortisone or a kendall of compound F! How stimulating to remember that with insulin one banting equals two bests, and how absolutely right that the adult dose of penicillin should be a whole fleming! But I see one snag. Difficulties might arise if we were asked to prescribe an armour of A.C.T.H., a squibb of isonicotinyl hydrazine, or a pfizer of terramycin.

* * *

"It's turned out quite a nice day!"

"Yes; they were wrong about it on the wireless—they said it was going to rain!"

The second woman's voice was quite aggrieved, as though the B.B.C. had done her a personal injury. Perhaps we are getting to rely too much on weather forecasts: it is seldom nowadays that I hear anyone declare forthrightly that he thinks it looks like rain, or snow, without immediately backing up his opinion by quoting the five-to-eight forecast or, worse still, apologising for having missed it. Just as the amateur musician has been discouraged by the perfection of broadcast performances, so we tend to give up faith in our amateur status as weather-forecasters, and lack the robust self-confidence that shepherds and farmers expressed in proverbial weather lore. Or is it another symptom of our dependence on the Welfare State that we expect protection even from the misfortune of being caught out without our mac?

* * *

Replete with whither articles, may I add one more to the series—"Whither Whither Articles?" It strictly adheres to the formalised style of mellow consideration of the past, general distrust of the present, and fiendish hope for the future characteristic of this genre.

Of proud heritage, these contributions are thought to spring from an unsigned parchment discovered at Cos "Whither Higher Qualifications?" The first definitive article, however, is, without doubt, "Ye Cruele Wynd—Whither doth it go?" (Sir Trumpet Agonie). This aroused the interest of the profession and in quick succession came "Whither Simples?" "Whither Ye Ravenous Leech?" "Whither Flies in Winter?" and "Whither Ye Drastick Purge?" Here the Soviet claim to originality may safely be discarded. Of later contributions "Whither Body-snatching?" (Burke et al.) may be noted.

In the twentieth century medicine moved so rapidly that there was no time to write, or even bother, whither things were going, and attention was only drawn to the neglected branch of medical literature by the outstanding "Whither the Descending Pile?" (Disgustis 1920). This reversed the trend, and henceforth, as a new concept was mooted, quickly in its wake appeared a whither article. A few landmarks may be quoted: "Whither Bloodletting?" (Hirudon 1920); "Whither Sex?" (Haffkrank 1930); "Whither Patients?" (Consultant 1948); "Whither Me?" (Registrar 1952). This technique, it must be admitted, left the field somewhat over-investigated, but out of this seeming danger the modern approach was evolved—viz., "Whither the Public Health?" "Whither Social Health?" "Whither the Nation's Health?" "Whither Community Health?" "Whither the People's Health?" "Whither Group Health?" "Whither State Health?" "Whither Health?"

Such new conceptions leave us, who have the welfare of whither articles at heart, looking confidently to the future. With the Minister's coöperation, and an indulgent Treasury, and as the gap between practitioner and specialist of whither articles closes, we envisage a bright new scene where community medical centres are busily, yet happily, engaged in the production of more, better, brighter, and more literate whither articles. The recent decision to give us trainee whither-article writers and the promise of a future College of Whither-Article Writing cannot fail to have the support and enthusiasm of us all. Proudly then can we, the practitioners of this difficult branch of medical art, say "Whither Do We Go From Here?"

* * *

Whenever I go out with a shotgun I am astonished how seldom the birds fly into my pattern; it seems that they bear a charmed life. Or at least so I thought till I spent an hour at a shooting school, which I can thoroughly recommend as a salutary, if expensive and humiliating, experience. You would think that you could hardly miss those footling little flying saucers lobbed out of a trap, but when you have failed at the first five bobs' worth it pays to listen to your instructor. According to mine the fact that I ever hit anything at all is little short of miraculous, for not only is my weight distributed wrongly but the wrong eye is in control. Further the venerable 12-bore which I have been using these thirty years doesn't fit and casts off to the left. However, all these things are now in process of being put right and next season it will be, I gather, virtually impossible for me to miss anything. In this unlikely event I shall, of course, give up shooting at once as anybody would, but somehow . . .

* * *

The practical psychiatrist—have we found him? The closing paragraph of a letter of application for a clerical vacancy in our hospital makes us think we have him on our staff!

> "I would like to tell you that I have been away from work owing to my nerve trouble, and at the moment I am seeing Dr. B—— in your Psychiatric Clinic, and he suggests I will be much better at work. Anticipating a favourable reply,
>
> Yours . . ."

Letters to the Editor

DENTAL TREATMENT OF CHILDREN

SIR,—In your leading article of Oct. 25 you describe the employment of ancillary workers for the dental treatment of children as an "unexceptionable development." But the evidence in favour of the *immediate* introduction of these ancillaries is hardly as conclusive as you suggest.

The abuse and quackery which flourished before the Act of 1921, after which all entrants to the profession had to obtain a qualification and be registered, have not unnaturally caused some concern as to the possible later results of the introduction of ancillary workers without degrees within the profession. Given adequate safeguards, many members of the profession are in favour of the introduction of these workers, since many routine procedures can be carried out by them under the direction of qualified practitioners, thus freeing the latter for more highly skilled or specialised work. The crux, however, is whether this is the right *time* for their introduction.

Much attention has recently been drawn to the fact that the school dental service is insufficiently staffed and that conservative treatment to preserve children's teeth is quite inadequate. This is unfortunately true; but the emotional aspect of helping the children should not be allowed to distract attention from the wider problem of providing an adequate dental service for all ages. The need for fillings to preserve the teeth may be just as important (or more important) at, say, 18 than at 12, and it is of little value to shift the emphasis from one section of the community to another if the main trouble is that there are far too few dental surgeons.

It is perhaps not generally appreciated that in this country there is one dentist to 4400 of the population, compared with approximately 2600 in New Zealand and 1730 in the United States. That this deplorably low ratio is likely to fall still further in the near future was forecast in the Teviot report 1946. Are we then to recruit and train more dental surgeons, or to fill the thinning ranks with ancillary workers capable of carrying out only limited sections of treatment?

There is one encouraging factor in an otherwise gloomy situation—the very large numbers of students at present applying for entry to the dental schools. But—and here comes the difficulty—these schools are already full to overflowing, and a high proportion of potential dental surgeons has to be turned away to be lost to the profession owing to lack of training facilities. It has been argued that with the shorter course given to ancillary workers more could be trained in the time and the cost to the country would be less. A factual and objective analysis in the *British Dental Journal* of Jan. 1, 1952, has produced, however, some disturbing information on these points. It is shown that the cost of educating an ancillary dental worker in New Zealand in a State school with only a 50% ratio of professional to non-professional teaching staff was only 19% less than the cost of production of a fully trained dental surgeon in the university dental schools. The article points out in addition that the Fulton report from New Zealand shows that of every 100 school dental nurses trained to do fillings 30 will have resigned in five years and 83 in twelve years. The accommodation for training dental surgeons in this country is already inadequate and overtaxed, yet it is this same accommodation which would have to be used for the training of ancillary workers. We should be forced therefore to reduce the output of qualified dental surgeons still further in order to train workers who in the end could only carry out limited forms of treatment.

It is clearly essential that the evidence should be most carefully examined and further statistical information obtained before the country is committed to this form of ancillary worker who appears to cost so much to produce and shows such a high rate of wastage in addition to diminishing still further the number of qualified dental surgeons that can be trained.

As I have said, there is a very real danger that the feeling that adequate treatment must at all costs be provided for children may mask the underlying facts of the situation. It is clearly of little value to provide an adequate service for children up to the age of 16 and then deny this service at a later age. In New Zealand, where dental ancillaries have been employed for thirty years 12% of army recruits examined at the age of 18 years in 1950 needed to have all their teeth removed. It is self-evident that the provision of a school dental service is not the answer to the problem. The suggested form of school dental service employing ancillary workers is, however, itself open to criticism. It is postulated that children's dentistry is simple routine and that workers trained for only half the time of a dental surgeon are quite adequate to fill children's teeth. Yet the fillings in permanent teeth in children have to last the longest and there is a graver responsibility at this time to make sure that the fillings are such that they will still be sound in adult life and not merely failures in extracted teeth.

A sound and adequate service must be provided for adults as well as children. The potential students are there, and more could be recruited. The one thing lacking is accommodation for their training. Surely the immediate answer is to build new dental schools or expand existing ones rather than to adopt an experiment which has so many obvious disadvantages. Panic legislation is seldom good legislation, and it is greatly to be hoped that those responsible will pause for thought before allowing emotional issues to override critical judgment to the detriment of all sections of the community.

London W.1. ALEXANDER B. MACGREGOR.

SIR,—Your leader of Oct. 25, like a similar one some months ago, shows how strongly you sponsor the scheme for creating a class of "ancillaries" similar to the school dental nurses of New Zealand. May I put some of the arguments in favour of opposing such a scheme?

You make several assertions which are quite unacceptable to the experienced dental practitioner:

1. Children's dentistry is far from being "simple routine"; rather the reverse is true. It can only be practised successfully by operators with considerable experience—experience which for the sake of *plain* humanity should be acquired through treating adults!

2. The school dental nurses' scheme of New Zealand is not generally recognised to be an unqualified success. It is wasteful of man-power and national resources, and has retarded the development of dentistry in New Zealand. If the money spent on it had been used for professional training, the treatment of all classes in New Zealand might have been much better.

3. During the passage of the Dentists Bill, 1951, through the House of Lords attempts were defeated to make the employment of ancillaries conditional upon their "personal" supervision by qualified dental surgeons. As the Bill stands, it permits the employment of dental nurses exactly as they are being employed in New Zealand—i.e., as operators nominally supervised by a professional man, but working often more than 200 miles distant from the man who is supposed to carry out this "supervision" and who, as a rule, will not see a particular nurse more than about twice a year. If the intentions of the scheme's sponsors and of H.M. Government are to introduce similar practices in this country, then the expression used in your article "A proposal . . . to employ ancillaries in clinics under professional supervision" is grossly misleading. In the absence of such intentions the determined resistance to amend the Bill so as to require "personal" supervision, is inexplicable.

Your readers may not realise that the New Zealand school dental nurse is in no way comparable to medical ncillaries, but is, as the *Journal of the Irish Dental ssociation* (April, 1952) has pointed out, not an ancillary worker at all in the accepted sense of the word, but rather member of a new profession which has been created without the usual safeguards. The most crushing argument against training school dental nurses in this country t present is that more dental surgeons cannot be trained ecause training facilities are lacking (no *new* dental chools have been opened in this country for almost hirty years !), and that the Ministry of Health has so far ntirely failed to explain *how* the creation of training acilities for dental nurses can but interfere with the much more urgent creation of training facilities for dental urgeons.

London, S.W.15. E. ROSENSTIEL.

SIR,—The questionary from the British Dental Associaion asked general dental service practitioners if they were willing to treat school-children in the school dental ervice on a sessional basis as well as in their own practices, being, therefore, in line with joint circular 22/52 (Ministry of Health), 254 (Ministry of Education) addressed to local authorities on June 30. From the replies received which you have analysed, a substantial amount of assistance is evidently available, although it s agreed that it is insufficient to provide complete treatment for every school-child in Great Britain. Nevertheless this reinforcement to the school dental service is particularly important as a short-term policy because the numerical strength of the school dental service is practically the same as it was in 1938, whereas local authorities since 1944 have assumed increased responsibilities to children in secondary schools and to the maternity and child-welfare groups.

In a letter to the *British Dental Journal* of Feb. 5, I reviewed objectively, but not unsympathetically, the question of the New Zealand dental nurses. I pointed out that their training rendered them technically competent in conservative work, but was inadequate to form a correct diagnosis, and that the great weakness in New Zealand was a lack of proper supervision due to local conditions. In spite of pressure from the dental profession, ably reinforced by Lord Webb-Johnson in the House of Lords, the Government have refused to amend clauses 18–20 in the Dentists Bill to tighten up supervision. In fact these clauses are so loosely worded that, according to competent legal opinion, the whole structure of dental practice in this country is capable of being undermined by the introduction of various classes of ancillaries. Public utterances by Ministry officials have not lessened this impression. It is not surprising under these conditions that the British Dental Association have shown little enthusiasm for the Government's suggestions. If the latter do in fact mean what they say, the relevant clauses can be easily amended to ensure that no other ancillaries are contemplated.

Your concluding paragraph does less than justice to the dental profession. The treatment of children, though, of course, largely routine like other forms of practice, offers in the field of orthodontics opportunities for the development of manipulative and scientific skill equal to those in any other branch of dentistry. The real reasons why so large a proportion of practising dentists appear unwilling to help are very different. The dental treatment of children involves great physical and nervous strain, and the more sympathetic the operator the greater the strain. It is pre-eminently a young person's job, and the dental profession is heavily overweighted by the older age-group due to the influx of practitioners in 1921. Moreover, for some inscrutable reason the Government have decreed that payment for the difficult and highly important work of treating children both in the National Health Service and on a salaried basis shall be lower than that for the treatment of adults.

It may be added that, as far as the local government service is concerned, dentistry still remains under direct medical control, opportunities for advancement to really high positions are non-existent, and there is little to attract the young progressive practitioner.

The solution to the problem of children's dentistry is no easy one, and must remain basically a long-term affair, but the following courses suggest themselves. Recruitment of fully trained dentists to the profession should be increased by every possible means. Conditions of pay and employment in the school dental service should be improved. Ancillaries should be limited to the New Zealand type and employed only in the school dental service under adequate supervision. The latter condition, though impracticable in New Zealand, *can* be and *must* be ensured over here. Overseas experiences suggest also that the total output of the ancillary training schools could be absorbed without difficulty in the school service.

London, W.1. E. E. WOOKEY.

ANÆSTHESIA FOR OUTPATIENTS

SIR,—If a relatively junior anæsthetist may comment on the methods of a master, I should like to discuss a few of the points raised by Dr. Bourne in his article of Oct. 11.

1. I feel that many anæsthetists will not accept Dr. Bourne's provocative statement that " outpatient anæsthesia will not be improved so long as nitrous oxide continues to be used." He agrees that the intermittent thiopentone/nitrous oxide and oxygen sequence (described by Broad and Organe before the late war) is widely regarded as ideal for inpatient anæsthesia. Here the nitrous oxide is not present merely " by tradition," nor is it occupying space in the mixture " which would be occupied to better advantage by oxygen." The analgesic properties of nitrous oxide supplement the narcotic properties of thiopentone—in the presence of very adequate oxygenation. If further evidence of the analgesic properties of nitrous oxide is required, one has only to inhale a few breaths of 50% nitrous oxide and oxygen. In outpatients the disadvantage of this technique is the long-continued effect of thiopentone—not the presence of nitrous oxide.

2. Dr. Bourne mentions the disadvantage of salivation caused by cyclopropane. In my hands 50% cyclopropane in oxygen causes most inconvenient salivation in a large proportion of unpremedicated patients. The routine administration of atropine, or its derivatives, would cause unpleasant postanæsthetic symptoms for the ambulant patient.

3. I suggest that the quick induction and the speed of the cyclopropane anæsthesia described by Dr. Bourne are not necessarily advantageous. His account of fifteen children undergoing dental extractions, taking an average of 3 minutes each (including presumably the seating of the patient in the chair, his reassurance, and finally his replacement by another patient), suggests the type of " smash-and-grab " technique deprecated by Gillies [1] and discussed in Dr. Bourne's paper. The replacement of the face mask and potentiation of anæsthesia in the midst of this dental haste, " as when a tooth was broken," must have its dangers.

4. The practised anæsthetist can usually induce nitrous oxide anæsthesia without the patient ever knowing that a mask has been on his face, unpleasantness being reduced to a minimum. This applies also to cyclopropane, though in the technique described by Dr. Bourne the mask is placed on the face at the outset—possibly somewhat frightening to small children who have just been hurried into the dental chair.

5. A sequence taught by Dr. I. W. Magill, and many other authorities,[2] consists in using cyclopropane to supplement nitrous oxide and oxygen. Here, the cyclopropane replaces the thiopentone of Broad and Organe's technique and, by virtue of its speed of elimination, disposes of the disadvantages of giving thiopentone to outpatients. It is known that 10% cyclopropane in oxygen maintains light anæsthesia, whilst 6% cyclopropane in oxygen will produce unconsciousness in the average person.[3] Experience shows that 6%

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1. Gillies, J. *Proc. R. Soc. Med.* 1945, 38, 235.
2. Gillies, J. Textbook of Anæsthetics. Edinburgh, 1948; p. 297.
3. Hewer, C. L. Recent Advances in Anæsthesia and Analgesia. London, 1948; p. 51.

cyclopropane in a nitrous oxide/oxygen mixture (20–25% oxygen) will maintain light anæsthesia in most cases.

By this method for most outpatient operations induction is with nitrous oxide. Oxygen and cyclopropane are soon introduced, the cyclopropane enabling the percentage of nitrous oxide to be reduced, whilst the oxygen is increased. The nitrous oxide (being analgesic even in the presence of a high percentage of oxygen) supplements the small percentage of cyclopropane. *Cyclopropane is not present in high enough concentration* to cause salivation, nor is nausea and vomiting so common as after inhalation of cyclopropane/oxygen mixtures. A typical "maintenance mixture" would be: Oxygen 1000 c.cm. per min., cyclopropane 200–300 c.cm. per min., nitrous oxide 3000–4000 c.cm. per min. For long-continued administration an absorber may be used. For dental operations a nasal mask relieves the dentist of the worry of a time limitation.

R.A.F. Hospital, Rinteln,
B.A.O.R.

H. BARRIE FAIRLEY.

THE CAUSE AND TREATMENT OF LEG ULCERS

SIR,—While reading Dr. Anning's excellent article (Oct. 25), I was struck by the curious anomaly that leg ulcers are commoner in those who stand at work than in those with sedentary occupations. At first thought this might not seem unexpected; but surely the leg muscles, the motive force of the "leg muscle pump," are more active when one is standing. The muscles of the most immobile of standing workers are in a state of ever-changing tonus to maintain balance; whereas the whole of the musculature of the sedentary worker, below the diaphragm, is comparatively flaccid for hours on end.

I suppose that the explanation is that in these cases the leg muscle pump is rendered useless by inefficient valves, and gravity becomes the most important factor; and thus, when Dr. Anning states that after compression has been applied the patient must be encouraged to walk, the benefits of walking are really only psychological (but no less important for that). To the undeluded physician, however, this should only indicate that well-applied compression can overcome the effects of gravity—not that it can make a valveless pump work.

London, E.17.

ROBERT HIGH.

SIR,—Dr. Anning reiterates his opinion that varicose veins are an uncommon cause of leg ulcers. This is based upon his personal observation of 715 patients, of whom no less than 79% are classed as post-thrombotic whilst a mere 7% are listed as truly varicose. This indeed is a small number; but let us take heart, for I have a feeling that in his endeavour to shift the pendulum of venous opinion Dr. Anning is merely putting the clock back, to conform with the myriad historical references with which his address is so liberally spiced.

I wonder whether he realises just how highly selected his patients are by the time they figure in his statistics. The family doctor has filtered off and successfully treated many of the varicose ulcers before they reach the hospital. In the hospital itself, the varicose-vein clinic achieves swifter results with the varicose ulcers than with their post-thrombotic brethren; and it is these latter—the long stayers—who are likely to be referred to the final dermatological court of appeal over which Dr. Anning so skilfully presides. There, they take their place quietly, uncomplainingly, and most misleadingly in his ætiological histogram of leg ulceration.

Can it be this conditioned bias towards a deep venous causation which makes him exclude varicose veins from his list of sources of failure of *the leg muscle pump*? It is curious that, in quoting a selection of Walker's (1950) figures in support of his thesis, he omits the very ones which demonstrate that superficial varices *alone* can lead to a deterioration of the muscle-pump mechanism.

Indeed, in his remarks on varicose veins Dr. Anning shows himself to be sadly *out of touch with contemporary* specialist opinion. The fact that his series includes 56 patients in whom saphenous ligation either exacerbated, precipitated, or failed to *prevent* ulceration, is merely a painful and poignant commentary on the poor treatment they had received at other hands.

London, W.1.

STANLEY RIVLIN.

SUBLINGUAL HEPARIN

SIR,—We were interested to see last week the report by Mr. Tomich and Mrs. Woollott (p. 888) on the sublingual administration of heparin. In March of this year we published results of a clinical trial of heparin given in this way, and we reported our failure to influence the coagulation-time with as much as 500 mg. of heparin sodium placed under the tongue.[1] *Our findings agreed* with those of McDevitt et al.[2] which were published about the same time in America, but were very different from the results described in the original report of Litwins et al.[3] These authors claimed that sublingual administration of 125 mg. of heparin sodium could be relied upon to prolong the coagulation-time to therapeutic levels for four hours. Indeed it seemed to us that their results suggested that heparin was as efficient sublingually as intravenously.

As heparin is not a fully homogeneous substance or a *single chemical entity, different* batches of the commercial product might show some variation in the predominant molecular size, and therefore in their ability to pass a membrane. Minor differences of this kind, if they do occur, might explain minor differences in the results of observers using different preparations of heparin, and particularly when in addition a different species is used as the test subject, as was done in Tomich and Woollett's experiments. The differences in the results of clinical trial with sublingual heparin were not minor, however, and it is most improbable that a reduction in molecular size accounts for the results of Litwins and his associates.

Department of Medicine,
Royal Infirmary, Glasgow.

A. BROWN
A. C. KENNEDY.

BOOKS INFECTED BY SCARLET-FEVER PATIENTS

SIR,—Your note of Oct. 18 (p. 783) states that a full account of the investigation in Leicester will appear elsewhere; but some comments seem to be worth making even at this stage.

As streptococci are well known to be transmitted by droplet spray it is extremely likely that they will be present in large numbers on books, usually held about 14 in. away for reading, from a patient with an acute streptococcal lesion of the throat. The *selection as* "controls" of Sonne dysentery cases seems puzzling, since two *layers of linen and* three or more blankets usually intervene between the book and the source of *infection. Moreover, transmission* by fingers from lesion to book is far more likely with streptococcal infection.

Will the fuller report adduce *clinical* evidence of spread? *Are we to learn how the pathogens* in the books, themselves lacking any power of locomotion, *are to infect others now that they lack the propulsion formerly* derived from the nasopharynx of their late *host*? Proof of the infection of books we have now *before us*; but this is a far cry from "an investigation in that city to establish the likelihood of patients with scarlet fever transmitting infection to others *through* library books."

Hildenborough, Kent.

C. GLAISHER.

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1. Kennedy, A. C., Brown, A. *Glasg. med. J.* 1952, 33, 89.
2. McDevitt, E., Huebner, R. D., Wright, I. S. *J. Amer. med. Ass.* 1952, 148, 1123.
3. Litwins, J., Vorzimer, J. J., Sussman, L. N., Applezweig, N., Etess, A. D. *Proc. Soc. exp. Biol., N.Y.* 1951, 77, 325.

SPECIALISTS AND PRACTITIONERS

SIR,—A consultant has said it. Sir Heneage Ogilvie, in his most stimulating address (Oct. 25, p. 820), has clearly shown the dangers inherent in the present system of selecting specialists and the evils of over-specialisation. He sees the general practitioner as the one remaining member of the health service with enough general medical knowledge to view the patient as a whole.

Thoughtful general practitioners will go a step further. If the present trend in the hospital world continues and the general practitioner allows himself to become, as many fear, a sorting clerk to the hospital departments, will not the sick person be completely submerged in the deep waters of scientific medicine ? Those of us who have watched the flow of the tide have been in no doubt as to the outcome, and we have tried to meet it as best we can. Hence the clamour for increased status for the general practitioner; hence the call for a College of General Practitioners.

With the extinction of the great race of general physicians and surgeons—an extinction which seems inevitable—a vacuum will be formed which only the general practitioner can fill. To fill this gap with distinction—nay, even with ordinary competence—the general practitioner must prove his skill; he must have freedom to use some hospital beds, access to pathological and radiological services, and, further, a corporate body to encourage and help him with advice and example.

We should all be profoundly grateful to Sir Heneage Ogilvie for putting the case so clearly.

Dartmouth. R. M. S. MCCONAGHEY.

VITAMIN B_{12} AND ISONIAZID

SIR,—Recently Ata and Tanaka[1] reported that a subcutaneous injection of vitamin B_{12} (0·30 mg. per kg. body-weight) appreciably diminished the acute toxicity of isoniazid in mice. In their experiments a definite increase in the subcutaneous L.D.$_{50}$ dose of isoniazid was obtained when the above-mentioned dose of B_{12} was administered thirty minutes after the isoniazid injection. We have been unable to confirm their results using aqueous solutions of crystalline vitamin B_{12}. Even a 16-fold increase in the dose of B_{12} failed to protect against the acute toxic effects of isoniazid in male albino mice. Isoniazid was administered as a 2% aqueous solution and vitamin B_{12} was injected as a 0·002 or 0·032% aqueous solution. The B_{12} test solutions were checked for qualitative and quantitative content by infra-red and ultraviolet absorption measurements. Dose volumes of the B_{12} solutions injected were 0·30 ml. per 20 g. body-weight. Isoniazid control mice received equivalent volumes of physiological saline subcutaneously instead of B_{12} solution. The results are shown in the following table:

EFFECT OF VITAMIN B_{12} ON TOXICITY OF ISONIAZID IN ALBINO MICE

Subcutaneous 30 minutes after treatment		Subcutaneous isoniazid L.D.$_{50}$ (mg. per kg.)	No. of mice
Agent	Dose (mg. per kg.)		
Saline	..	190 (170–213)	50
B_{12}	0·30	196 (180–214)	50
B_{12}	4·80	185 (167–205)	50

19/20 confidence limits[2] indicated in parentheses.

Neither of the two B_{12}-isoniazid L.D.$_{50}$ doses differed significantly from the saline-isoniazid L.D.$_{50}$.

Among more than fifty compounds screened as possible prophylactics against isoniazid acute toxicity in mice, only barbiturates and some related central depressant agents appeared to offer therapeutically useful protection. Certain thiol compounds, including dimercaprol (BAL), offered only a transient suppressive action in high doses. A large series of other agents, which included carbohydrate metabolites, amino-acids, and vitamins, failed to protect mice unequivocally against the acute toxic effects of isoniazid. These results are to be published in detail elsewhere at a later date.

Squibb Institute for Medical Research,
New Brunswick, N.J., U.S.A.

BERNARD RUBIN
JOHN C. BURKE.

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[1] Ata, S., Tanaka, K. *Lancet*, Sept. 20, 1952, p. 589.
[2] Litchfield, J. T. jun., Wilcoxon, F. *J. Pharmacol.* 1949, 96, 99.

HALLUX VALGUS

SIR,—I have read with great interest the article by Dr. Hardy and Mr. Clapham.[1] Here in the South of Madagascar I have very often observed hallux valgus in older people who have never worn shoes; it is almost always associated with flat-feet. I have never seen hallux valgus in people under 20 years of age.

Betioky, Madagascar. B. KALCEV.

WITHDRAWAL OF TEACHING

SIR,—I agree that, as you implied in your leading article on Oct. 11, the abolition of the travelling film units of the Central Office of Information is an example of "penny wise and pound foolish."

During the last few years the Ministry of Health has produced six films on the early diagnosis of cancer, specially in order to help general practitioners. These films, which were described in your leading article, have been shown at conferences in many European countries and in Africa, where they were much admired; but I have not yet met a general practitioner in England who has seen one of them, and to make matters worse the Central Film Library has removed the copies from the film department of the British Medical Association. I do not know how much money was spent in producing these films; but if they are not circulated and seen by the practitioners of this country, the money has been largely wasted.

MALCOLM DONALDSON
Chairman, Medical Committee,
Scientific Film Association.

London, W.14.

SIR,—May I join with Dr. Cardew in admiring your leading article on the damage done by the withdrawal of the C.O.I. mobile projection units and the Crown Film Unit.

When the blow fell I wrote to the *Times* drawing attention to the fact that the harm would be felt most severely by those groups, whether of nurses or small study groups, whose financial resources are smallest and whose need for the broadening effects of the film is greatest.

Dr. Cardew pointed out that the money, time, and labour required to make a film, although great, are justifiably expended because the results can be shown to audiences all over the country for as long as the subject remains of interest. An elaborate and expensive film dealing with details of treatment, whether surgical or medical, is likely to have a much shorter useful life than a descriptive film dealing with the clinical appearances of a disorder. In other words, although it is relatively easy to make a well-composed film about a surgical operation, the time and trouble might be better spent tackling the more difficult subject of making films which would increase the clinical experience of medical students, and so improve their diagnostic ability.

One wants to record the clinical history of rare disorders. I think the last cases of tetanus seen at Guy's were in 1948 and seven years earlier than that. Many students never see a case of tetanus. What is needed is a single-bedded side ward, fitted with permanent lighting equipment, to which a patient with tetanus, for example, could be admitted for treatment, and in which films of his condition could be made from time to time. With the permission of the patient, these could be edited into a very useful teaching film.

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[1] Hardy, R. H., Clapham, J. C. R. *Lancet*, 1952, i, 1180.

Guy's Hospital, London, S.E.1. RONALD MAC KEITH.

THE NOTIFICATION OF DISEASE

SIR,—Although, in the light of Professor Bradford Hill's remarks (Oct. 18, 1952), I acknowledge that the comparison I made in my paper did not do justice to the Medical Research Council's inquiry, I still think that the basic contention underlying my remarks is true—that compulsory notification of disease, as being more comprehensive, is a better basis for such an inquiry than other forms of certification.

May I mention two points which were inadvertently omitted from my paper: first, that ice-cream makers and dealers are required to notify the medical officer of health of the occurrence of certain milk-borne diseases in persons living or working in the premises on which the ice-cream is manufactured, stored, or sold; and, secondly, that a copy of any food-poisoning notification received must be sent within twelve hours by the district medical officer of health to the county medical officer.

E. D. IRVINE
Exeter. Medical Officer of Health.

ADOPTION

SIR,—In thanking you for your annotation of Oct. 25 on my book *Child Adoption in the Modern World*, may I touch on one or two points where I think it is a little misleading?

Perhaps first I should mention that I wrote my book in a spirit of splendid impartiality, since I then had no connection with the adoption societies. I express myself here too as an ordinary private person and not as representing anything.

Perhaps you believe that opposition to third parties in adoption cases is a kind of crank or partisan attitude on the part of the adoption societies. This is far from being the position, and all informed opinion in the adoption world, so far as I know, is against third-party placements.

The medical practitioner has a special temptation to become an occasional go-between in adoption cases. But these opportunities to do what seems to be a good turn all round are fraught with special perils, and perhaps some doctors still do not realise the serious responsibility they at times incur on behalf of emotionally distressed patients. Most medical men and women experienced in adoption work would, I believe, fully endorse the view expressed by a prominent member of the medical profession who spoke on a television programme in September. He said that he thought private adoptions should be permitted only with the help of a recognised agency. He also said that doctors should not recommend a child to a woman with "nerves," or encourage adoption as a means of keeping a marriage off the rocks. What the adoption worker feels about the participation of a doctor in a third-party adoption he probably owes in some measure to the lead given by other members of the medical profession!

If I may quote you as a witness, it would seem that a doctor's very professional zeal may sometimes lead him astray in adoption matters. You say: "The doctor is obliged to take the welfare of all parties into consideration. His opinion that an emotionally disturbed woman may be helped, sometimes to lasting recovery, by having a child to look after, is not always, or necessarily, ill founded." This attitude is opposed to the adoption principle embodied in the Adoption Act, which says that the court hearing an adoption application must assure itself that "the [adoption] order if made will be for the welfare of the infant." One cannot too strongly stress that the child's welfare takes absolute precedence of the welfare of the would-be adopters. The plea that it is justifiable in any circumstances to use a child to bring about a problematical and perhaps merely temporary cure of an emotionally disturbed woman is a melancholy tribute to the desire of the physician to cure his patient at all costs. But would-be adopters have no rights vis-à-vis the child; their needs, grievous though these may be, establish no sort of claim—in law or sentiment—on a small stranger. On the contrary, the child has a right to be protected in his helplessness.

It is true that when people do not get a child from an adoption society or welfare authority, as often happens, they may get one privately. But this does not mean that it is a good thing. Carefully planned adoptions are the safeguard of the adopters just as much as of the children.

Of course, as you say, the adoption of a baby by affectionate people, even if they are imperfect, is a great blessing to the child. Practically all social workers now agree that private home life is better for most children than a Home. But we have no need to be indiscriminate about it. The choice for the adoptable child need never be the dubious one as between a casually arranged third-party adoption and a Home upbringing. Every deprived baby living in this country who has reasonable health and background has at least twelve sets of worth-while adopters queued up and waiting for him, and any adoption society would be pleased to place him.

One knows there are would-be adopters who do not care to submit to the inquiries that are made before placing both by adoption societies and the adoption departments of local authorities. This resentment is in itself suspect. Some of those who apply to a doctor for a child have already been turned down by an adoption society—not necessarily because they are not nice people, but because they are considered too old, or have not the right accommodation, or something of that kind.

Doctors who have placed children for adoption or who contemplate doing so might be interested to buy a copy of the Adoption Act and of the Regulations made under the Act. The Regulations binding on adoption societies do not, of course, relate to third parties, but they indicate what the law of the land considers is essential procedure in good adoption work. The societies are bound to make inquiries on 61 points relating to the child, his parents, and the adopters. No less than 23 of these questions (about the child's health) must be answered by a doctor.

Unfortunately, adoption is not and never can be a sure-fire mass method of emptying institutions and orphanages, as your reviewer hopes. It is a selective method for certain children. But really there is no vested interest in keeping large numbers of children in Homes.

The practised adoption worker brings to the task at least three things: experience; humility, and the desire to go on learning; and a large number of good contacts with potential adopters, local officials and welfare people, other voluntary organisations, moral welfare workers for mothers and babies, clerics and religious organisations, hospitals, doctors, nursing homes—and other adoption workers. Good contacts are very important indeed, for they help to remove adoption work from the hit-or-miss realm of casual placement and to make it a matter of team-work. If there were no other reason why third parties are undesirable it would be a decisive point against them that they act in isolation and without perspective, as well as without in the majority of cases knowing what they are doing.

The medical profession has a very great deal to give to good adoption work. The help of doctors is important and much valued, and if more of them could give up precious time and consent to sit on adoption society committees the benefit would be enormous. To those busy doctors who already make their services available in an advisory capacity as members of "adoption teams," the adoption societies concerned are, I feel sure, extremely grateful. There should be such a team in every area.

Bromley, Kent. MARGARET KORNITZER.

BARBITURATE POISONING

SIR,—During the past week we have obtained some publicity regarding our "Barbiturate Unit," and we feel that the following information may help to clarify the situation.

The unit, consisting of a small number of beds, will be primarily for the treatment and investigation of cases of *acute* barbiturate intoxication. We are not a unit for the admission of cases of "drug addiction." We should be delighted to admit cases from any doctor in any area, provided he feels that the case is within reasonable travelling distance of the hospital. Admissions should normally be arranged through our admission officer, who is available for emergencies throughout the twenty-four hours.

Before admission, patients should, where necessary, be given the appropriate first-aid treatment, such as artificial respiration or oxygen administration.

S. LOCKET
P. G. SWANN
W. S. M. GRIEVE.

Oldchurch Hospital,
Romford, Essex.

FUTURE OF THE OCCUPATIONAL HEALTH SERVICES

SIR,—I am glad that Dr. Lloyd Davies showed in his letter last week how the terms of reference of the Dale Committee precluded them from making sweeping suggestions for a reorganisation of the occupational health services, even if they had felt it desirable to do so. There are, however, certain statements in Dr. Lloyd Davies's letter which I cannot allow to pass, lest it should be thought that the views he expressed were held by all medical members of the Dale Committee.

In his enumeration of the difficulties besetting planners, he states that "employers are responsible for the health, safety, and welfare of their workers." It is true that employers have important legal responsibilities for the worker while at work, but the employer is not the only person with a responsibility. While general practitioners, health departments, and caterers also have responsibilities for making a good and contented worker, surely one of the most important factors is a satisfactory home life. Managerial interest and responsibility is only one aspect of satisfactory industrial relationships.

As regards the attachment of the industrial medical officer to the employer—"an integral part of management"—this is of course only good as long as the doctor, employer, and employee not only play fair but demonstrably do so. I have never seen any evidence to the contrary, but surely it is desirable that the doctor should be independent and feel fully able to proffer his advice without any suggestion of bias.

The imposition of minimum standards does of course postulate some authority with power to impose. But how does Dr. Lloyd Davies know that it would be impossible for a local authority, in conjunction with other interested bodies, to evolve an acceptable scheme of supervision? Medical officers of health, do, I hope, know their manners, but they have learnt to carry out strange tasks in the past.

My most important point of disagreement results from his prognostication that "action based on knowledge will be toward a small, highly skilled cadre of doctors rather than towards unwieldy and untrained regiments." Surely the aim of every specialty should be to bring its special knowledge and experience into the general body of medicine, and if possible make it an accepted part of general medical practice. The occupational health service should not become a closed shop. In any case the diversity and size of industry and its problems, which affect all medical practitioners to some extent, require the coördinated assistance of all kinds of doctors; general practitioners and specialists must all contribute and, frankly, I am looking forward to the not inconsiderable part which I hope the public-health departments will play in the development of industrial medicine and the care of the worker.

The difference between Dr. Lloyd Davies and myself surely lies in the question of execution and not of aim, for we all appreciate the importance of a fit and happy industrial population in a healthy nation. The final shape of the industrial medical service is not yet known and many inquiries and investigations into the problems are necessary. In particular, the position of the small factory requires careful study. At present there is a danger that the presence of small factories may be used as a propaganda weapon by persons who think of industrial relationships as they existed half a century ago. No-one denies of course that there are many small organisations which are slum factories, but they should not be lumped together as undesirable just because they are small.

With our difficulties of man-power and resources, the development of an industrial medical service is likely to be slow. This is fortunate for it provides opportunities for interested parts of the profession to get together. As a medical officer of health I would like to see the public-health department doing some spadework; local reviews of sickness and death rates in relation to occupation should be made, for vital statistics are a very necessary guide. Industrial medicine may or may not be primarily a medical matter, but it is a matter in which the medical profession as a whole must interest itself.

Despite my pleading, I too was a member of the Dale Committee. These opinions are my own and do not necessarily reflect those of my authority.

Sheffield. LLYWELYN ROBERTS

Parliament

Organisation of General Practice

IN the House of Commons on Oct. 30, Mr. H. A. MARQUAND said that the first three years' experience of the National Health Service had revealed defects in the working of the general-practitioner service. Some doctors complained about the large number of patients they were asked to look after, some suggested that they had insufficient opportunities for hospital practice, or insufficient access to modern diagnostic aids in their practice. The younger men complained of the difficulties of entering practice as principals. Patients complained of the time they had to wait in surgeries. Ministers had their complaints, too, especially about the size of the drug bill. When he became Minister of Health, Mr. Marquand thought that an amendment in the method of remunerating general practitioners might help to remedy these defects.

A LOST OPPORTUNITY?

At that time, he continued, a sharp difference of opinion had arisen between the doctors and the Ministers as to whether the findings of the Spens report had been implemented. To get this bone of contention out of the way it was agreed to submit the question to an independent adjudicator. At the same time it was decided to set up a Working Party to suggest a new method of distributing the money, and enable them to advance to an improved service in a better atmosphere. He confessed that the Danckwerts award had surprised him, but when an independent opinion had been sought it must be accepted, and he understood that the money was in course of being paid. What remained was the second part of the bargain, and here he felt an opportunity had been missed.

The Working Party proposed to reduce the size of the maximum list from 4000 to 3500. Was it true, he asked, that the number of patients released from those over-large lists, and made available to other doctors with smaller lists and incomes, was only 500,000? Mr. IAIN MACLEOD, the Minister of Health, interposed that the figure was probably 2 million. Mr. MARQUAND said that was encouraging. But even so 3500 patients was a large number for one doctor to look after. He regretted that no provision had been made to taper the capitation fee. Most of the complaints about the Working Party's report had come from the small-list doctors.

The Working Party had also been asked to make it easier for new doctors to enter practice. He was told that today the number of salaried assistants was 2300 and that in addition there were 500 hospital registrars seeking employment. He agreed that the Working Party had found a useful way of encouraging practitioners to take partners rather than assistants by means of a loading which would not apply to patients attributed to an assistant. Would it not be possible to go further and prohibit the continued employment of assistants by any principal after a certain time? Or would it not be more reasonable to reduce the number of patients who could be attributed to an assistant from 2000 to 1000 or 1500?

Mr. Marquand considered the Working Party's most important task had been to devise ways of stimulating group practice. Yet only one short paragraph in their report mentioned this subject.

GROUP PRACTICE v. FAMILY DOCTOR

Mr. SOMERVILLE HASTINGS had no quarrel with the Danckwerts award, because he believed it essential to raise the status of the general practitioner. On the other hand he quarrelled with the Working Party's report because it did not do enough for the general practitioner. For instance he regretted that the Working Party had not suggested special rewards at the top of the service. He also wished that more had been done to stimulate partnerships. In his view we should not get the best medical service until health centres were developed, and he could only conceive health centres developing among doctors who were working in partnership. Again, unless doctors were working together, we should not promote that minor specialisation which made general practice interesting. One of the ways to get health centres was to help doctors to work in partnership; then persuade a local authority to build or secure a house into which they could transfer their practices; and then later, when the money was available, to attach to that health centre all the other preventive services. It might be possible, he suggested, to add something to the capitation fee of all doctors practising in registered partnerships.

Mr. ANGUS MAUDE found little to object to in the report as a whole, but confessed he was uneasy about the position of the small-list doctors. There was, he thought, great prejudice against them. We heard about elderly doctors and "pin-money" doctors. But he would rather entrust the health of his family to a competent "pin-money" doctor than to one with a list of 3500 who had not enough time for diagnosis and treatment. Admittedly there might be undesirable doctors in this group, but he thought there were many good doctors taking great trouble with their patients. He did not believe that group practice was the ideal at which to aim, but rather a return to the family doctor giving a good family service. Yet at the moment we were probably going further away from it. A small minority of doctors were not giving a proper service, either because their desire for income was greater than their desire to produce a decent service, or because some of them were rather idle. But that, he thought, was a problem with which the medical profession itself should deal. He would rather have a system where the profession had reasonable control over the standard of quality than one where the State had such a firm grip that it could dilute the service as it pleased, lower the quality of its standard, and fiddle the remuneration as it pleased. He thought they had nearly the best solution they could possibly have.

Dr. BARNETT STROSS, on the other hand, was convinced of the importance of group practice. It was, he believed, our essentially British way of trying out a new form of public service. If not ideal, it was certainly one of the best methods by which the general-practitioner service could move forward. He pointed out the difference between the improvement in the service offered by the family doctors as compared with the spectacular improvement recently offered by the hospital service. Everyone was anxious to help the general-practitioner service to play a notable part, and perhaps the most important part of all, in the health service. But what was the good of £100,000 a year as proposed by the Working Party? The least it would cost those forming a group practice to buy a house and alter it would be £5000, and that meant that in any one year only 20 group practices could be helped. The sum offered should be at least £500,000, and it should be awarded not as grants but as loans at low interest. The award allowed doctors a not ungenerous standard of life, and he suggested that the Minister should ask the local executives to help medical practitioners to improve their standard of accommodation for the public in surgeries and waiting-rooms.

IN DEFENCE OF THE MEDIUM LIST

Mr. MACLEOD, replying to the debate, said that something like 2 million people would have to be shuffled in one way or another on the doctors' lists. To ask that number of people to change their doctors was a serious interference with the liberties of the subject, and could not be ignored. The size of the ideal list could not be settled by rule of thumb. We would not necessarily get a better service by levelling the size of lists, and patients' choice of doctor could not be ignored. He deplored the attacks which had been made in professional journals on the big-list man as much as he deplored the sneers at the small-list man. It was unrealistic to suggest that they could move faster and bring down the figure to say 3000 at the present time. To do that we should need more doctors in the industrial areas where the big lists were concentrated.

It was often assumed that the Working Party's task was to help those with a small list. The terms of reference did not say that. The people who were "least favourably placed" were not only the people with small lists, but most particularly those with medium-sized lists, who were not in industrial areas and who perhaps previously had a measure of private practice and were now doing a full job in the health service.

It had been suggested that there should be a flat rate of something like £1; but that would mean giving more money both to the small groups and large groups at the expense of the middle groups. It had also been suggested that they should load the first 1000, but that would make it more difficult to attract doctors to the designated areas, where they were needed if there was to be a really good service. Calculations about the effects of the new proposals on the small-list and medium-list doctors did not take into account three factors. First, they forgot that up to 2 million patients would have to find another doctor. That was bound to make it easier for small-list doctors to increase their practices or join a partnership with someone who had already a big list. Secondly, they forgot the £200 transitional payment which could be claimed during this year while the redistribution was taking place. Thirdly, they made the depressing assumption of a static position in their practices. Younger doctors who had a small list now would not always have a small list, and he did not believe that it was the duty of the State to subsidise them for ever. He frankly admitted that he did not intend to take competition out of medical practice. He believed that we should try to match rewards with effort and achievement. It had never been part of the policy of this Government, he affirmed, to have a salaried service in the medical profession. A sum of £50,000 had been reserved for cases of hardship, and a portion of the final settlement money was to be put aside to meet any particular difficulties. He could not agree that this was charity. He had every sympathy for the small-list man, and indeed with private practice, but it was his duty to encourage doctors to go where they were needed in the health service.

He also believed that the scheme would make it easier to enter practice. The initial practice allowance was an improvement on the fixed annual payment and the reduction in the maximum lists was bound to help. The 2000 patients who could be attributed to an assistant did not qualify for loading, and this was a further inducement to a principal to take an assistant into partnership.

Mr. Macleod confessed that he shared the common confusion as to what was meant by group practice. He therefore proposed to invite Sir Henry Cohen's Committee on General Practice to consider the subject and advise him. In conclusion he said that he made no extravagant claims for the scheme as it stood, nor would he even say that there was no hardship here and there. But he did claim that in all honour the Working Party strove to implement their terms of reference. In his view they had on the whole succeeded, and he asked that the scheme should go forward in goodwill.

New Medical Act Regulations

In the House of Lords on Oct. 28 the EARL OF ONSLOW explained that the Medical Act of 1950 provided that the General Medical Council should prescribe a period of preregistration service for doctors before they went into practice It was originally intended to prescribe a period of 12 months in the Bill itself, but this was amended and the matter was left to the G.M.C., who had, in fact, decided on 12 months as the preregistration period.

Lord WEBB-JOHNSON asked for an assurance that these men or women should be posted without undue delay to these preregistration appointments. There seemed to him to be no provision by which applicants for provisional registration could receive any remuneration, whereas in the old days, a student who was registered and waiting for a house-appointment, could earn his living in some other sphere. The EARL OF ONSLOW said the G.M.C. had published a formidable list of approved house-posts, which he was informed gave every opportunity for the young doctor to find an adequate position when he qualified and left the hospital medical school.

Insanity and the Criminal Law

In the House of Lords on Oct. 29, Lord MANCROFT asked the Government if they would consider setting up a Royal Commission to examine the problem of insanity and the criminal law.

The LORD CHANCELLOR said that this problem had been examined by the Royal Commission on Capital Punishment appointed in 1949. The Government expected that the Royal Commission would include observations on the problem in their report, which was likely to be available within the next few months. In the circumstances the Government did not consider that any occasion arose for appointing a new Royal Commission with the particular function suggested by Lord Mancroft.

QUESTION TIME

Notification of Poliomyelitis

Mr. S. P. VIANT asked the Minister of Health to what extent his department received records of the history as regards vaccination or immunisation of cases of poliomyelitis notified in England and Wales; whether medical officers of health obtained such particulars; and whether such information would be obtained in future in every case of this disease notified.—Mr. IAIN MACLEOD replied: Medical officers of health have been asked to obtain such information about every notified case of poliomyelitis and to send it to a committee set up by the Medical Research Council, including medical officers of my department, which is investigating the subject of inoculation procedures and neurological lesions. It cannot be decided at present whether it will be necessary to go on obtaining such reports in future.

School Dental Service

Replying to a question, Miss FLORENCE HORSBRUGH, Minister of Education, said that the number of school dentists in England and Wales on Oct. 1 was equivalent to 827 full-time officers, an increase of 100 since January last. A further similar increase would bring the service back to its 1948 level, but an equivalent of over 1000 additional dentists would still be needed to give a ratio of 1 dentist to 3000 children.

Cancer Research

Replying to a question, Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that the Minister did not propose to incorporate into the national medical scheme the cost of fully financing all cancer research. He regarded cancer research as a very suitable field for private generosity which he would not wish to discourage.

Obituary

JOHN ALEXANDER DRAKE

M.D. Lond. F.R.C.P.

Dr. Drake died on Oct. 29 at King's College Hospital, where he had been for many years physician for diseases of the skin and dean of the medical school.

He was born at Clifton, Bristol, in 1878, the son of Alfred Drake, and he received his early education at Malvern College. In 1896 he entered King's College, where he won the Warneford and Junior scholarships and the Sambrooke exhibition. These took him on to the hospital and he qualified in 1902, and obtained a house-appointment under Sir Watson Cheyne.

After taking the M.B. Lond. in 1903 he entered general practice at Tenby, Pembrokeshire. His health had never been robust but this did not prevent him from doing excellent work there. Ten years later, in 1915, he was unfit for military service, but he succeeded in joining the 4th London General Hospital as physician in charge of the medical division. King's College Hospital had moved to Denmark Hill just before the war and the 4th London formed part of the new buildings as well as extending into Ruskin Park as a hutted hospital. Drake's interest in dermatology was enhanced by the opportunity now given him to attend Prof. Arthur Whitfield's clinic regularly. After the war he became a clinical assistant there, having decided to specialise seriously. To this end he took both the D.P.H. and the M.R.C.P., and in 1920 he was appointed assistant physician to the skin department at his old hospital. At the same time he took charge of the venereal diseases department. He was elected a fellow of the Royal College of Physicians in 1926 and soon afterwards became physician in charge of his department.

During these early years he found time to act as assistant editor to the *British Journal of Dermatology and Syphilology* and as secretary to the section of dermatology of the Royal Society of Medicine, and he was one of the few dermatologists who have served as examiners in medicine to the Conjoint Board. He held the appointment of vice-dean at King's College Hospital Medical School for some twelve years and of dean from 1932 until his retirement in 1937.

S. T. writes: "Drake's rare contributions to the medical journals were characterised by the great care which he showed in all he undertook. But his real interest lay in his own hospital and particularly in its medical school. That he held the appointments of vice-dean and dean for so long is testimony of the trust placed in him by his colleagues. No-one ever had cause to regret this trust, whether patient, student, or friend. His chronic ill health had never warped his kindly outlook; his quiet voice and friendly smile will be long remembered."

In 1908 Dr. Drake married Lorna, daughter of Mr. C. J. Stewart, who survives him.

Major-General MITCHINER

Lieut.-General F. Harris writes: The great services of Major-General P. H. Mitchiner to the Territorial Army, both before and during the war, have already been outlined in your columns; and I should like to endorse all that has been said. Nevertheless I feel that it is appropriate that I, as director-general of Army Medical Services, should add my personal tribute to a great and loyal officer of the R.A.M.C.

"I first met him in 1934 at a weekend training exercise at Brighton, where I had gone as a Regular R.A.M.C. officer to help the Territorial medical officers with their training; but I soon found that Colonel Mitchiner, as he then was, and the officers trained by him knew at least as much about the tactical handling of field medical units as I did. Ever since, he and I have been friends and latterly close friends; and a wonderful friend he was, not only to me but to the whole of the R.A.M.C., both Regular and Territorial.

"From the end of the war until his death he was, as adviser to the D.G.A.M.S., his right-hand man on all matters concerning the T.A. Medical Service. In this responsible task he was of the greatest help; and his wide knowledge of the Territorial Army and indeed, it seemed, of every officer in it, were invaluable. His grasp of training problems was remarkable; his comments were always candid and outspoken but mellowed by wit and a sense of fun. He never spared himself, and during the last few years, though his health was far from good, he visited during the training season numerous T.A. units throughout the United Kingdom, giving advice to the officers in command and taking part in their social activities. The present high standard of training of the T.A. Medical Services is in large measure due to his enthusiasm, knowledge, and personality. Mitch was a great and loveable personality who will be missed by the whole of the Army. We shall not soon see his like again."

R. O. L., who worked under Mitchiner as house-surgeon, registrar, and resident assistant surgeon at St. Thomas's Hospital, writes:

"Undoubtedly he was a brilliant teacher and his own peculiar rhetoric left an indelible imprint on the student mind. But his teaching extended beyond the classroom, out-patient clinic, and ward round. Being essentially practical, he taught also in the operating-theatre. He believed that a student should perform at least one operation; and how many of his students remember the thrill of that first removal of the hernial sac under the expert guidance of P. H. M. in the rôle of assistant? To the house-surgeon, with operating opportunities already sadly diminished by the influx of registrars, the arrival of his junior chief for the evening acute appendix constituted the highlight of 'major week.' Like as not, it would be followed by the genial command, 'Get on with it, Boy.' To the registrars he displayed the same generosity and encouragement in so far as his then limited bed complement allowed, and when the time came for them to move on, his recommendation carried great weight, no matter where the next appointment lay, for he seemed to know everybody. To his juniors Mitchiner's outstanding characteristic was his loyalty and this, amongst many great qualities, will long remain an affectionate memory to the many St. Thomas's men who worked under him."

Births, Marriages, and Deaths

BIRTHS

BARCLAY.—On Oct. 23, at the Women's Hospital, Nottingham, to Cecilia, wife of Mr. Robert Barclay, F.R.C.S.—a son.

FOX.—On Oct. 25, at the London Hospital, to Kathleen (née Welply), wife of Dr. D. G. R. Fox—a daughter.

JANNEY.—On Oct. 24, at King's College Hospital, London, to Susan Marguerite (née Müller), wife of Dr. B. A. Janney—a son.

RYDER RICHARDSON.—On Oct. 27, at The Beeches, Saxmundham, to Eleanor (née Mosse), wife of Dr. J. P. Ryder Richardson—a son.

SAUNDERS.—On Oct. 24, at Bushey Maternity Hospital, to Nancy (née Janes), wife of Dr. D. R. S. Saunders, M.R.C.P.—a son.

STENHOUSE.—On Oct. 29, at the Westminster Hospital, to Joy (née Crouch), wife of Mr. A. B. Stenhouse, M.R.C.O.G.—a daughter.

MARRIAGES

[illegible]—On Nov. 1, John Kingston Baker, M.R.C.O.G., [illegible] t. Stephen's, Canterbury, to Pamela [illegible] Canterbury.

[illegible] 25, John Cordner Foster, M.B., of [illegible] on Rogers, of Chatham.

DEATHS

CONNELL.—On Oct. 31, William Kerr Connell, M.B. Glasg., F.R.C.S., F.R.F.P.S., of Wellshot Drive, Cambuslang, Glasgow, aged 58.

DRAKE.—On Oct. 29, at King's College Hospital, John Alexander Drake, M.D. Lond., F.R.C.P., D.P.H., consulting physician for diseases of the skin, King's College Hospital, and sometime Dean of the Medical School.

JOHNSON.—On Oct. 30, William Crosby Johnson, M.B. Victoria, of Mayfield Lodge, Haslemere, late of Manchester and St. Andrews, aged 77.

MALONE.—On Oct. 22, at Mid-Herts Hospital, St. Albans, William Aloysius Malone, M.R.C.P.I., late Colonial Medical Service.

Notes and News

GENERAL PRACTICE IN LONDON

IN London the number of general practitioners on the executive council's list increased from 2005 at the end of March, 1949, to 2204 at the end of March this year. This is revealed in the executive council's report for 1951-52,[1] which also shows that the average number of patients per list was 1620 on April 1 this year, compared with 1656, 1670, and 1638 on April 1 in the years 1949-51. In 1951 the average number of patients per list ranged from 490 in Hampstead to 2886 in Battersea. During the year 1951-52 practices were disposed of as follows: vacancies advertised, 12; practices dispersed, 39; practitioners with no patients, 10; practices transferred to "logical successor," 36; small practice vacancy, not advertised, 1.

W.V.S. APPEAL

THE Women's Voluntary Services have issued a national appeal for clothing. "W.V.S. wants any type of clean clothing—not only to meet big emergencies such as floods and fires, but also so that we may be able to help the many calls made upon us daily by people in real trouble. The old-age pensioner, the 14-year-old schoolgirl whose mother has died and who is keeping the home together for her father and three younger children, the family where ill-health has prevented the father from working—all are going through a sad and difficult time which a little assistance with clothing can help to alleviate. We are asking everyone in the country to look into their cupboards and drawers and turn out what they can spare in the way of clothing, linen, blankets, shoes, and bits and pieces of wool which can be knitted into small squares and joined up to make blankets. W.V.S. work-parties will mend and alter anything."

Parcels will be accepted at any W.V.S. office or at the organisation's headquarters, 41, Tothill Street, London, S.W.1.

University of Cambridge

On Oct. 11 the following degrees were conferred:

M.D.—M. O. J. Gibson, Portia G. Holman, R. G. Law, I. C. K. Mackenzie.

M.B., B.Chir.—*Andrew Fairley, *J. D. Richardson.

* By proxy.

Royal College of Surgeons of England

On May 5 the Queen will lay the foundation stone of the college's new buildings which will replace the museum destroyed by enemy action and also house the Nuffield College of Surgical Science.

Society of Apothecaries of London

Dr. H. Seaward Morley has been elected senior warden, and Sir Cecil Wakeley junior warden.

Osler Club of London

Prof. Henry E. Sigerist will speak on Medical History in Medical Education at a meeting of this club to be held on Friday, Nov. 21, at 7.45 P.M., at 11, Chandos Street, W.1.

New Neurosurgical Unit

Viscount Waverley, F.R.S., will open the Guy's-Maudsley Neurosurgical Unit at the Maudsley Hospital, Denmark Hill, London, S.E.5, on Thursday, Nov. 20, at 3 P.M.

International Pharmacopœia

The eleventh session of the World Health Organisation's expert committee on the International Pharmacopœia opened on Oct. 27 at Geneva. For the eleventh time, Dr. C. H. Hampshire (London) was elected chairman, by acclamation. This "enthusiastic tribute," his colleagues said, went to the man who had been principally responsible for the successful publication of the *International Pharmacopœia*. Other officers appointed were: Prof. H. Flück (Zürich) vice-chairman, and Dr. T. Canbäck (Stockholm) and Dr. L. C. Miller (New York) rapporteurs. In his opening statement to the committee, Dr. Pierre Dorolle, deputy director-general of W.H.O., reported that since the publication of vol. I of the *International Pharmacopœia* in English and in French a number of member States of W.H.O. and national pharmacopœia commissions had indicated that they were using the book in establishing or revising their own national pharmacopœias. Publication of vol. II would be a further important step in giving unified standards for important drugs.

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[1] Published by the council, Insurance House, Insurance Street, London, W.C.1.

Royal College of Physicians of London

At a quarterly comitia of the college held on Oct. 30, with Sir Russell Brain, the president, in the chair, Dr. Geoffrey Bourne, Dr. E. C. Dodds, Dr. Robert Platt, and Dr. J. T. Ingram were elected councillors; Dr. A. Feiling was elected representative on the Committee of Management; and Sir Russell Brain, Sir Harold Boldero, Dr. W. G. Barnard, Dr. A. M. Cooke, and Sir Allen Daley were re-elected members of the Standing Joint Committee of the three Royal Colleges.

The following candidates were elected to the membership:

J. A. Balint, M.B. Camb., Charles Berman, M.D. Witwatersrand, S. O. Boldy, M.D. Lond., T. H. Bothwell, M.B. Witwatersrand, P. D. Bryant, M.D. Lond., A. R. Buckley, M.B. Camb., E. J. M. Campbell, M.D. Lond., T. B. Cullity, M.B. Adelaide, R. A. Dale, M.B. Melb., H. E. F. Davies, M.D. Lond., W. E. B. Edge, M.B. Witwatersrand, A. W. H. Evans, M.B. Lpool, B. J. S. Harley, M.D. Lond., Gavin Hildick-Smith, M.B. Camb., B. I. Hirschowitz, M.B. Witwatersrand, D. G. Julian, M.B. Camb., L. H. Klugman, M.B. Witwatersrand, C. D. Lacey, M.B. Camb., W. L. B. Leese, B.M. Oxfd, Mohamed Ajawad Macan-Markar, M.D. Lond., Lisa E. Mandelbaum, M.B. Brist., Jamshed Sorab Moos, M.D. Bombay, L. M. Reid, M.B. Melb., H. R. C. Riches, M.B. Lond., S. J. G. Semple, M.B. Lond., N. K. Shinton, M.B. Birm., Premji Valji Thacker, M.B. Bombay, A. B. Tompkins, M.B. Lond., S. M. Vine, M.B. Camb., Geoffrey Walker, M.B. Lond., P. R. Walsh, L.R.C.P., Glyndwr Walters, M.B. Brist., D. G. C. Whyte, M.D. Belf., major R.A.M.C., G. M. Woodwark, M.B. Camb., C. R. Woolf, M.D. Cape Town.

Licences to practise were conferred on the following 123 candidates (95 men and 28 women) who have passed the final examination of the Conjoint Board:

C. W. M. Adams, H. R. Alpin, Ursula M. Anderson, J. L. Andrews, J. A. R. Anson, D. T. C. Barber, D. W. Barnes, I. R. Beale, J. K. H. Benson, S. W. Bissell, Stanford Bourne, A. J. Bowdler, J. A. D. Briggs, J. J. Brown, J. R. G. Brown, H. P. Charles, Rabindranath Das Choudhury, C. S. M. Chown, Evelyn Coates, J. H. Corbett, B. J. Cremin, L. M. Davis, J. C. Denmark, Ludlow Essex, Anne C. Evans, M. D. C. Evans, John Fairley, Patricia M. Firkins, Margaret Fisher, W. A. Forrest, J. M. Foster, A. I. Fram, Hannah French, Anna L. Frenkiel, G. R. K. Frost, R. E. Fryer, H. G. Gage, R. A. Gawn, H. M. Georgeson, R. B. Glover, G. R. Grant, D. J. Green, J. M. S. Grieve, Elizabeth A. Grimditch, E. H. L. Harries, Joyce Harrison, M. N. Harrison, Derek Harvey, Alan Haylock, Natalie J. Holloway, H. A. Hosking, Neville Howard, C. K. Hudson, Kathleen M. Huntington, C. F. Hutchison, I. B. Johnson, H. S. Jones, H. D. Jones, T. P. Jupp, Patricia M. Kenney, J. B. Kenyon, D. W. King, J. R. Kirkup, W. R. Kynan, S. R. S. Laing, Lesley P. Leader, Rachel E. Lee, Monica C. Lewin, R. J. Lewis, H. E. Lichtenstein, W. J. McCall, Kathleen M. McCartie, Thomas McCormick, I. R. McDonald, J. U. MacWilliam, W. B. Manley, R. A. Matthews, P. D. Meers, D. C. Morrell, T. F. Morris, R. J. Murray, M. R. Newell, A. S. Nicholas, F. I. Partington, Naomi I. Penfold, D. E. Phillips, Grace D. Pinkerton, A. J. Platts, J. F. W. Rail, J. E. Rees, H. F. Reichenfeld, J. W. Rentoul, C. E. Rhodes, W. A. G. Roper, A. D. Rowlands, J. F. Ryan, Mary S. Shenai, Eva H. Short, Anne M. Shuffrey, Elizabeth L. Siddle, I. F. Smith, D. N. Stathers, Kathleen M. Stevenson, J. W. Strain, J. F. Sturridge, J. H. Swallow, E. M. Sycamore, Eva S. Szmulewicz, Audrey M. Tabor, B. D. Thomas, Constance P. F. Thomas, Heather B. Thompson, Lorna G. Tolchard, B. L. M. Turner, J. R. Turner, N. D. Walsh, David Watkins, J. H. White, Roy Wilton, R. P. Wise, A. R. Worters, D. A. Wright, J. D. Wright.

Diplomas were conferred on those named in the report of the meeting of the Royal College of Surgeons in our issue of Oct. 18 (p. 789). The following diplomas were also conferred:

D.M.R.-D.—W. A. Copland, R. S. Crone, E. O. Field, J. V. Goodman, R. G. Grainger, Dinah C. M. Henderson, Maurice Hurwitz, Sarva Prakash Kumar, J. W. Laws, J. C. Linn, Gopendra Nath Mukherjee, R. W. Wilkinson, S. F. Wyner.

D.M.R.-T.—Daphne S. A. Anderson, P. B. Kunkler, G. D. Smith.

British Hospitals Contributory Schemes Association (1948)

The annual conference of the association was held in Cardiff on Oct. 23 and 24 under the presidency of Mr. Henry Lesser. The speakers included Dr. Ffrangcon Roberts who said that in his opinion there was a lack of research and of health education. If people were properly informed about immunisation and other preventive measures they would be able to help themselves more and cost the National Health Service less.

Fulbright Travel Grants

The United States Educational Commission in the United Kingdom are offering these grants to citizens of the United Kingdom and Colonies who wish to visit America for an academic or educational purpose, such as study, research, or lecturing, during 1953–54. The grants will cover the cost of direct travel between the candidate's home in the United Kingdom or Colonies and the destination in America, but since the funds of the commission are in non-convertible sterling, it is not possible to offer grants for maintenance, tuition, or incidental expenses within the United States. Further particulars may be had from the commission at 55, Upper Brook Street, London, W.1.

Charterhouse Rheumatism Clinic

Sir Adolphe Abrahams will deliver the Gilbert Scott lecture on Thursday, Nov. 20, at 5 P.M., at the clinic, 54, Weymouth Street, London, W.1. He will speak on the Simplicity and Profundity of Rheumatism. Further particulars will be found in our advertisement columns.

Medical Art Society

At a meeting of this society, to be held on Thursday, Nov. 13, at 8 P.M., at 11, Chandos Street, London, W.1, Mr. Roland Penrose will talk on Modern Painting.

Helping the Patient to Read

The Miller General Hospital, Greenwich, has installed a Pilgrim microfilm reader which throws reading matter on the wall or ceiling. The patient who cannot use his hands can operate the instrument by pressing a lever to advance or retard the pages. Libraries of films of books for adults and children are available. The instrument is made by Educational Productions Ltd., 17, Denbigh Street, S.W.1. A similar American projector was described in our columns some years ago (1945, ii, 31).

Medical Women's Federation

In celebration of its 35th anniversary the Medical Women's Federation held a congress in London last weekend. After the opening on Saturday morning by Helen Duchess of Northumberland, the Christine Murrell memorial lecture was delivered by Dame Hilda Lloyd, who spoke on Domiciliary Midwifery. Saturday afternoon was devoted to the meeting reported on p. 930, and on Sunday there were clinical and other demonstrations at hospitals and laboratories.

A dinner on Saturday evening was attended by several hundred members and many guests. Sir Cecil Wakeley, P.R.C.S., proposing the Medical Women's Federation, said he thought that medical women were still not accorded the equality they ought to have. He had welcomed the appointment of a woman examiner for the Primary Fellowship, and he looked forward to women examining for the Final Fellowship. The present congress was a large and representative gathering, and the federation had nearly as many members as the Royal College of Surgeons had fellows. Moreover, some departments of medicine were better run by women than by men. Why, for example, were the maternity and child-welfare services not run by women, and why was there only one woman medical officer of health? Women could teach their subjects better than men. His own first house-surgeon, a woman, had been regarded with misgiving but had taught him more about patients than anyone else had done. And every practising doctor had got to be a psychologist and learn how to treat patients. Dr. Doris Odlum, the president, said that, as the war had prevented the federation from celebrating its first 25 years, it was celebrating its first 35 instead. The women who founded it certainly had no thought of separation—no sense of grievance. Then and since, the federation had had help and kindness from the British Medical Association and 100% loyalty in the fight for equality for women. Attempts had been made to get women to undercut men; but the women too had played fair; and their solidarity had enhanced the dignity and status of the whole profession. As a minority of 1 in 10, women doctors found it difficult to get full representation on committees and the like; and there was a place for a minority group which could express the group's point of view. With their practices preponderantly (though by no means wholly) among women, members of the federation were apt to get a rather different view from that of men, and Dr. Odlum believed they were making a very real contribution to medicine and especially to social medicine. This was done partly through the evidence presented by the council at inquiries; and service on the council, with its 65 members, had an additional value in helping members to look at subjects nationally. In all these years the federation had never had a congress for combined scientific and social activity; but the success of this one suggested that it would not be the last. The toast of The Guests was proposed in friendly terms by Dr. Janet Aitken, and Miss Patricia Hornsby-Smith, parliamentary secretary to the Ministry of Health, responded.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 970. The proportion admitted was 92·6%.

The Order of the Crown of Johore of the rank of Data Paduka Mahkota Johore, has been conferred upon Dr. H. B. C. Wallace, State physician to the Sultan of Johore.

Diary of the Week

NOV. 9 TO 15

Monday, 10th

London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1
5.15 P.M. Dr. Henry E. Sigerist (Yale): Galen's *Hygiene.* (First of five Heath Clark lectures.)

Royal Institute of Public Health and Hygiene, 28, Portland Place, W.1
4.30 P.M. Major-General H. C. D. Rankin: Review of Army Health. (Blackham lecture.)

Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Prof. T. J. Bosworth, D.V.S.M.: Pathogenesis and Control of some Diseases of Newborn Animals.

Institute of Psychiatry, Maudsley Hospital, Denmark Hill, S.E.5
4.30 P.M. Dr. E. Stengel: Lecture-demonstration.

Royal Eye Hospital, St. George's Circus, Southwark, S.E.1
5 P.M. Prof. Arnold Sorsby: Criteria for Diagnosis of Hereditary Affections.

Medical Society of London, 11, Chandos Street, W.1
8.30 P.M. Meeting of fellows. Mr. Rodney Smith, Mr. Guy Blackburn: Acute Intestinal Obstruction.

Tuesday, 11th

Royal College of Physicians, Pall Mall East, S.W.1
5 P.M. Prof. A. A. Moncrieff: Infection in the Newborn Baby. (Charles West lecture.)

London School of Hygiene and Tropical Medicine
5.15 P.M. Dr. Sigerist: *Regimen Sanitatis Salernitanum* and some of its Commentators. (Second of five Heath Clark lectures.)

Royal Society of Medicine, 1, Wimpole Street, W.1
8 P.M. *Section of Psychiatry.* Dr. G. Garmany, Dr. H. J. Shorvon, Dr. S. Lowy: Abreaction.

Institute of Dermatology, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. C. O. Carter: Genetics.

West End Hospital for Nervous Diseases, 73, Welbeck Street, W.1
5.30 P.M. Dr. Gerald Parsons-Smith: Neurological demonstration.

Chelsea Clinical Society
8.30 P.M. (South Kensington Hotel, 41, Queensgate Terrace, S.W.7.) Mr. Richard Eve, F.R.I.B.A.: Architecture and Health.

Manchester Medical Society
5 P.M. (University of Manchester.) *Section of Surgery.* Mr. H. Bolton: Surgery of the Hand.

Wednesday, 12th

London School of Hygiene and Tropical Medicine
5.15 P.M. Dr. Sigerist: Quest for Long Life in the Renaissance. (Third of five Heath Clark lectures.)

Royal Society of Medicine
4.30 P.M. *Section of Physical Medicine.* Future Rôle of Occupational Therapy in Rehabilitation.
8 P.M. *Section of Proctology.* Mr. O. Lloyd-Davies: Diverticulitis. (Presidential address.)

Royal Eye Hospital
5.30 P.M. Mr. L. H. Savin: Surgery of the Eyelids, Lacrimal Sac, and Orbit.

Royal Institute of Public Health and Hygiene
3.30 P.M.: Dr. J. W. Starkey: Caring for the Very Young Child.

Institute of Dermatology
5.30 P.M. Dr. H. Haber: Diagnosis by Biopsy and Cytology.

Institute of Urology, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. J. D. Ferguson: Prostatic Cancer.

Harveian Society of London, 11, Chandos Street, W.1
8.15 P.M. Sir Clement Price Thomas: Rôle of Surgery in Treatment of Pulmonary Tuberculosis.

University of Oxford
5 P.M. (Radcliffe Infirmary.) Dr. E. E. Pochin: Radio-iodine in the Diagnosis and Treatment of Thyroid Disease. (Litchfield lecture.)

Manchester Medical Society
4.30 P.M. *Section of Pathology.* Dr. L. Parker, Mr. G. K. Tutton: Cerebral Abscess.

Royal Faculty of Physicians and Surgeons, 242, St. Vincent Street, Glasgow, C.2
5 P.M. Prof. A. C. Frazer: Causes and Effects of Defective Intestinal Absorption. (Weild lecture.)

Thursday, 13th

Imperial Cancer Research Fund
5 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Prof. M. J. Stewart: Synovial Tumours, Simple and Malignant.

London School of Hygiene and Tropical Medicine
5.15 P.M. Dr. Sigerist: John Peter Frank (1745–1821), pioneer in Social Medicine. (Fourth of five Heath Clark lectures.)

Royal Society of Medicine, 1, Wimpole Street, W.1
5 P.M. *Section of Ophthalmology.* Prof. W. J. B. Riddell: Stenosis of the Tear Duct in Babies.

Royal Eye Hospital
5.30 P.M. Miss M. Savory: Newer Therapeutic Measures.

St. George's Hospital Medical School, Hyde Park Corner, S.W.1
5 P.M. Dr. M. A. Partridge: psychiatry lecture-demonstration.

Institute of Dermatology
5.30 P.M. Dr. R. W. Riddell: Skin Infections due to Yeast-like Organisms.

Institute of Obstetrics and Gynæcology
2 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Dr. Denis Hill: Puerperal Insanity.

Alfred Adler Medical Society
8 P.M. (11, Chandos Street, W.1.) Dr. T. A. Werner: Principles of Psychodynamics in Psychotherapy.

University of Oxford
8.30 P.M. (Wingfield-Morris Orthopædic Hospital.) Sir Harry Platt: Significance of Anatomical Findings in Open Operations in Congenital Dislocation of the Hip.

Liverpool Medical Institution, 114, Mount Pleasant, Liverpool, 3
3 P.M. Mr. A. Rocyn Jones: Evolution of the Treatment of Joint Tuberculosis and the Influence of Hugh Owen Thomas. (Hugh Owen Thomas lecture.)

Honyman Gillespie Lecture
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Dr. I. Simson Hall: Cancer of the Larynx.

University of St. Andrews
5 P.M. (Medical School, Small's Wynd, Dundee.) Mr. T. McW. Millar: Chronic Ulcerative Disease of the Colon.

Friday, 14th

London School of Hygiene and Tropical Medicine
5.15 P.M. Dr. Sigerist: Changing Pattern of Medical Care. (Last of five Heath Clark lectures.)

Royal Eye Hospital
4.30 P.M. Mr. A. J. Cameron: Red Eye and its Differential Diagnosis.

Institute of Dermatology
5.30 P.M. Dr. R. T. Brain: Epithelial Tumours.

Lloyd-Roberts Lecture
4.30 P.M. (St. Mary's Hospitals, Whitworth Street West, Manchester.) Prof. Miles Phillips: Percivall Willughby, Gentleman: Man-Midwife of the 17th Century.

Saturday, 15th

Biochemical Society
10.30 A.M. (London School of Hygiene and Tropical Medicine.) Symposium on Immunochemistry.

Appointments

Caldwell-Nichols, M. A., M.B. Edin., D.M.R.D.: asst. radiologist (S.H.M.O.), York A and Scarborough group.

Coulter, H. H., M.B. Belf.: appointed factory doctor, Westbury-on-Trym district, Gloucestershire.

Douglas, Mary, M.D. Edin., D.M.R.T.: consultant, radiotherapy department, Royal Infirmary, Edinburgh.

Duncan, J., M.B. Aberd., D.M.R.D.: radiodiagnosis department, Royal Infirmary, Edinburgh.

Greening, W. P., F.R.C.S.: consultant surgeon, Royal Cancer Hospital, London.

Hill, T. W., M.D. Glasg., D.P.H.: asst. school M.O., Middlesbrough.

Hood, W. G., M.B. St. And., D.L.O.: asst. E.N.T. surgeon, Glasgow E.N.T. Hospital.

Mayer, Helen, M.R.C.S., M.R.C.O.G.: part-time obstetrician and gynæcologist (consultant), The Mothers' Hospital (Salvation Army), London.

Radley-Smith, E. J., M.D., M.S. Lond., F.R.C.S.: asst. surgeon (consultant), Royal Free Hospital, London.

Sloan, J. B., M.B. Glasg.: appointed factory doctor, Southampton district.

Summers, Frank, M.B. Lond., D.P.H.: deputy M.O.H., Tottenham.

Manchester Regional Hospital Board:

Knowles, E. W., M.CH.ORTH. Lpool, F.R.C.S.E.: consultant orthopædic surgeon i/c orthopædics and accident services, Wigan and Leigh hospitals.

Martin, A. A., L.R.C.P.E., D.P.M.: consultant psychiatrist, Barrow and Kendal areas and Lancaster Moor Hospital.

Milner, E. A., M.B. Durh., D.A.: consultant anæsthetist, Blackburn and district hospitals.

Russell, J. Y. W., M.B. Edin., F.R.C.S.E.: consultant (asst.) general surgeon, Preston and Chorley hospitals.

Silverman, Maurice, M.D. Leeds, D.P.M.: consultant psychiatrist, Blackburn and Burnley hospitals.

Smith, A. E., M.B. Edin., D.A.: consultant anæsthetist, Wigan and Leigh hospitals and Wrightington.

Stalker, Randal, M.B. Edin.: tuberculosis physician, Blackburn and district hospitals.

Warrington, H. C., M.B. Manc., F.F.R., D.M.R.T.: consultant radiotherapist, Christie Hospital and Holt Radium Institute, Manchester.

Oxford Regional Hospital Board:

Rydlewski, Stanislaw, M.B. Polish School of Medicine, D.P.M.: asst. psychiatrist (S.H.M.O.), St. Crispin's Hospital, Duston, Northants.

Thompson, Robert, M.B. Belf., D.P.M.: consultant psychiatrist, St. Crispin's Hospital, with duties in the child-guidance clinics of the Northampton area.

Walker, Oliver, M.D. Lpool, D.A.: consultant in anæsthetics, hospitals of the Aylesbury-High Wycombe area.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

THE FUTURE OF SURGERY IN THE TREATMENT OF SPONTANEOUS CEREBRAL HÆMORRHAGE*

MURRAY A. FALCONER
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SPONTANEOUS cerebral hæmorrhage is common and often fatal. It may present in one of two main forms: (1) *intracerebral hæmorrhage* characterised by abrupt onset of severe headache followed quickly by drowsiness and even coma, and by the rapid development of signs of focal cerebral damage, such as hemiplegia, aphasia, or hemianopia; and (2) *subarachnoid hæmorrhage* characterised by a similar sudden onset of cerebral symptoms but differing in that there is usually little or no evidence of focal cerebral damage apart from cranial nerve lesions, such as a third-nerve palsy or a subhyaloid hæmorrhage. In subarachnoid hæmorrhage blood is found in the cerebrospinal fluid (C.S.F.) on lumbar puncture, whereas in intracerebral bleeding the C.S.F. may be either clear, xanthochromic, or bloodstained, according to the extent to which blood has leaked into the ventricular or the subarachnoid spaces. Either form of bleeding can affect a person at any age, although both are seen more often between the ages of 40 and 60 (Hyland 1950, Falconer 1951). Both have hitherto been regarded as "vascular accidents" outside the scope of any direct intervention, and consequently have been treated routinely only by rest in bed in the hope that bleeding would cease spontaneously and not recur.

With such conservative treatment, however, the mortality from both forms of cerebral hæmorrhage is high. Precise figures relating to primary intracerebral bleeding (as distinct from cerebral thrombosis) are not available; but nearly all these patients die, and cerebral hæmorrhage ranks predominant as a killing disease of the nervous system (Wilson 1940). As regards subarachnoid hæmorrhage, many workers have pointed out that among hospital patients the mortality-rate is generally 50–60%, and that many of those who recover are left disabled (Hyland 1950, Falconer 1951, Mount 1951). An important factor is the frequency of recurrent attacks; about a third of patients who reach hospital die from their initial attack, and nearly half the survivors subsequently develop a recurrent attack while they are still in hospital, with further loss of life (Magee 1943). These recurrent attacks reach their peak between two and four weeks from the first attack, but the possibility of recurrence remains for months and years. Ask-Upmark and Ingvar (1950) have summarised the position by saying that of 5 patients who develop subarachnoid hæmorrhage 3 will probably die, 1 will be left crippled, and only 1 will make a good recovery.

ÆTIOLOGY OF SPONTANEOUS CEREBRAL HÆMORRHAGE

If the mortality of cerebral hæmorrhage is to be lessened, we must first know its common causes and how they can be recognised during life. In this connection the distinction between intracerebral and subarachnoid forms of bleeding is a secondary consideration, for the same causal lesion may produce both types.

Intracerebral hæmorrhage.—The chief cause of primary intracerebral bleeding is rupture of an atheromatous artery in a person with high blood-pressure, and in most instances this occurs in late middle life. The syndromes of rupture of the lenticulostriate arteries in relation to the internal capsule and of the perforating arteries in the pons are well known, but they are really the terminal events of widespread disease processes that remain outside the scope and possibilities of surgery. Other lesions, however, may also cause intracerebral bleeding, and these lesions, which include aneurysm, vascular malformation, and occasionally even a vascular cerebral tumour, although in the aggregate not so common as rupture of an atheromatous artery, account for many cases of apoplexy not only in young persons but also in the elderly. Sometimes no source for the bleeding is apparent even at necropsy.

Subarachnoid hæmorrhage.—As regards subarachnoid hæmorrhage, the commonest cause is rupture of an intracranial aneurysm and this cause accounts for about 75–80% of cases (Richardson and Hyland 1941, Falconer 1951). Vascular abnormalities account for 5–10% of cases, and usually in the remainder no source for the bleeding can be demonstrated (Richardson and Hyland 1941). Rupture of an atheromatous vessel possibly accounts for some of these cases and occasionally a vascular cerebral tumour first manifests itself in this way.

Now two of the causes of cerebral hæmorrhage, aneurysms and vascular malformations, deserve special consideration for they are common, can be readily recognised and located during life, and are remediable by surgical treatment.

Intracranial aneurysms are saccular or "berry-shaped" pouches generally situated in the angle of branching of a major cerebral artery. Once mistakenly subdivided into congenital and arteriosclerotic varieties, they are really all acquired lesions which develop as a result of degenerative processes affecting the arterial wall at a site already weakened by a congenital deficiency of the muscular coat (Simpson 1947, Carmichael 1950). Generally small, and often only a few millimetres in diameter, they may occasionally be large, reaching three or more centimetres across, but such large aneurysms, when they do occur, are more likely to cause symptoms by compressing neighbouring structures than by causing cerebral hæmorrhage. Intracranial aneurysms have certain sites of predilection, and these are well shown in fig. 1. They occur most frequently in the anterior half of the circle

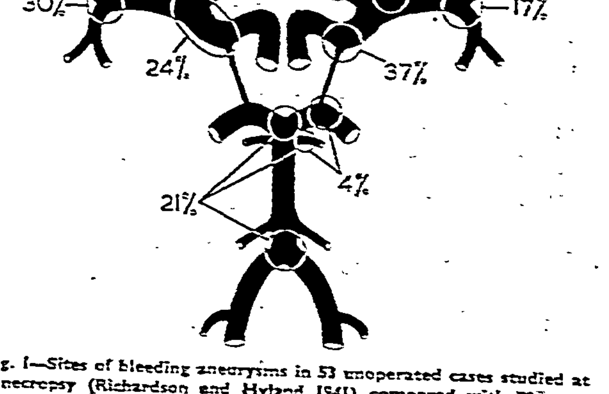

Fig. 1—Sites of bleeding aneurysms in 53 unoperated cases studied at necropsy (Richardson and Hyland 1941) compared with 70 cases operated on by the author.

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* Fifth Alex Simpson Smith Memorial Lecture delivered at the West London Hospital Medical School on June 19, 1952.

of Willis, sometimes on arterial branches distal to the circle, notably the anterior cerebral artery and the middle cerebral artery, and only occasionally on the posterior half of the circle or on the basilar arterial system. These facts have *important bearings* :

(1) Most intracranial aneurysms, particularly those which rupture, are supplied by the internal carotid artery and consequently can be demonstrated by carotid arteriography, whereas only a few aneurysms are so situated that vertebral arteriography is required to demonstrate them.

(2) Whereas aneurysms of the circle of Willis lie within basal cisterns and so bleed primarily into the subarachnoid space, aneurysms of the anterior cerebral artery distal to the circle and also of the middle cerebral artery tend to be surrounded by brain tissue and consequently on rupture produce a primary intracerebral hæmorrhage, which may only *secondarily* burst into a ventricular cavity or the subarachnoid space. Indeed, in the event of death, the pathologist, unless he carefully dissects out the distal cerebral arteries, may not find the causal aneurysm and may mistakenly label the case as one of idiopathic apoplexy.

(3) Aneurysms on the intracranial internal carotid artery—e.g., those situated in relation to the posterior communicating artery—may lie astride the arachnoid mater and can thus bleed into the subdural space, producing a subdural hæmatoma (Logue 1951, also my personal observations).

(4) Anomalies of the circle of Willis are often associated with intracranial aneurysms, perhaps in as much as a third of cases (personal observations), and these often have to be considered when planning surgical intervention.

Arteriovenous malformations have been described under different labels, of which cirsoid angiomas, arteriovenous aneurysms, arteriovenous hamartomas, and angiomatous malformations have each had wide acceptance. The lesion consists of a mass of coiled vessels, some arterial and some venous, which is fed by one or more large branches direct from a major cerebral artery and is drained by several large venous channels which each pass to a major venous sinus. The malformation may vary in diameter up to 10 cm. or even more and is essentially an arteriovenous fistula, the degree of shunting of arterial blood into the venous system sometimes being such as to influence adversely the circulation of blood through neighbouring parts of the brain. Some of these lesions are situated over the convexity of a cerebral hemisphere, others are deeply placed. Although of congenital origin (Olivecrona and Riives 1948), they gradually but steadily increase in size. Rarely do they produce symptoms before the age of 10 years. Epilepsy is then the common symptom, particularly with the larger malformations, but sometimes, especially with the smaller lesions, bleeding may occur instead. Such bleeding is generally intracerebral, but often it shortly spills into the subarachnoid fluid. There is a distinct tendency for the bleeding to be limited in amount but recurrent, so that several attacks may occur over the years before a fatal episode is reached (Wechsler and Gross 1948).

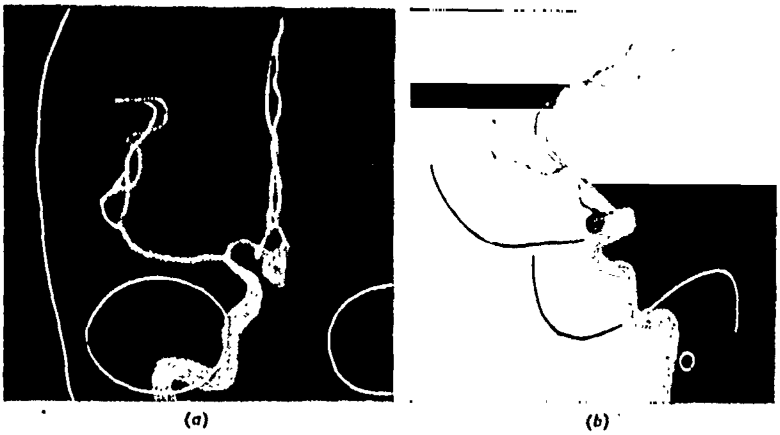
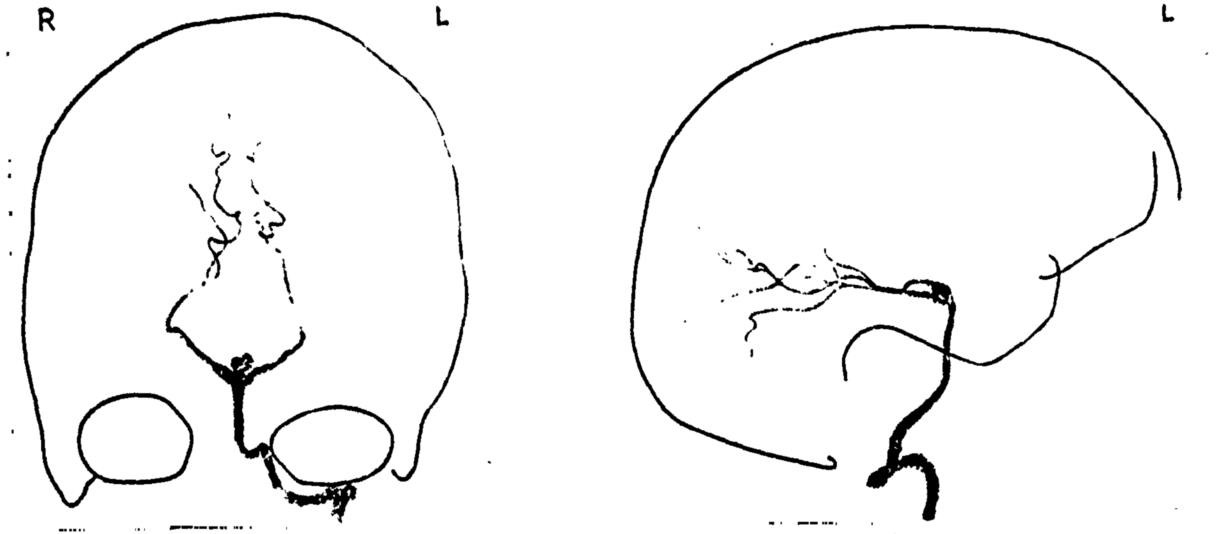

(a) (b)

Fig. 2—Tracings of carotid arteriograms showing aneurysm of anterior communicating artery. Both anterior cerebral arteries distal to this level are being filled. Treatment recommended : direct operative approach with possibly packing of aneurysm with muscle pledgets.

RECOGNITION OF CAUSES DURING LIFE

Most aneurysms and angiomas can be identified and located during life by cerebral arteriography (figs. 2 and 3), and the question therefore arises what are the indications and contra-indications for this procedure. The development by the Scandinavians (Lindgren 1947) during the 1939–45 war of a technique involving needle puncture of the carotid artery through the intact skin (percutaneous carotid arteriography) and the supersession



(a) (b)

Fig. 3—Tracings of left vertebral arteriograms showing aneurysm at bifurcation of basilar artery. Treatment recommended : ligation of left vertebral artery.

of ‘ Thorotrast ’ as the contrast medium by the excretable diodone solutions have made this investigation widely applicable. Indeed in expert hands percutaneous carotid arteriography has become safe and satisfactory, and can be readily used in most cases of recent cerebral hæmorrhage with little fear of upsetting the patient. It has, however, some important contra-indications. One of these is arterial hypertension with advanced vascular degeneration, for in such patients the introduction into an artery of even a slightly irritant medium may provoke vasospastic and thrombotic effects. Consequently it is not yet applicable to the large group of cases of internal capsular or pontine hæmorrhage occurring in hypertensive persons, which anyway, as stated earlier, is a group that is outside the scope and possibilities of surgery. In most cases of primary subarachnoid hæmorrhage, however, whatever the age-period, and in many cases of primary intracerebral hæmorrhage, especially in young or middle-aged persons, there is no such objection to the procedure. Our practice in such cases is to recommend that carotid arteriography be done early, preferably within a week of the onset of symptoms, so that the causal lesion may be recognised and its treatment begun before risk of recurrent bleeding rises to its peak. Mount (1951) in the United States and Norlén (1952) in Sweden make similar recommendations. Even in elderly and middle-aged people with subarachnoid hæmorrhage and a blood-pressure about 200/140 mm. Hg we would do percutaneous arteriography if the cardiovascular system otherwise seemed healthy, for in many such patients a bleeding intracranial aneurysm is responsible for the symptoms. We have noted that, when the acute symptoms subside, the blood-pressure sometimes returns to normal.

Our routine is to obtain in all cases of subarachnoid hæmorrhage bilateral carotid arteriograms, because in more than 10% of cases two or more aneurysms are present. Bilateral carotid arteriography is also useful in demonstrating the effectiveness of the collateral circulation of the circle of Willis; for, if the carotid of one side is compressed while that of the other is being injected, the contrast medium can often be demonstrated to pass across the midline to the opposite cerebral hemisphere. If carotid arteriography is negative, we usually proceed a few days later to vertebral arteriography (fig. 3), for which several techniques are available (Takahashi 1940, King 1942, Radner 1951). In these ways we feel that we can demonstrate most intracranial aneurysms or arteriovenous malformations. We can also deduce the presence of any sizable intracerebral or subdural clots adjacent to these lesions, and now and then we have located an intracerebral clot due to some other cause, such as a perforation of a cerebral vessel or the presence of a vascular tumour. The treatment of these various lesions now requires our attention.

TREATMENT OF BLEEDING INTRACRANIAL ANEURYSMS

Proximal Ligation

The sheet-anchor of treatment in intracranial aneurysms is ligation of either a carotid or a vertebral artery. Carotid ligation acts by reducing the arterial pressure within the aneurysm, so favouring its shrinkage or even its thrombosis. Always a somewhat risky procedure, in the presence of recent intracranial bleeding it seems to carry increased hazards. Schorstein (1940), for instance, reported a mortality-rate of 14% in 22 non-bleeding cases of aneurysm treated by carotid ligation, whereas in a comparable group of bleeding aneurysms the mortality was 55%. Jefferson (1952) and Johnson (1952) report having treated by carotid ligation 142 cases of aneurysm, both bleeding and non-bleeding, with only 12 deaths (mortality-rate 8%), but these deaths all occurred in a subgroup of 29 cases in which the carotid was ligated within a few hours of a severe hæmorrhage (mortality-rate in the presence of active bleeding 41%). Presumably in such cases the intracranial bleeding either kills by producing a large space-occupying lesion or it renders the brain more susceptible to anoxic effects of a partial diminution in the cerebral blood-supply, which otherwise would have been tolerated.

Several techniques of ligation have been tried in attempts to eliminate the risks of carotid ligation, but no one method has proved its superiority. There is, however, general agreement that ligation of a common carotid artery carries less risks than does ligation of an internal carotid artery. My own preference is to ligate the common carotid artery in two stages, and then the internal carotid artery in a further stage. Various precautions have usually to be taken beforehand to ensure that the ligation would be tolerated (Falconer 1950, 1951), and after these in 36 cases, nearly all of recent bleeding, I experienced a mortality of 17%.

Ligation of one vertebral artery, that artery being selected which had been successfully filled on arteriography, has now been done by me in three cases of aneurysm of the basilar or of the posterior cerebral artery. In each instance the artery was exposed under local analgesia at its origin low in the neck, and was only tied after a trial period of occlusion had been tolerated. All three patients recovered, but it is difficult to judge the merits of the procedure from so few cases. Although Dandy (1944) stated that he had ligated one vertebral artery “perhaps 20 times without any untoward effect,” the procedure has risks, and fatalities following ligation of one vertebral artery have been reported by Guthkelch (1949) and by French and Haines (1950). Moreover its efficiency is diminished by the fact that the other vertebral artery remains patent and will still supply the arterial segment which carries the aneurysm.

Intracranial Approach

Carotid ligation by itself is of great value for aneurysms of the internal carotid artery, but for aneurysms on the circle of Willis or its distal arterial branches its benefits may be only transient because of the collateral circulation from the opposite carotid artery through the circle of Willis. Several surgeons (Falconer 1951, Mount 1951, Norlén 1952) therefore recommend that most aneurysms should be tackled by a direct operative approach along the lines advocated by Dandy (1944). By means of a frontal craniotomy it is generally possible to expose an aneurysm of the internal carotid artery or of the anterior or middle cerebral arteries without damaging or sacrificing any cerebral substance. The intracranial internal carotid artery and its bifurcation are readily exposed by a subfrontal approach, the anterior cerebral artery by retracting the frontal lobe from off the falx and the opposite cerebral hemisphere, and the middle cerebral artery by opening up the fissure of Sylvius. Any sizable clots from within the adjacent frontal or temporal lobes should be removed so that their space-occupying effects can be relieved. Such intracerebral clots occur particularly with aneurysms of the anterior and middle cerebral arteries.

Once an aneurysm is exposed, various local measures can be applied to it according to circumstances. Its neck, if narrow and accessible, can be clipped or ligated with silk. If the collateral circulation is adequate, the parent artery can be clipped or ligated on either side of the aneurysm, thus trapping it. Now and then the aneurysm may be excised, as when it is situated on a relatively unimportant vessel, such as the distal part of the anterior cerebral artery. The method which I have found most generally applicable is to wrap pledgets of hammered muscle round the aneurysm, after its sac has been carefully freed on all sides. This method, first introduced by Dott (1933), seems in my experience to be of permanent value. It does not impair the flow of blood through the diverging parent arteries, and thus has particular merit when the aneurysmal neck is inaccessible or is too wide to carry a clip or a ligature. Occasionally one encounters an aneurysm which is too large to be treated in any of these ways, and can be treated only by proximal arterial—e.g., carotid—ligation.

One of the risks in exposing an intracranial aneurysm is that it may burst while it is being dissected out. This has happened to me several times, but fortunately I have always managed to control the bleeding by packing the aneurysm round with hammered muscle. This complication, however, can be obviated through lowering the blood-pressure during operation by producing a postural hypotension with the hexamethonium drugs (Enderby 1951). The method has its hazards, but the secret seems to be not to lower the systolic blood-pressure in the brachial artery, where it is normally recorded, too far—e.g., below 80-90 mm. Hg—for the intracranial arterial pressure may be even less than this, especially when the head is postured a little above the rest of the body. In an early stage of our experience we lowered the blood-pressure to 60-70 mm. (a level advocated for some other fields of surgery) and in one patient we encountered an alarming cessation of respiration. Further experience is necessary before we become acquainted with all the major hazards of this refinement of anæsthesia, but the method holds much promise.

By March, 1952, I had operated on 70 cases of intracranial aneurysm, mostly with recent bleeding: 47 patients have made a good recovery, 11 have been left with a residual disability, and 12 have died in the postoperative period (mortality-rate 17%). One death, however, was from paroxysmal tachycardia and disease of the coronary artery. Nine of the deaths were in a subgroup of 57 patients submitted to an intracranial operation, often after a preliminary carotid ligation (mortality-rate 21%). The remainder were treated by proximal arterial ligation. These results are a great improvement on the prospects of patients treated conservatively, and probably most of the patients who survived will prove to have permanently recovered. But the chance of later rupture from a second aneurysm remains. My cases have now been followed up for periods of up to six years. The follow-up is fairly complete, and I have learnt of 2 deaths occurring two or three years after operation. In each instance a necropsy revealed a second and untreated intracranial aneurysm which had ruptured.

TREATMENT OF BLEEDING ARTERIOVENOUS MALFORMATIONS

Until recently these lesions were regarded as rare and hopeless propositions. Attempts at treating them were limited to either carotid ligation or to deep X-ray therapy. There was never any good evidence that either procedure conferred benefit. Carotid ligation could even be dangerous, as Olivecrona (1944) learnt when hemiplegia supervened in 4 of 7 cases in which he applied this treatment, the hemiplegia proving permanent in 2 cases in which the ligature was not removed. The explanation probably is that the short-circuiting of blood through the fistula heightens the risk of severe anoxæmia of the affected hemisphere when the total blood-supply to the brain is diminished by tying off one carotid artery. Olivecrona and Riives (1948) reported having observed a continued increase in the size of the malformation in a case which was treated intensively by deep X-ray therapy.

As a result of the more frequent use of cerebral arteriography (fig. 4) we now know that these lesions are much more common than was hitherto thought. We also know that most of them are directly operable, preferably by complete excision or, if that is not practicable, by clipping of the feeding arteries. The technique of excising these lesions was worked out particularly by the Swedish neurosurgeons (Olivecrona and Riives 1948, Norlén 1949) and is readily applicable if the lesion is accessible, as when it is situated over the convexity of the cerebral hemisphere. Any associated intracerebral clot is, of course, removed. Sometimes, however, the malformation is deep-seated or is situated in a particularly eloquent region, such as Broca's area, and then excision of the lesion may be either impossible or fraught with grave risks of maiming. In such circumstances surgical intervention is limited to evacuation of the clot plus ligation or clipping of the arterial branches which feed the malformation (Jaeger 1950). Even this simpler measure will usually render the malformation impotent as regards further bleeding, and in postoperative arteriograms the arteries in other regions of the cerebral hemisphere will be seen to fill more normally because the arteriovenous shunt has been corrected (personal observations).

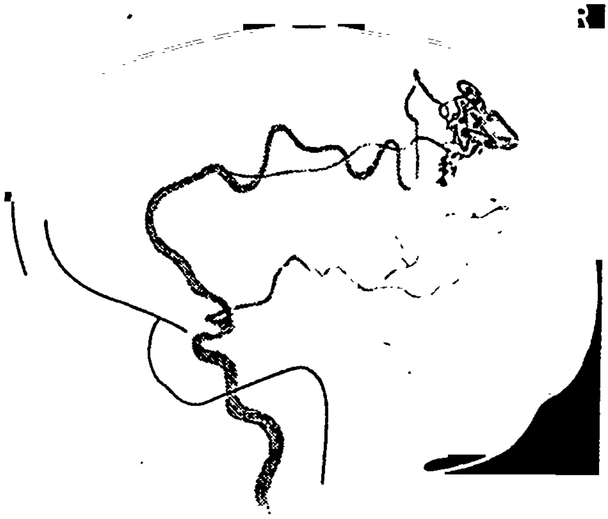


Fig. 4—Tracing of carotid arteriogram showing arteriovenous malformation at termination of anterior cerebral artery. Treatment recommended: excision.

My own experience of bleeding arteriovenous malformations now extends to 9 cases, of which 3 were excised, 1 was treated only by evacuation of the clot, and the remainder were treated by clipping the feeding arteries. All the patients recovered after craniotomy. The 3 malformations which were excised were all cortical lesions situated close to the superior longitudinal fissure; all 3 lesions had bled intracerebrally, and subsequently each patient was left with a mild permanent monoplegia attributable to such bleeding. Two other cortical malformations, both small but situated on the upper lip of the Sylvian fissure in the dominant hemisphere, were treated by clipping of the feeding arterial branches with almost no residual disability. Three further cases all had lesions deep-seated on a posterior cerebral artery, and in 2 of these the lesion appeared to be situated within the trigone of a lateral ventricle. All were treated by clipping of the posterior cerebral artery as it wound backwards and lateral to the crus cerebri, and just anterior to the point at which the artery gave off its posterior choroidal branch. The necessary access in each instance was obtained by lateral craniotomy with elevation of the temporal lobe from off the middle cranial fossa. In 2 of 3 patients this procedure was followed by a permanent homonymous hemianopia, but not in the third. My remaining case was in a child, aged 3 years, from whom I evacuated an intracerebral clot which had caused symptoms of semicoma and vomiting lasting a few days. At operation a small arteriovenous malformation was seen in the adjacent brain. This was several years ago, before my present interest in these lesions; but, so far as I know, the child still survives. My personal experience therefore is that bleeding arteriovenous malformations, whether superficial or deep, can usually be dealt with by surgery.

TREATMENT OF SPONTANEOUS PRIMARY INTRACEREBRAL HÆMORRHAGE

Spontaneous intracerebral hæmorrhage from causes other than aneurysm and arteriovenous malformation is a field which is awaiting developments in surgery. Overshadowing the field is the grim spectre of the type of intracerebral hæmorrhage which so often terminates the life of hypertensive and arteriosclerotic people. Such hæmorrhages are usually deep-seated, often in the basal ganglia or internal capsule, are usually rapidly fatal, and offer surgery no prospects, because the lesion is inaccessible and extensive damage is usually caused to deep structures in the brain. Rose (1948) has shown that 80% of such patients die within 2–24 hours of the onset of symptoms. Fortunately not all cases of arteriosclerotic bleeding follow this pattern, and there are also other causes of primary intracerebral hæmorrhage which are favourable for surgical treatment (Penfield 1933, Craig and Adson 1936, Beck 1952).

The following four personal case-records indicate something of the surgical possibilities. Bleeding presumably took place from an arteriosclerotic artery in a hypertensive person in case 1, from an obscure arterial perforation in a child in case 2, and from metastatic tumour with an apparently favourable prognosis in case 3; and no cause for the bleeding was found in case 4.

Case 1.—A man, aged 56, suddenly found, while driving his car, that he could not see the left-hand side of the road, and shortly afterwards developed a severe headache. That night he became drowsy and confused, vomiting frequently. When examined three days later he exhibited a left-sided hemiparesis and a left homonymous hemianopia. His blood-pressure was 180/110 mm. Hg. His C.S.F. was xanthochromic. Right carotid arteriography disclosed displacement upwards and forwards of the right middle cerebral artery, indicating a large space-occupying lesion within the parietal lobe. At operation a large amount of dark clotted blood was evacuated from within that lobe. No source of bleeding was seen. The patient subsequently recovered, but hemianopia persisted.

Case 2.—A boy, aged 9 years, suddenly slumped across his desk in class. He rallied shortly afterwards but became unconscious again within twenty-four hours. When admitted to a neurosurgical unit on the second day he responded only to painful stimuli. Neck retraction, opisthotonos, and right hemiparesis were present. The C.S.F. was much bloodstained. Bilateral carotid arteriography showed considerable displacement of both anterior cerebral arteries to the right side, with depression of the left middle cerebral artery. At operation a massive clot was evacuated from within the left frontal lobe. Inspection showed a tiny intramural hæmorrhage in the left anterior cerebral artery close to its origin. This was evidently a tiny perforation, and seemingly had been the site of bleeding. The boy recovered completely.

Case 3.—A man, aged 46, suddenly developed headache with vomiting, and during the next few days became increasingly drowsy and confused. When admitted six days later he was stuporose and exhibited bilateral papillœdema, scanty localising signs, and xanthochromic C.S.F. Ventriculography indicated a right temporal space-occupying lesion. At operation this proved to be an intracerebral clot surrounding a small tumour, which was removed and proved to be a metastatic hypernephroma. Renal investigations, including a unilateral kidney exploration, revealed no abnormality. The patient remains symptom-free eight years later.

Case 4.—A girl, aged 12 years, but not yet menstruating, had complained, for more than three months, of morning headaches with occasional vomiting. There was no history of trauma. The symptoms seemed to be gradually increasing. Examination disclosed bilateral papillœdema and an incomplete right homonymous hemianopia as the only neurological signs. At operation an encapsulated hæmatoma containing solid clot was found. The source of the bleeding was not seen. Postoperative carotid and vertebral arteriograms showed no abnormality. The patient recovered completely.

Such case-histories could be multiplied by the experience of other workers (Penfield 1933, Craig and Adson 1936, Beck 1952). Primary intracerebral hæmorrhage can occur at all ages. Bleeding aneurysms, arteriovenous malformations, trauma, and unsuspected tumours account for some cases, but often no source of bleeding can be found. Presumably in some of these cases leakage from a degenerate artery is responsible for the bleeding, but in others there is no evidence of widespread arterial disease. As regards the mode of presentation, those intracerebral hæmorrhages which have surgical possibilities may present one of two patterns (Craig and Adson 1936, and my own observations). In the usual pattern the onset is abrupt, but instead of succumbing rapidly the patient shortly afterwards begins to revive, presumably because active bleeding has ceased. The patient then presents signs of focal cerebral damage, such as a monoplegia or a hemianopia, but in contrast to the deep-seated capsular hæmorrhages the hemiplegia is seldom complete. In cases which conform to this pattern a diagnosis of cerebral vascular accident offers no difficulties. In the second pattern, however, the appearance of symptoms is gradual and progressive, suggesting a brain tumour. Case 4 was an example of this. Such cases will, of course, continue to be regarded as neoplasms until the true nature of the lesion is disclosed at operation. They are, however, less common than cases presenting the first pattern.

The inference from these various observations is that every patient whose history strongly suggests a primary intracerebral hæmorrhage, who does not succumb shortly after the onset, and who is not grossly hypertensive, should be investigated by carotid arteriography. If such a rule were followed, many more cases of intracerebral hæmorrhage suitable for operation would be recognised.

THE FUTURE

Surgery thus has much to offer for the treatment of most varieties of spontaneous cerebral hæmorrhage. In the development of this field Dott (1933) and Jefferson (1937) in this country, Moniz (1934), Krayenbühl (1941), and Olivecrona (1944) on the Continent, and Dandy (1944) in the United States must be regarded as the chief pioneers, but many others have also contributed. Mount (1951) has collected statistics relating to the mortality of subarachnoid hæmorrhage and has shown that in 752 medically treated cases, comprising his own as well as seven large series previously published, there was a mortality-rate of 48%. On the other hand, in 469 surgically treated cases from thirty-seven sources, also published, there was a mortality of 14%. Although there may be objections to a strict comparison of these two groups, these findings clearly show that the prognosis of subarachnoid hæmorrhage can be greatly improved by timely surgical intervention.

Surgery in these conditions is still in its early stages, and we have a great deal yet to learn about the handling of these various lesions. Without doubt there will be many more advances. The statistics of the Registrar-General show that in 1949 the crude death-rate in England and Wales for cerebral hæmorrhage was 737 cases per million living persons and for subarachnoid hæmorrhage 30 cases per million. (Comparable figures for cerebral embolism and thrombosis were 536 deaths per million living persons [Registrar-General, personal communication].) The scope for surgery is thus large, for cerebral hæmorrhage is the principal killing disease of the nervous system, and many of these deaths undoubtedly could be prevented. The time may well come when our neurosurgical units find that the number of patient, referred to them with these conditions surpasses the number referred with brain tumour.

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RESULTS OF TREATMENT OF CANCER OF THE CERVIX

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IN 1944 a joint clinic was set up between the Chelsea Hospital for Women and the Royal Cancer Hospital for the treatment of cancer patients requiring radiotherapy. The organisation of the clinic is simple: a cancer reference clinic is held once a week at the Chelsea Hospital for Women; a surgeon appointed by the Chelsea Hospital for Women (J. B. B.) and a radiotherapist appointed by the Royal Cancer Hospital (M. L.) conduct the clinic together. Patients with cancer may be referred directly to the clinic, or the radiotherapist may see a case with one of the members of the staff of the Chelsea Hospital for Women; in either event, decisions about treatment are taken jointly by surgeon and radiotherapist. Where radiotherapy is agreed upon the patient is transferred to the Royal Cancer Hospital and undergoes examination under anæsthesia, biopsy, and cystoscopy.

TABLE I—PATIENTS SEEN IN 1944–46

—	1944	1945	1946	Total
No. of cases seen:	48	41	50	139
No. previously untreated	46	37	50	133
No. previously treated (recurrent)	2	4	0	6
No. treated	46	39	46	131
No. not treated	2	2	4	8

TABLE II—AGE-DISTRIBUTION OF PATIENTS IN 1944–46

—	Age of patients (yr.)						Total
	30–	40–	50–	60–	70–	80–	
No. of cases	12 *(9%)*	35 *(25%)*	42 *(30%)*	38 *(27%)*	9 *(7%)*	3 *(2%)*	139

In most cases decisions about the precise form radiation treatment should take are readily reached when the patient is first seen; in difficult cases, however, decisions of this sort are taken only after an examination under anæsthesia. It is an invariable rule that final decisions are only taken after full consultation between the surgeon and the radiotherapist conducting the clinic, and repeated consultations are held throughout the course of treatment. In this way the radiotherapist has the help of the surgeon on clinical matters, and the surgeon has the help of the radiotherapist in the complicated technique of radiotherapy.

TABLE III—HISTOLOGY OF TUMOURS 1944–46

—	No. of cases
Squamous-cell carcinoma	108 *(78·0%)*
Adenocarcinoma	11 *(8·0%)*
Anaplastic carcinoma	5 *(3·5%)*
No biopsy	15 *(10·5%)*
Total	139

From the point of view of technical approach, the patients in stages I and II are usually treated first by radium and in nearly all cases receive post-radium X-ray therapy. Patients in stages III and IV receive X-ray therapy first and a modified radium treatment thereafter. The planning of the X-ray treatment and the technical details of the radium treatment are entirely the responsibility of the radiotherapist, whereas the insertion of radium is largely the work of the gynæcological surgeon, the radiotherapist deputising for him when necessary. When large numbers of patients have to be treated, the insertions are shared so that the risks of exposure to each operator may thereby be lessened. The radium technique used is a modified Stockholm method. Three

TABLE IV—DISTRIBUTION OF PREVIOUSLY UNTREATED CASES ACCORDING TO STAGE AND RESULTS OF TREATMENT FOR 1944–46

—	Stage I	Stage II	Stage III	Stage IV	Total
No. of cases seen	32 *(24%)*	60 *(45%)*	33 *(25%)*	8 *(6%)*	133
No. of cases treated	32	57	32	4	125
No. of cases not treated:	0	3	1	4	8
No. refusing treatment	0	3	1	0	4
No. too advanced for treatment	0	0	0	4	4
No. of patients alive and well 5 years after treatment:	17	*27*	*5*	*0*	49
Cure-rate of cases seen	53%	45%	15%	0	37%
Cure-rate of cases treated	53%	47%	16%	0	39%
No. of patients not traced (counted as dead of disease)	0	1	0	0	1
No. of patients dead of intercurrent disease	3	2	1	0	6

insertions of radium are made, each for twenty-two hours, at intervals of a week between the first and second insertions and two weeks between the second and third insertions. The total amount of radium used is 50–60 mg. in the uterus and 30–75 mg. in the vaginal vault. For the X-ray treatment a 400 kV apparatus is used. Two main techniques are used depending on whether the radium treatment is given before or after the X-ray treatment.

Table I shows the number of cases seen in 1944–46, table II gives the age-distribution of the patients forming the series, and table III the histological types of tumours seen. Of the 15 patients in table III without histological confirmation 13 died of cancer of the cervix within five years and only 2 patients, both in stage II, are alive and well without histological confirmation. Table IV shows the distribution of the material according to stage and the results of treatment according to stage (classification according to League of Nations method of staging 1950).

TABLE V—METHOD OF TREATMENT OF PREVIOUSLY UNTREATED CASES

—	1944	1945	1946	Total
No. of cases treated by radiotherapy	36	25	41	102
No. of cases treated by Wertheim's hysterectomy	4	9	3	16
No. of cases treated by other methods	4	1	2	7

Table V shows the different methods by which the previously untreated cases were subsequently treated. The bulk of the patients were treated by radiotherapy, Wertheim's hysterectomy being used only occasionally. The decision to treat the patients by Wertheim or "other methods" was usually made by the surgeon in charge of the case.

TABLE VI—RESULTS OBTAINED WITH TREATMENT BY RADIOTHERAPY 1944–46

—	Stage I	Stage II	Stage III	Stage IV	Total
No. of cases treated	19 (*19%*)	49 (*48%*)	30 (*29%*)	4 (*4%*)	102
No. of patients alive and well 5 years after treatment ..	9 (*47%*)	25 (*51%*)	4 (*13%*)	0	38 (*37%*)
No. of patients not traced ..	0	0	0	0	0
No. of patients dead of intercurrent disease	3	2	1	0	6
No. of patients alive and well 5 years after treatment expressed as percentage of no. treated, excluding no. dead of intercurrent disease ..	56%	53%	14%	0	40%

Table VI gives the results obtained by radiotherapy. Apart from the stage I cases, the results obtained compare well with those obtained at other centres. The reasons for the unsatisfactory stage I results we believe to be the statistically insignificant number of cases, and the fact that 6 of the 19 patients received their radium treatment at the Chelsea Hospital for Women without reference to the radiotherapist. Of these 6 patients 4 died of recurrent disease. Of the 13 patients referred via the Cancer Clinic and treated at the Royal Cancer Hospital 3 died of cancer, 3 died of intercurrent disease, and the remaining 7 are alive and well.

TABLE VII—RESULTS OBTAINED BY WERTHEIM'S HYSTERECTOMY 1944–46

—	Stage I	Stage II	Stage III	Total
No. of cases treated ..	11	4	1	16
No. of patients alive and well 5 years after treatment	7	1	1	9 (*56%*)
No. of patients not traced	0	0	0	0
No. of patients dead of intercurrent disease ..	0	0	0	0

TABLE VIII—RESULTS OBTAINED WITH TREATMENT OTHER THAN RADIOTHERAPY OR WERTHEIM'S HYSTERECTOMY

—	Stage I	Stage II	Stage III	Total
No. of cases treated	3	3	1	7
No. of patients alive and well 5 years after treatment ..	1	1	0	2
No. of patients not traced ..	0	1	0	1
No. of patients dead of intercurrent disease	0	0	0	0

It is our conviction that, for radiotherapy to be successful, it must be given under proper conditions by people thoroughly experienced in the method.

TABLE IX—RESULTS OBTAINED BY RADIOTHERAPY AT CHELSEA HOSPITAL FOR WOMEN 1936–43

—	Stage I	Stage II	Stage III	Stage IV	Total
No. of cases treated	52 (*15%*)	116 (*34%*)	147 (*43%*)	29 (*8%*)	344
No. of patients alive and well 5 years after treatment ..	20 (*39%*)	32 (*28%*)	22 (*15%*)	1 (*3%*)	75 (*22%*)
No. of patients not traced (counted as dead of cancer)	6	10	12	1	29

Table VII gives the results obtained with surgical treatment. The numbers are too few to be statistically valid, but one can safely form the opinion that the radotherapy results compare more than favourably.

In table VIII are collected 7 cases treated by means other than radiotherapy or Wertheim's hysterectomy. Three of these cases had already been treated inadequately before the diagnosis was made, and in the remaining 4 cases an attempt at Wertheim's operation was abandoned, owing to technical difficulties, and radiation treatment was given. If these 4 cases are included with those on whom the operation was completed, the cure-rate is 50%, and not 56%, for cases treated by Wertheim's hysterectomy.

The advantage to those patients with cancer of the cervix who attend the cancer clinic at the Chelsea Hospital for Women is shown by comparing table VI with table IX. The latter table gives the results obtained by radiotherapy at the Chelsea Hospital for Women for the years 1936–43 before the joint clinic with the Royal Cancer Hospital was set up. For comparison the results obtained by Wertheim's hysterectomy over the same period are given in table X.

TABLE X—RESULTS OBTAINED WITH TREATMENT BY WERTHEIM'S HYSTERECTOMY AT CHELSEA HOSPITAL FOR WOMEN 1936–43

—	Stage I	Stage II	Stage III	Total
No. of cases treated	43 (*60%*)	26 (*37%*)	2 (*3%*)	71
No. of patients alive and well 5 years after treatment	19 (*44%*)	11 (*42%*)	0	30 (*42%*)
No. of patients not traced	6	3	0	9

We are indebted to our surgical colleagues on the staff of the Chelsea Hospital for Women for referring cases to us and for their coöperation and encouragement.

THE REVERSIBILITY OF MALIGNANT HYPERTENSION

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With illustrations on plate

Volhard and Fahr (1914) were the first to point out that essential hypertension might behave in one of two ways. In most patients the course of the disease was long, the patient's condition showing little change year by year, and death, when at length it came, being due to heart-failure, to apoplexy, or to intercurrent disease. This they named the benign form. In a few patients, usually younger, the disease followed a rapidly fatal course. The onset of this form, which they named malignant hypertension, was heralded by the appearance of albuminuric retinitis, soon followed by albumin and red cells in the urine and by progressive renal failure terminating in uræmia, usually within a year from the first appearance of retinitis.

Volhard showed that the distinctive clinical feature of malignant hypertension is albuminuric retinitis (hypertensive neuroretinopathy). This can be distinguished from arteriosclerotic retinitis (Foster Moore 1916–17) by the presence of bilateral neuroretinal œdema, which is absent in arteriosclerotic retinitis except as a local consequence of venous thrombosis. As Foster Moore showed, arteriosclerotic retinitis carries a much better prognosis, and it is found chiefly in benign hypotension.

Albuminuric and arteriosclerotic retinitis are, as a rule, easily distinguished, but they overlap; some cases present features of both, and one may pass into the other. Partly for this reason it is generally agreed that the most important distinction between malignant and benign hypertension is the presence in malignant hypertension, and the absence in benign hypertension, of acute arteriolar necroses (Fahr 1919). These necroses are most frequent and severe in the kidney, where they are presumably responsible for the onset and rapid progress of renal failure; they occur also in gut, pancreas, adrenal, eye, brain, heart, and liver, but not in skeletal muscle and skin.

Since Volhard and Fahr's original description it has become apparent that malignant hypertension is a syndrome that may occur in hypertension due to many causes. Ask-Upmark (1929) observed it in children with unilateral renal deformities; Klemperer and Otani (1931) in nephritis; and MacMahon et al. (1934) in Cushing's syndrome. Derow and Altschule (1935) gathered together these pieces of evidence, added more of their own, and suggested that malignant hypertension "is a syndrome which may occur (*a*) with no evidence of previously existing hypertension, (*b*) as the end stage of essential hypertension, (*c*) as the end stage of a miscellaneous group of conditions characterised by hypertension secondary to acute, subacute, or chronic glomerulonephritis, pyelonephritis, adrenal tumour, pituitary basophilism, periarteritis nodosa, hyperemesis gravidarum,* chronic lead poisoning, et cetera." In a later paper (Derow and Altschule 1941) they said that "the mechanism by which the benign course of primary or secondary hypertension is suddenly and dramatically transformed into the rapid progressive downhill course of the syndrome of malignant hypertension is not understood. Attempts to incriminate infectious toxins, mental stress, or other factors have been inconclusive."

In 1942 one of us (G. W. P.) put forward the hypothesis "that the benign and malignant courses of hypertension are merely expressive of the severity of the hypertensive process, irrespective of the lesion which ultimately determines it." It was suggested that, whatever the underlying disease, the course of the hypertension would be of the malignant type if the arterial pressure was sufficiently raised, and of the benign type if the rise was less. On this hypothesis the answer to Derow and Altschule's question would be that the benign is transformed to the malignant type of hypertension if the arterial pressure rises and is maintained above a certain critical level.

This hypothesis was based on two chance observations relating to the mechanisms by which the characteristic features of malignant hypertension are produced. It was observed that in albuminuric retinitis the pressure of the cerebrospinal fluid (C.S.F.) is nearly always above the level at which papillœdema occurs in tumour of the brain, whereas in arteriosclerotic retinitis the pressure of the C.S.F. is lower. The presence of neuroretinal œdema in the albuminuric but not in the arteriosclerotic form of retinitis can thus be accounted for by the level of C.S.F. pressure. The level of C.S.F. pressure seemed to be determined, at least in part, by the diastolic arterial pressure. And so the differences in the retinal lesions of malignant and benign hypertension seemed to be in part, at least, a consequence of the intensity of the hypertension (Pickering 1934).

Acute arteriolar necroses in hypertension following constriction of a renal artery in the dog were described by Goldblatt (1938) and in the rabbit by Wilson and Pickering (1938). These necroses were found in the same organs as in man, with the important exception that they were absent from the kidney whose artery had been clamped. Because of this, and because they were only found in animals with the highest arterial pressures, Wilson and Pickering attributed the lesions to a rise of intra-arterial pressure above a certain point.

Wilson and Byrom (1939) found that in the rat severe and persistent hypertension followed constriction of one renal artery, the other kidney being intact; in the early stages of hypertension the lesions were present in the kidney with the intact artery but not in the other kidney, whose artery had been clamped. These observations showed clearly that hypertension was the cause of the arteriolar necroses and of the renal lesions of malignant hypertension, which were shown to be identical in the unclamped kidney of the rat and in the kidneys of patients with malignant hypertension.

Though Wilson and Pickering had found in the rabbit that necroses occurred only in animals with greatly raised arterial pressures, Wilson and Byrom did not find any correlation between the presence or absence of arteriolar necroses and the level of the blood-pressure in the rat; but in the rabbit no anæsthetic was used, whereas the blood-pressure was measured in the rat under anæsthesia, which may itself influence arterial pressure.

Byrom and Dodson (1948) have shown that, if one renal artery is temporarily occluded by a ligature, and saline solution is injected forcefully through the carotid into the aorta so that the intra-aortic pressure is briefly and repeatedly raised by more than 80–90 mm. Hg, acute arteriolar necroses are found in the unprotected, but not in the protected, kidney three days later.

This experiment, though unphysiological, provides unequivocal evidence that acute arteriolar necroses can be produced by rise of pressure in the lumen above a certain point. Whether the necrosis is due to death of the tissues of the wall or merely to deposition in the wall of protein and, in some cases, cells from the blood is not accurately known.

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* Nowadays presumably pre-eclamptic toxæmia would be substituted.

If this hypothesis concerning the nature of benign and malignant hypertension is correct, it follows that, if the arterial pressure can be reduced sufficiently and for long enough, albuminuric retinitis should disappear and arteriolar necroses cease to be produced; in short, the hypertensive disease should revert from the malignant to the benign form. There is already a great deal of evidence that treatments which produce a considerable and long-continued reduction in blood-pressure will cause albuminuric retinitis to disappear, and some evidence that they prolong life.

The evidence for relief of albuminuric retinitis by sympathectomy and other operations designed to reduce sympathetic vasomotor tone has been reviewed by Hollenhorst and Wagener (1949). That sympathectomy prolongs life in malignant hypertension has been shown by Woods and Peet (1941), Hammarström and Bechgaard (1950), and Smithwick (1951). Reduction in arterial pressure and resolution of albuminuric retinitis have also been produced by pyrogens (Page and Taylor 1949), restriction of sodium intake (Kempner 1948), and hexamethonium bromide (Smirk and Alstad 1951) in the malignant phase of essential hypertension, and by nephrectomy in unilateral pyelonephritis (Langley and Platt 1947, and case 1 in the present series).

Nevertheless, there has not yet been reported any case in which malignant hypertension, proved histologically, has been converted to the benign course. We therefore present the following three cases in which this evidence was obtained. All three cases were of pyelonephritis; all showed gross albuminuric retinitis with bilateral papillœdema and large exudates; and all showed typical acute arteriolar necroses in suprarenal glands and kidneys. All showed a fall of arterial pressure and resolution of albuminuric retinitis following operation, and now, five to six years later, all the patients are alive and subjectively well, with normal blood-urea levels and mild to severe hypertension.

THE FIRST CASE

A meter reader, aged 33, attended the Western Ophthalmic Hospital in December, 1945, with failing vision. He was found to have albuminuric retinitis, albuminuria, and an arterial pressure of 240/170 mm. Hg, and was referred to St. Mary's.

History

In 1932 he had a hæmoptysis and was treated with an artificial pneumothorax, first at the Brompton Hospital and subsequently at Frimley Sanatorium. In 1932 his left testicle, and in 1937 his right testicle, were removed for tuberculous orchitis. His father had died at the age of 69, two days after gastrectomy for stomach trouble; his mother had died twelve hours after a fit in which she became unconscious. He had four brothers and a sister alive and well. He had been well until November, 1945, when he began to get frontal headaches worst on waking and disappearing about midday, and failing vision first in the left and later in the right eye. He had no abnormalities of micturition.

Examination (Dec. 14, 1945)

He was a spare man with fine hair and thin skin and no beard or axillary hair. The cardiac impulse was 4½ in. from the midline in the fifth space, and the second sound was loud. The arterial pressure was 226/148. No masses were felt in the abdomen. The fundus showed bilateral papillœdema with large woolly exudates and a macular star figure on both sides (fig. 1). The arteries were rather small and the veins rather full.

Condition on Admission

When he was admitted to hospital under Dr. Thomas Hunt on Feb. 5, 1946, the clinical findings were essentially the same. The blood-urea was 37 mg. per 100 ml., and urea concentration to 2·6%. Examination of a twenty-four-hour specimen of urine on two occasions showed no tubercle bacilli. Intravenous pyelography showed a non-excreting right kidney.

Operation (Feb. 25 1946)

The right splanchnic nerves, the right 1st and 2nd lumbar ganglia, the right adrenal, and the right kidney were removed. The arterial pressure (fig. 2) fell precipitously after operation, subsequently settling to 150–170 systolic and 100–120 diastolic, at which level it was maintained for the next six years.

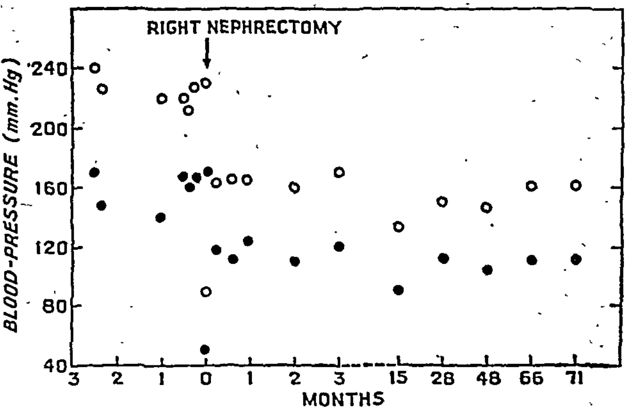

Fig. 2—Case 1: course of arterial pressure.

Progress

The blood-urea was 30 mg. per 100 ml. on March 14, 1946, and urea concentration to 3·6% the next day and to 2·7% on Sept. 25, 1947. The fundus cleared rapidly (fig. 3). A month after operation the papillœdema had gone and the woolly exudates had resolved completely or become small and sharply defined. At two months the exudates had gone, but the star figure was unchanged. The star figures slowly resolved during the fifteen months following operation (fig. 4).

In February, 1950, he had a hæmatemesis. Three weeks later a barium meal showed a duodenal ulcer. Blood-pressure 145/105. Fundi: no papillœdema or exudates.

On Aug. 22, 1951, he was very well and at work. Blood-pressure 160/110. Fundi: no papillœdema or exudates. Urine: no albumin, no excess of cells. Blood-urea 38 mg. per 100 ml.

On Jan. 18, 1952, he was well. Blood-pressure 160/110. Blood-urea 36 mg. per 100 ml. Fundi normal. Urine: no albumin or excess of cells.

On March 14, 1952, he was well. Blood-pressure 175/120.

Operation Specimens

Right kidney.—This measured 7·0 × 4·0 × 2·5 cm. Its surface was coarsely nodular, and on section the parenchyma appeared reduced in width, especially in the areas corresponding to the scars. The pelvis and calyces were dilated, and the pelvic wall was thickened.

Histologically the general picture was of chronic pyelonephritis, the affected areas showing interstitial fibrosis, lymphocytic infiltration, and reduction of the glomeruli. The tubules were lined with atrophic epithelium and contained deeply eosinophil casts. The pelvis was thickened with fibrous tissue and numerous lymphocytes were present beneath the epithelium. Relatively normal areas of kidney tissue intervened between the scars.

In the scarred areas the arterioles were thickened, and some presented the picture of fibrinoid necrosis (fig. 5). In its fully developed form fibrinoid necrosis was characterised by a diffuse replacement of the vessel wall by deeply eosinophil granular material closely resembling fibrin. This imparted a smudgy appearance to the vessel wall, and nuclear structure and elastica had largely disappeared. The material stained blue with phosphotungstic acid hæmatoxylin. This type of change is to be differentiated from the bland hyaline thickening of arteriolosclerosis seen in the benign types of hypertension. The larger arterioles and small arteries were affected by a fine proliferative fibrosis of the intima, and the larger arteries presented a coarser type of fibrous intimal thickening with some degree of elastic reduplication.

In the non-scarred areas arteriolar necroses were just as plentiful, especially in relation to the pelvis (fig. 6). By contrast, cellular intimal thickening of the smaller arteries was inconspicuous in the areas of the kidney not involved in the inflammation. The main renal vessels were small but otherwise healthy.

Adrenal.—The vessels in the fat surrounding the adrenal gland showed medial hypertrophy but no other striking change. In the arterioles deep to the capsule there were fibrinoid necroses like those already described (fig. 7).

THE SECOND CASE

A girl, aged 11 years, was admitted to St. Mary's Hospital on April 2, 1946, under Dr. Lightwood.

History

For a year she had had attacks of headache, nausea, and vomiting: they lasted about twenty-four hours and occurred at first at three-month intervals and lately at weekly intervals. She had had frequency of micturition and thirst for the same period. She had got thinner in the last two months. She had had the usual childish illnesses, and her legs had been treated surgically for rickets. A year previously her perineum had been lacerated by falling on a spike. Her father, mother, and two sisters were alive and well; an aunt had high blood-pressure.

Examination

She was a pale and thin child, with arterial pressure 240/170 mm. Hg. Her heart showed no definite enlargement clinically. Her urine contained albumin, pus cells, and granular casts. There were no abnormal signs in her central nervous system.

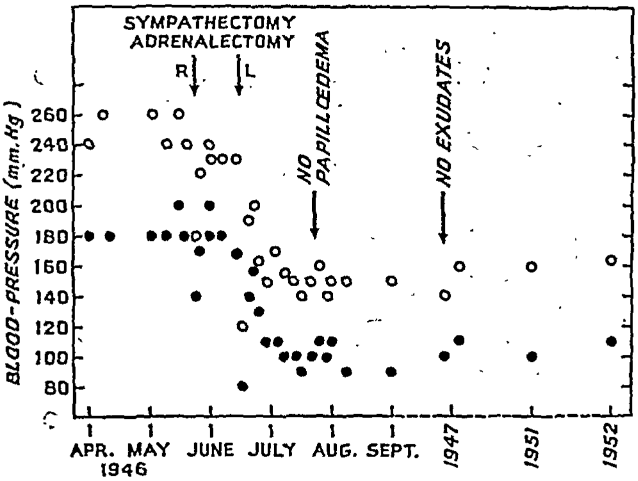

Fig. 8—Case 2: arterial pressure.

Her fundi showed bilateral papillœdema, with large ill-defined exudates, hæmorrhages, and star figures at both maculæ. Her blood-urea was 39 mg., falling later to 29 mg., per 100 ml.; urea concentration to 2·3%. Cultures of the urine were sometimes sterile, and sometimes grew *Bacterium coli*, *Staphylococcus albus*, or *Streptococcus fæcalis* (probably contaminants). Intravenous pyelography showed both kidneys functioning. Catheterisation of the ureters after administration of urea 15 g. yielded urine which on the left side contained albumin and up to 2·2% urea, and on the right albumin and 0·5% urea.

A diagnosis of bilateral pyelonephritis with malignant hypertension was made and 'Sulphamezathine' 1 g. was given six-hourly. The urine continued to show an excess of white cells. The arterial pressure continued to run between 240 and 260 mm. Hg systolic and 170 and 180 diastolic.

Operation (May 20, 1946)

The adrenal, the splanchnic nerves, and the upper lumbar sympathetic ganglia were excised on the right side. The right kidney was seen to be scarred. The operation was followed by no significant change in her blood-pressure or in her fundi. On June 13, 1946, three-quarters of the left adrenal, the left splanchnics, and the upper left lumbar ganglia were removed. The left kidney appeared normal.

Progress

After the second operation the blood-pressure fell and became steady at 130–145 mm. Hg systolic and 90–110 diastolic. When she was discharged on Aug. 3, the papillœdema had disappeared and the exudates were smaller and more sharply defined. Eucortone and deoxycortone were given after the second operation as for an addisonian crisis: no significant abnormality in blood-urea or serum-sodium was found, nor was pigmentation apparent; but the Kepler test on Aug. 1, 1946, was positive.

On March 3, 1947, papillœdema and exudates had quite disappeared, apart from a small circumscribed exudate on the left. Blood-pressure 140/100.

On March 13, 1951, the patient's breasts were well developed for her age, and she had grown as tall as her mother. Her fundi showed no papillœdema or exudates, and her blood-pressure was 164/104. Blood-urea 46 mg. per 100 ml. Urea concentration to 2·6%. Urine: trace of albumin, numerous red cells and pus cells, and a few hyaline and granular casts.

On March 27, 1952, she was well and living a fully active life. She had continued to grow and was taller than her mother. Blood-pressure 165/110. Fundi: no papillœdema, exudates or hæmorrhages. Blood-urea 41 mg. Urine: trace of albumin; red cells, white cells, and casts in excess. Fig. 8 shows the arterial pressure in this patient.

Operation Specimens

Right adrenal.—The right adrenal gland had a prominent medulla. The periadrenal arteries presented some degree of medial hypertrophy. The arterioles in the parenchyma, especially those underneath the capsule, showed the typical necrotising lesions described in case 1 (fig. 9).

Right kidney.—A small fragment of the right renal cortex was examined. One area was somewhat fibrotic, contained a hyalinised glomerulus, and was infiltrated with lymphocytes. The rest of the section was relatively normal with some arteriolar hyalinisation. No necroses were present, but the number of vessels examined, even when the entire block was sectioned serially, was of necessity small.

Left adrenal.—This had a well-developed cortex and medulla. A few subcapsular arterioles showed fibrinoid necrosis. Apart from medial hypertrophy of periadrenal arteries there were no other vascular changes.

Left kidney.—A small portion of the left renal cortex was examined. One area was fibrotic, contained a few atrophic tubules with colloid casts, and was infiltrated with lymphocytes. One arteriole in a normal part of the specimen showed fibrinoid change (fig. 10), whereas others were hyalinised.

THE THIRD CASE

A girl, aged 13, was admitted to Great Ormond Street Hospital under Dr. Donald Paterson in June, 1946.

History

She had had headache and listlessness on and off for four years and vomiting for a month. There was no history of œdema or of frequency of micturition, but a year previously she had passed blood in her urine. At the age of 2½ years she had been taken to Tite Street Hospital with attacks of listlessness. Her father, aged 38 (blood-pressure 124/82 mm. Hg), and her mother (blood-pressure 136/90) were both well, as were her younger sister and brother.

Examination

She was thin but maturely developed for her age; her blood-pressure was 256/180 mm. Hg; her fundi showed bilateral papillœdema, large soft exudates, and great narrowing of arteries. She had no pyrexia. A catheter specimen of urine showed 0·1% albumin and a moderate amount of red cells; culture grew *Bact. coli*. Urea clearance was 48 and 56% of normal; the blood-urea was 82 mg. per 100 ml. Excretion pyelography showed moderate excretion from both kidneys and some dilatation of the pelves. The left kidney was the smaller, excreted less well, and had a double ureter. The blood-urea fell to 34 mg., but the blood-pressure remained at about the same level. She had several attacks of very intense headache and disorientation.

Operation

On July 3, 1946, Mr. Twistington Higgins removed the left kidney. It was small, adherent, and fibrotic.

LEGENDS TO ILLUSTRATIONS ON PLATE

PROF. PICKERING AND OTHERS

Fig. 1—Case 1: fundus oculi on Feb. 28, 1946, just before operation.

Fig. 3—Case 1: fundus oculi on May 3, 1946, after operation.

Fig. 4—Case 1: fundus oculi on Aug. 20, 1947, after operation.

Fig. 5—Case 1: fibrinoid necrosis in arteriole situated in pyelonephritic area of kidney. (Hæmatoxylin and eosin.) (× 375.)

Fig. 6—Case 1: necroses in vessels situated in renal pelvis. (H. and E.) (× 260.)

Fig. 7—Case 1: arteriolar necrosis in adrenal. (H. and E.) (× 375.)

Fig. 9—Case 2: arteriolar necrosis in right adrenal. (H. and E.) (× 375.)

PROFESSOR PICKERING,
MR. DICKSON WRIGHT,
DR. HEPTINSTALL:

REVERSIBILITY OF MALIGNANT HYPERTENSION

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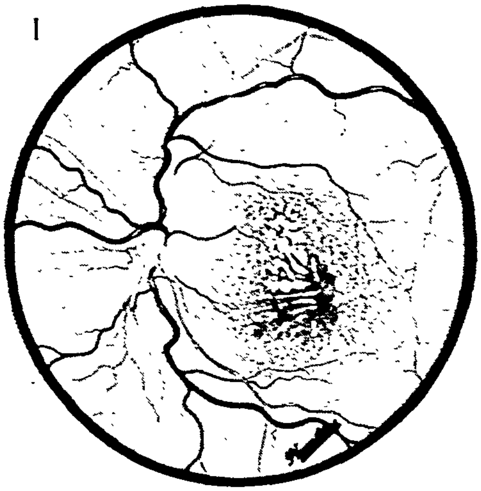

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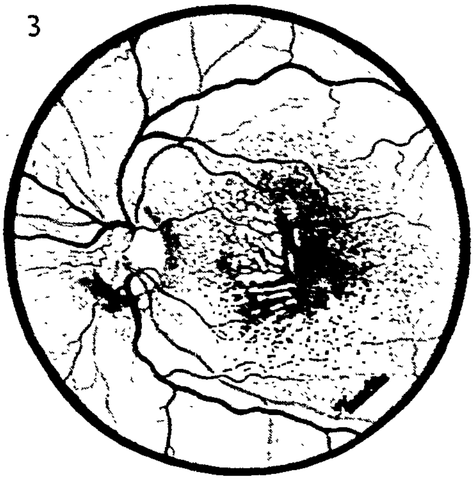

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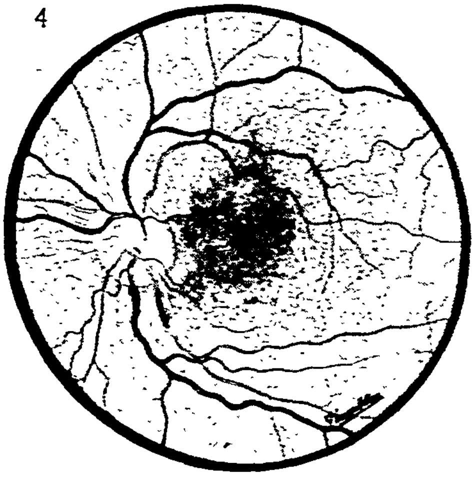

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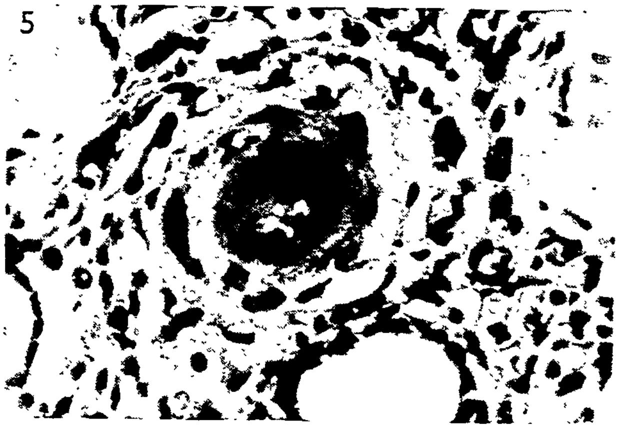

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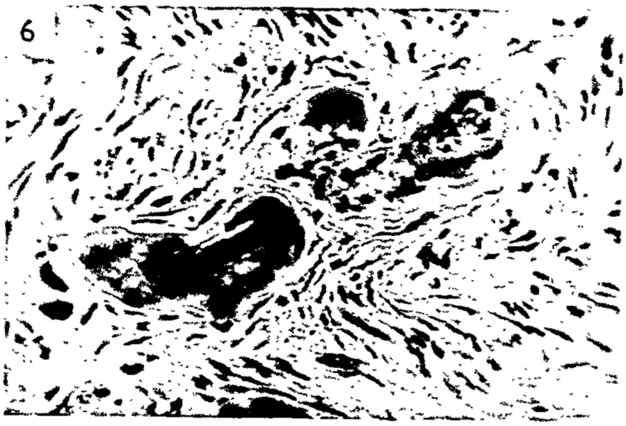

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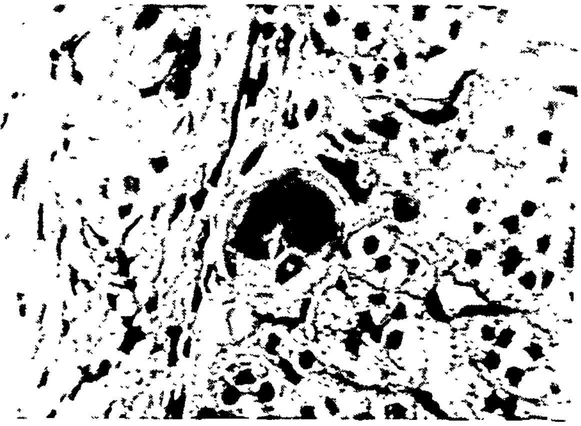

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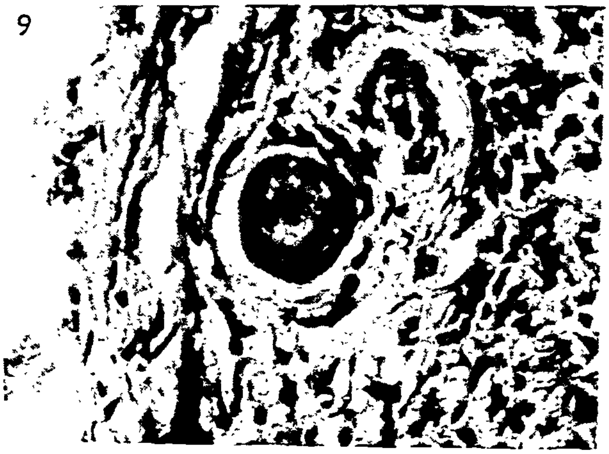

THE SECOND CASE

A girl, aged 11 years, was admitted to St. Mary's Hospital on April 2, 1946, under Dr. Lightwood.

History

For a year she had had attacks of headache, nausea, and vomiting: they lasted about twenty-four hours and occurred at first at three-month intervals and lately at weekly intervals. She had had frequency of micturition and thirst for the same period. She had got thinner in the last two months. She had had the usual childish illnesses, and her legs had been treated surgically for rickets. A year previously her perineum had been lacerated by falling on a spike. Her father, mother, and two sisters were alive and well; an aunt had high blood-pressure.

Examination

She was a pale and thin child, with arterial pressure 240/170 mm. Hg. Her heart showed no definite enlargement clinically. Her urine contained albumin, pus cells, and granular casts. There were no abnormal signs in her central nervous system.

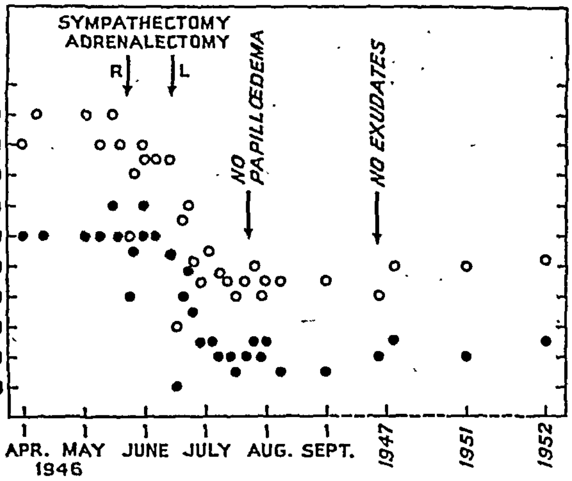

Fig. 8—Case 2: arterial pressure.

Her fundi showed bilateral papillœdema, with large ill-defined exudates, hæmorrhages, and star figures at both maculæ. Her blood-urea was 39 mg., falling later to 29 mg., per 100 ml.; urea concentration to 2·3%. Cultures of the urine were sometimes sterile, and sometimes grew *Bacterium coli*, *Staphylococcus albus*, or *Streptococcus fæcalis* (probably contaminants). Intravenous pyelography showed both kidneys functioning. Catheterisation of the ureters after administration of urea 15 g. yielded urine which on the left side contained albumin and up to 2·2% urea, and on the right albumin and 0·5% urea.

A diagnosis of bilateral pyelonephritis with malignant hypertension was made and 'Sulphamezathine' 1 g. was given six-hourly. The urine continued to show an excess of white cells. The arterial pressure continued to run between 240 and 260 mm. Hg systolic and 170 and 180 diastolic.

Operation (May 20, 1946)

The adrenal, the splanchnic nerves, and the upper lumbar sympathetic ganglia were excised on the right side. The right kidney was seen to be scarred. The operation was followed by no significant change in her blood-pressure or in her fundi. On June 13, 1946, three-quarters of the left adrenal, the left splanchnics, and the upper left lumbar ganglia were removed. The left kidney appeared normal.

Progress

After the second operation the blood-pressure fell and became steady at 130–145 mm. Hg systolic and 90–110 diastolic. When she was discharged on Aug. 3, the papillœdema had disappeared and the exudates were smaller and more sharply defined. Eucortone and deoxycortone were given after the second operation as for an addisonian crisis: no significant abnormality in blood-urea or serum-sodium was found, nor was pigmentation apparent; but the Kepler test on Aug. 1, 1946, was positive.

On March 3, 1947, papillœdema and exudates had quite disappeared, apart from a small circumscribed exudate on the left. Blood-pressure 140/100.

On March 13, 1951, the patient's breasts were well developed for her age, and she had grown as tall as her mother. Her fundi showed no papillœdema or exudates, and her blood-pressure was 164/104. Blood-urea 46 mg. per 100 ml. Urea concentration to 2·6%. Urine: trace of albumin, numerous *red cells and pus cells, and a few hyaline and granular casts.*

On March 27, 1952, she was well and living a fully active life. She had continued to grow and was taller than her mother. Blood-pressure 165/110. Fundi: *no papillœdema, exudates or hæmorrhages.* Blood-urea 41 mg. Urine: *trace of albumin*; red cells, white cells, and casts in excess. Fig. 8 shows the arterial pressure in this patient.

Operation Specimens

Right adrenal.—The right adrenal gland had a prominent medulla. The periadrenal arteries presented some degree of medial hypertrophy. The arterioles in the parenchyma, especially those underneath the capsule, showed the typical necrotising lesions described in case 1 (fig. 9).

Right kidney.—A small fragment of the right renal cortex was examined. One area was somewhat fibrotic, contained a hyalinised glomerulus, and was infiltrated with lymphocytes. The rest of the section was relatively normal with some arteriolar hyalinisation. No necroses were present, but the number of vessels examined, even when the entire block was sectioned serially, was of necessity small.

Left adrenal.—This had a well-developed cortex and medulla. A few subcapsular arterioles showed fibrinoid necrosis. Apart from medial hypertrophy of periadrenal arteries there were no other vascular changes.

Left kidney.—A small portion of the left renal cortex was examined. One area was fibrotic, contained a few atrophic tubules with colloid casts, and was infiltrated with lymphocytes. One arteriole in a normal part of the specimen showed fibrinoid change (fig. 10), whereas others were hyalinised.

THE THIRD CASE

A girl, aged 13, was admitted to Great Ormond Street Hospital under Dr. Donald Paterson in June, 1946.

History

She had had headache and listlessness on and off for four years and vomiting for a month. There was no history of œdema or of frequency of micturition, but a year previously she had passed blood in her urine. At the age of 2½ years she had been taken to Tite Street Hospital with attacks of listlessness. Her father, aged 38 (blood-pressure 124/82 mm. Hg), and her mother (blood-pressure 136/90) were both well, as were her younger sister and brother.

Examination

She was thin but maturely developed for her age; her blood-pressure was 255/180 mm. Hg; her fundi showed bilateral papillœdema, large soft exudates, and great narrowing of arteries. She had no pyrexia. A catheter specimen of urine showed 0·1% albumin and a moderate amount of red cells; culture grew *Bact. coli.* Urea clearance was 48 and 56% of normal; the blood-urea was 82 mg. per 100 ml. Excretion pyelography showed moderate excretion from both kidneys and some dilatation of the pelves. The left kidney was the smaller, excreted less well, and had a double ureter. The blood-urea fell to 34 mg., but the blood-pressure remained at about the same level. She had several attacks of very intense headache and disorientation.

Operation

On July 3, 1946, Mr. Twistington Higgins removed the left kidney. It was small, adherent, and fibrotic.

LEGENDS TO ILLUSTRATIONS ON PLATE

PROF. PICKERING AND OTHERS

Fig. 1—Case 1: fundus oculi on Feb. 28, 1946, just before operation.

Fig. 3—Case 1: fundus oculi on May 3, 1946, after operation.

Fig. 4—Case 1: fundus oculi on Aug. 20, 1947, after operation.

Fig. 5—Case 1: fibrinoid necrosis in arteriole situated in pyelonephritic area of kidney. (Hæmatoxylin and eosin.) (× 375.)

Fig. 6—Case 1: necroses in vessels situated in renal pelvis. (H. and E.) (× 260.)

Fig. 7—Case 1: arteriolar necrosis in adrenal. (H. and E.) (× 375.)

Fig. 9—Case 2: arteriolar necrosis in right adrenal. (H. and E.) (× 375.)

Progress

After operation the arterial pressure fell to 160/95, but by the following day it had risen to 210/170. Subsequently there was little change in blood-pressure or fundi. On Sept. 11, 1946, the blood-urea was 50 mg., and the urea clearance 87·6 and 101% of normal average. On Jan. 23, 1947, the blood-pressure was 220/150, and the albuminuric retinitis had not improved.

On Jan. 28, 1947, the patient was admitted to St. Mary's Hospital under Dr. Lightwood. The arterial pressure was 230/170: no pulsus alternans or gallop. The fundi showed gross papillœdema and peripapillary œdema. The arteries were very narrow and showed gross variation of calibre: the veins were full. Exudates were mainly sharply defined. The blood-urea was 32 mg. Urea concentration to 2·7%.

Further Operations

On Feb. 13, 1947, three-quarters of the right adrenal and a biopsy specimen of the right kidney were removed. The arterial pressure after an initial fall remained unaltered. On April 24, 1947, when the blood-pressure was 240/170, the whole of the left adrenal was removed. The splanchnics were left untouched on both sides.

Treatment and Progress

Preoperative and postoperative treatment with deoxycortone and adrenal cortical extract was given from April 21 to May 1, 1947. The arterial pressure was 206/160 on the evening of April 24, and fell to 170/104 on April 26. From then to discharge on May 23 it remained between 150/110 and 210/170. The serum-sodium, serum-potassium, and blood-urea levels remained normal. On Sept. 25, 1947, it was noted that conspicuous addisonian pigmentation had developed in the creases of the palms, on the backs of both hands, in the flexures of the knees, in the linea alba, in the areolæ of the breasts, and in the scar of the left lumbar incision. Blood-pressure 185/145. Both optic discs were clear, with a sharp nasal edge and a few small sharply defined punctate exudates.

When the patient was seen at intervals, her blood-pressure remained between 250/150 and 220/115. On Jan. 4, 1951, it was 230/154. Fundi: discs clear and pale; arteries thin, conspicuously irregular and rather pale, a few small branches seen as white streaks: a small exudate at 2 o'clock rather far out; several scars of old exudates; and several new vessels on the left disc. The urine contained albumin.

On Aug. 22, 1951, the patient felt well; her height was 5 ft. 5 in. and weight 8 st. 4 lb.; her blood-pressure was 235/155; and her urine contained albumin and a slight excess of white cells. Her pigmentation was less but still pronounced on the dorsum of the fingers. Her fundi were as before.

She was readmitted on Nov. 21, 1951, for further treatment of her hypertension. She was subjectively well and doing a full day's work. Her arterial pressure was 220/150 on admission, but settled to between 180–200 systolic and 110–120 diastolic when she had rested for a week. Her urine contained albumin and a slight excess of red cells, leucocytes, and granular casts; it was sterile on culture. Her blood-urea level was 22 mg. per 100 ml. Urea concentration to 2·4%. An excretion urogram of the right kidney was normal. She was treated with chloramphenicol and hexamethonium. Fig. 11 summarises the changes in blood-pressure.

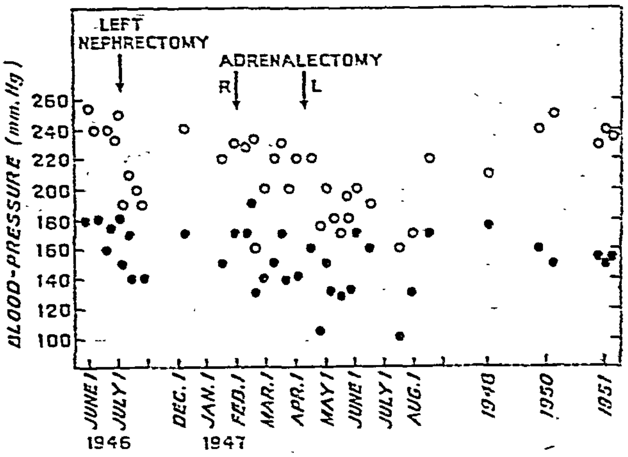

Fig. 11—Case 3: arterial pressure.

Operation Specimens

Left kidney.—This measured 6·0 × 2·5 × 1·5 cm. and had a coarsely nodular surface. Two ureters were present, one draining the upper calyx, and the other the remainder of the kidney. The pelvic wall was thickened and fibrous, and the calyces were dilated. In the scarred areas the parenchyma was reduced to 0·2 cm. Microscopy showed chronic pyelonephritis. The areas of old inflammation showed increased fibrosis, considerable numbers of lymphocytes, and no glomeruli. In places the glomeruli had not disappeared completely but were represented by hyalinised spheres. The tubules were atrophic and contained colloid-like casts. As in case 1, there were relatively normal areas of parenchyma between the scarred zones. The pelvis was thickened by fibrous tissue and infiltrated with lymphocytes and plasma cells.

Vascular changes again differed in the scarred and non-scarred areas. Fibrinoid necroses were present in both in exactly the same way as in case 1, and intimal proliferation occurred in the small arteries in the scars, but only to a minor degree in the non-scarred parts. The general pattern was very similar to that of case 1, except that necroses were more numerous.

Right adrenal.—Very many typical necroses were present among the arterioles and small arteries in the substance of the gland (figs. 12 and 13), and were more numerous and much more conspicuous in this than in any other adrenal here described. Similar widespread necroses were present in the periadrenal vessels (fig. 14), in one instance being associated with a well-marked cellular reaction, such as is seen in periarteritis nodosa.

Left adrenal.—Vascular changes were much less conspicuous. Necroses were, however, present in the parenchymal arterioles, especially in those underneath the capsule.

DISCUSSION

In each of these three patients the lesion underlying the hypertension was pyelonephritis. In case 1 the persistent reduction of arterial pressure following operation may be attributed to removal of the diseased kidney, the other being apparently normal; other such cases are being reported elsewhere (Pickering and Heptinstall 1952). It seems unlikely that the excision of sympathetic nerves and adrenal had anything to do with the fall of blood-pressure, since in other cases in which these structures alone have been excised unilaterally, hypertension has not been materially or persistently altered. In case 3 removal of the more affected kidney produced a transient fall of arterial pressure that was not maintained, but the disease was bilateral. Since albuminuric retinitis persisted and the arterial pressure remained very high, the whole of one adrenal and three-

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LEGENDS TO ILLUSTRATIONS ON PLATE

PROF. PICKERING AND OTHERS

Fig. 10—Case 2: fibrinoid degeneration in arteriole of left kidney. (H. and E.) (× 375.)

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Fig. 13—Case 3: necrotic vessels in substance of right adrenal; solid appearance of one of these is due to tangential cutting of its wall. (H. and E.) (× 125.)

Fig. 14—Case 3: eccentric necrotic area in periadrenal vessel (right side). (H. and E.) (× 250.)

DR. GILROY AND OTHERS

Fig. 2—Necropsy specimen of lung injected with radio-opaque solution into azygos vein. Injection of azygos vein has filled pulmonary veins.

Fig. 3—Dissection of mediastinum showing dilated tortuous pleurohilar veins at mediastino-pulmonary junction in a case of severe mitral stenosis.

PROFESSOR PICKERING, MR. DICKSON WRIGHT, DR. HEPTINSTALL: REVERSIBILITY OF MALIGNANT HYPERTENSION

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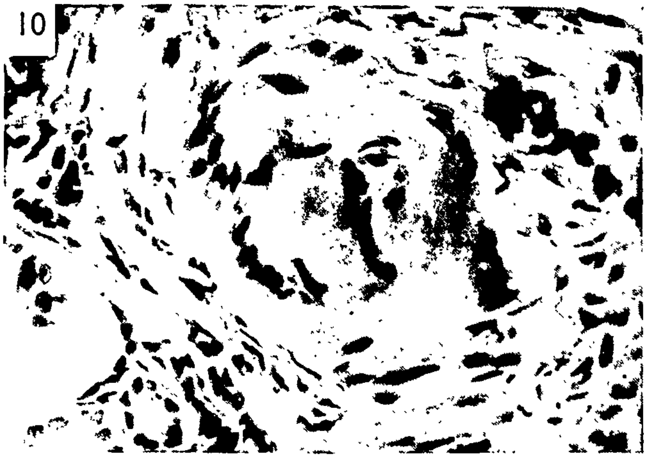

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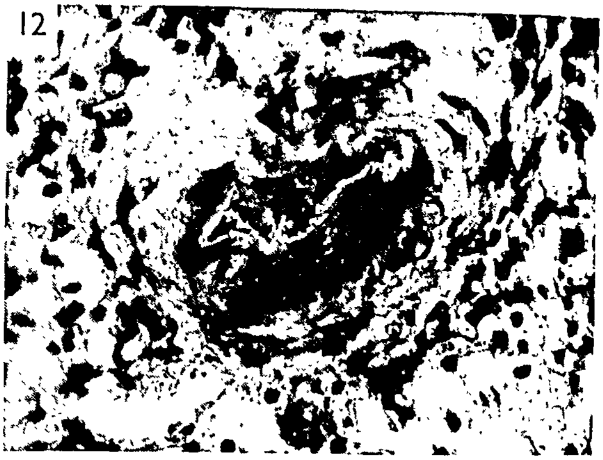

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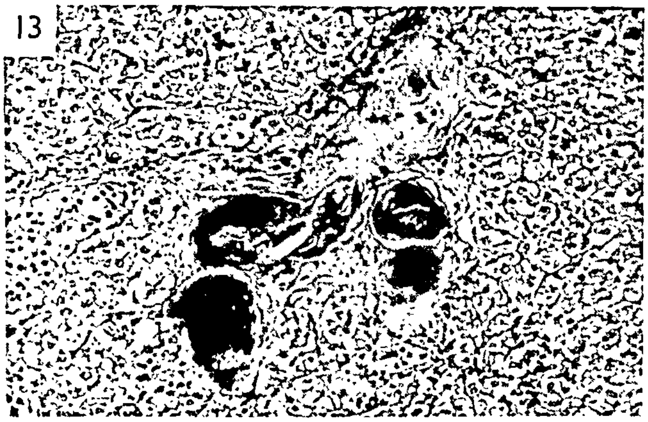

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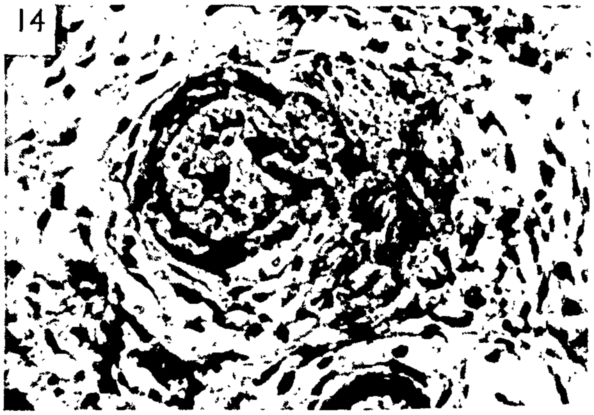

DR. GILROY, MR. MARCHAND, DR. WILSON: RÔLE OF BRONCHIAL VEINS IN MITRAL STENOSIS

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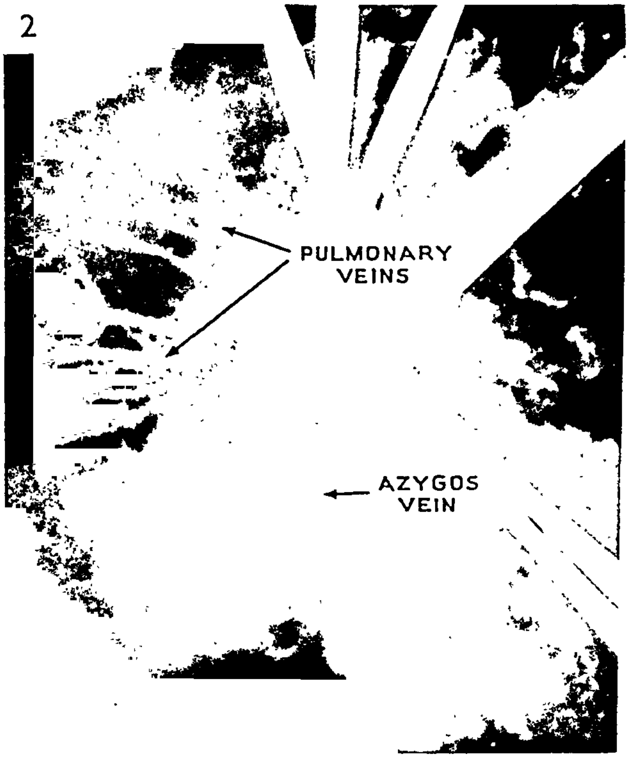

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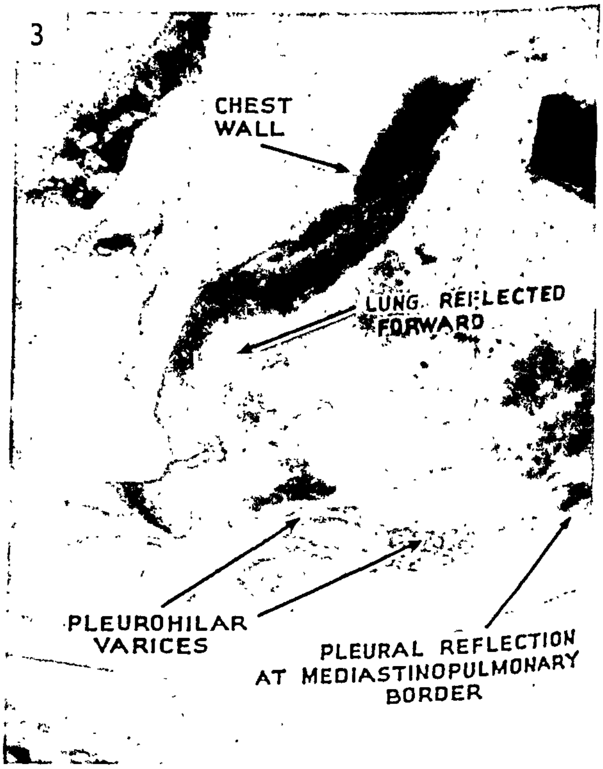

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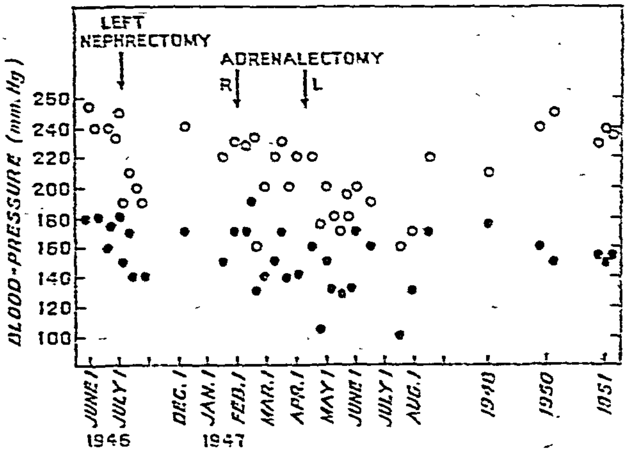

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DR. GILROY AND OTHERS

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quarters of the other were removed, substitution therapy being given for three days before and seven after the operation; as this was withdrawn, the arterial pressure fell profoundly, later rising, but never quite to the preoperative level. In case 2, also of bilateral disease, neither kidney was excised, but an infradiaphragmic sympathectomy with removal of one adrenal and three-quarters of the other produced a profound and persistent fall of arterial pressure.

Though the intervention that caused the arterial pressure to fall thus differed, the effects of the fall in pressure were similar in the three cases. Albuminuric retinitis cleared, and the pattern of its clearing was similar in all. Neuroretinal œdema resolved first. Papillœdema went next, and the exudates became smaller and sharply defined, the picture now resembling that of arteriosclerotic retinitis except for bilateral involvement and the macular star, which in case 1 resolved last. C.S.F. pressures were not measured, but the resolution of the retinitis supports the idea previously presented (Pickering 1934) that neuroretinal œdema is a separate, and the distinctive, component of albuminuric retinitis.

Acute arteriolar necroses were found in kidney and adrenal of all three patients at operation. Since these were the only tissues examined, the necroses may be presumed to have had their usual distribution in the organs of the body. No further biopsy specimens were obtained, but the absence of subjective symptoms, a normal blood-urea, and an ability to concentrate urea in the urine to over 2% five or six years after operation provide strong evidence that these acute arteriolar necroses had ceased to occur and had presumably healed. Acute arteriolar necroses in the pyelonephritic areas of the kidney might have been due to the inflammation; but their occurrence in those areas of kidney that were not inflamed, especially in the adrenal, excludes this cause. None of the patients were uræmic, and there is nothing in the case records to suggest that a renal substance was the cause of the necroses. In fact, the presence of these acute necroses at operation and their subsequent behaviour are easily explained only by the hypothesis that they are caused by a rise in intravascular pressure above a certain point. In case 3, with a diastolic pressure of 160–180 mm. Hg before operation and a diastolic pressure which six months after adrenalectomy and subsequently lay between 130 and 160 mm. Hg, this threshold level must have been high. She alone after operation presented gross evidence of organic disease in the retinal arteries, presumably representing healed acute lesions; how far such healed lesions, which presumably healed during the period of low pressure following adrenalectomy, protected the vessels distally from raised arterial pressure is problematical.

Volhard (1931) originally suggested, and Wilson and Byrom (1941) produced experimental evidence for, the idea of a vicious circle in Bright's disease. According to this hypothesis ischæmia produced by acute arteriolar necroses in the kidney releases a renal substance which maintains and enhances hypertension. There is no direct evidence for this hypothesis in man, and the striking and maintained fall in arterial pressure following nephrectomy in case 1, with severe necroses in both kidney and adrenal, is against its being an important factor in the maintenance of hypertension. Even if a vicious circle exists it can clearly be broken.

The therapeutic implications of the hypothesis supported here are plain. Malignant hypertension is characterised by acute arteriolar necroses, and these necroses usually kill by producing renal failure. Sometimes they develop quickly, and the transition from intact renal function to death in uræmia may be a matter of a few weeks only. Once malignant hypertension is diagnosed—and it is diagnosed by the fundus oculi—treatment is urgent and is directed to one single end, the reduction of arterial pressure. Sometimes this may be achieved by removing the cause, a unilaterally diseased kidney or an adrenal medullary or adrenal cortical tumour. Sometimes it can be achieved only by a less direct approach—sympathectomy, salt-free diet, pyrogens, or hexamethonium compounds. Of these, sympathectomy, because it involves no prolonged restrictions and may have a persistent effect, will have a large place until something better is available. Hexamethonium compounds have the great virtue that they can be effective at once and in nearly all cases, except those too advanced for any therapy. Their chief disadvantage is the extent to which they interfere with the patient's way of life. Subtotal adrenalectomy was used in two of the cases reported here, combined with sympathectomy in one, and it was used in a similar case to be reported elsewhere (Pickering and Heptinstall 1952). It was, up to a point, effective. We have also used it in three adults in the malignant phase of essential hypertension, but with less success. Whether the success in the pyelonephritics was due to their youth, to the mechanism of hypertension, or to their being in a less advanced stage of the disease, is a question we leave without further comment.

SUMMARY

Three cases are reported in which the malignant was converted to the benign form of hypertension by operations persistently reducing arterial pressure. All three patients had pyelonephritis. Arterial pressure was reduced by nephrectomy in one, by subtotal adrenalectomy in another, and by sympathectomy and subtotal adrenalectomy in a third.

At operation all three patients had albuminuric retinitis, and acute arteriolar necroses in kidney and adrenal. All are alive and symptomatically well five or six years after operation, with less severe hypertension, a normal blood-urea level, and normal urea concentration.

These observations demonstrate conclusively that malignant hypertension is reversible, and support the hypothesis that the benign and malignant forms are simple consequences of the severity of the hypertension.

We wish to thank our colleagues for referring these cases to us and Dr. Martin Bodian for the kidney of case 3. Cases 1 and 3 are summarised as cases 11 and 3 in the article by Pickering and Heptinstall (1952).

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THE RÔLE OF THE BRONCHIAL VEINS IN MITRAL STENOSIS

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With illustrations on plate

Anatomical studies of the bronchial vascular system have directed our attention to the possible rôle of the bronchial veins as a decompressive mechanism in pulmonary venous hypertension. In previous papers we have described two systems of bronchial vessels:

(1) The true bronchial vessels which accompany the bronchi as far as the respiratory bronchiole.

(2) The "pleurohilar" vessels which supply and drain the hilar structures and the subpleural plane. (Marchand et al. 1950).

The arrangement of the pleurohilar system seemed so well adapted to afford a decompressive mechanism in pulmonary venous hypertension that we began to look for evidence of a functional alteration in these veins in cases of mitral stenosis.

It is generally accepted that mitral stenosis causes a rise in pressure within the pulmonary veins largely due to the mechanical obstruction to the passage of blood from the pulmonary into the systemic circulation. The rise in pulmonary venous pressure may in itself act as a compensatory mechanism by creating a greater speed of blood-flow through the narrow mitral orifice. When the left auricle is relatively healthy, this effect may be augmented by muscular hypertrophy of the auricle. Increase in the pulmonary venous pressure raises the pulmonary arterial pressure. The precise cause of this rise is uncertain, but the effect is to maintain an effective pressure gradient between pulmonary artery and vein. As a consequence of the pulmonary hypertension the right ventricle hypertrophies, and as the pulmonary engorgement progresses the pulmonary artery dilates. Engorgement of the pulmonary circulation is considered to be intimately concerned with the dyspnœa of mitral stenosis even before congestive cardiac failure supervenes (Wood 1950), and is probably closely connected with the occurrence of pulmonary œdema. It has long been recognised that, where a defect in the auricular septum is present, pulmonary œdema may be long delayed (Bedford et al. 1941). Bland and Sweet (1949) evolved an operation to relieve the symptoms of severe mitral stenosis by making an anastomosis between a branch of the pulmonary vein and the azygos vein. The rationale of this operation was based upon the work of Ferguson et al. (1944), who postulated a shunt of blood from the engorged pulmonary veins of mitral stenosis into the bronchial veins which, they maintained, drained into the azygos and hemiazygos veins. The conclusions of these workers were based largely on the anatomical descriptions of Miller (1947) and they themselves undertook no detailed anatomical studies to confirm their views. It is therefore well recognised that pulmonary engorgement may, to some extent, be compensated for by a shunting of blood from the pulmonary to the systemic veins. We have been especially concerned with the exact anatomical route whereby this effect is accomplished. Certain other features, such as the so-called stiff lung or *Lungenstarre* described by German workers, and the hæmoptysis of mitral stenosis, can also, we believe, be explained upon an anatomical basis.

MATERIAL AND METHODS OF EXAMINATION

The true bronchial veins have been studied in five necropsy specimens of normal lungs, and the pleurohilar veins in fourteen specimens: the results have been described in detail elsewhere (Marchand et al. 1950) but are summarised here.

Six patients with mitral stenosis were investigated at necropsy. In these cases the pleurohilar veins were dissected. Thirty patients were observed during valvulotomy for mitral stenosis.

NORMAL ANATOMY

Two distinct systems of bronchial veins have been distinguished: (1) the true bronchial veins, which drain the intrapulmonary bronchi and the supporting interstitial framework of the lung; and (2) the pleurohilar veins, which drain the hilar structures and the subpleural planes of the lung. The true bronchial veins drain into

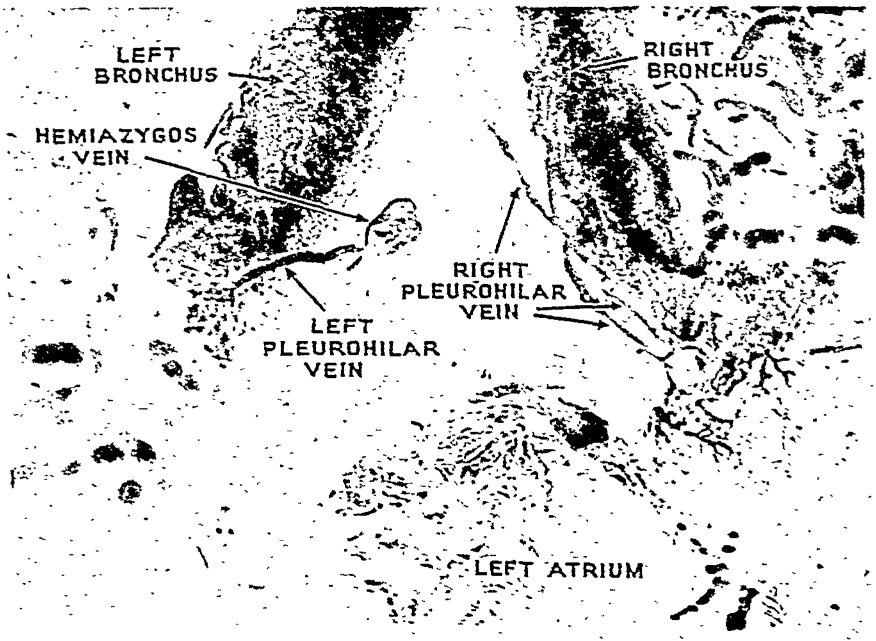

Fig. 1—Vinylite cast of normal lung viewed from behind. Bronchus is filled with Wood's metal, pulmonary arteries with blue vinylite, and pulmonary veins with red vinylite. Pleurohilar veins have been filled through pulmonary veins, and on left side entry of pleurohilar vein into hemiazygos vein has been demonstrated. Entry of right pleurohilar vein into azygos vein is not shown.

quarters of the other were removed, substitution therapy being given for three days before and seven after the operation; as this was withdrawn, the arterial pressure fell profoundly, later rising, but never quite to the preoperative level. In case 2, also of bilateral disease, neither kidney was excised, but an infradiaphragmic sympathectomy with removal of one adrenal and three-quarters of the other produced a profound and persistent fall of arterial pressure.

Though the intervention that caused the arterial pressure to fall thus differed, the effects of the fall in pressure were similar in the three cases. Albuminuric retinitis cleared, and the pattern of its clearing was similar in all. Neuroretinal œdema resolved first. Papillœdema went next, and the exudates became smaller and sharply defined, the picture now resembling that of arteriosclerotic retinitis except for bilateral involvement and the macular star, which in case 1 resolved last. C.S.F. pressures were not measured, but the resolution of the retinitis supports the idea previously presented (Pickering 1934) that neuroretinal œdema is a separate, and the distinctive, component of albuminuric retinitis.

Acute arteriolar necroses were found in kidney and adrenal of all three patients at operation. Since these were the only tissues examined, the necroses may be presumed to have had their usual distribution in the organs of the body. No further biopsy specimens were obtained, but the absence of subjective symptoms, a normal blood-urea, and an ability to concentrate urea in the urine to over 2% five or six years after operation provide strong evidence that these acute arteriolar necroses had ceased to occur and had presumably healed. Acute arteriolar necroses in the pyelonephritic areas of the kidney might have been due to the inflammation; but their occurrence in those areas of kidney that were not inflamed, especially in the adrenal, excludes this cause. None of the patients were uræmic, and there is nothing in the case records to suggest that a renal substance was the cause of the necroses. In fact, the presence of these acute necroses at operation and their subsequent behaviour are easily explained only by the hypothesis that they are caused by a rise in intravascular pressure above a certain point. In case 3, with a diastolic pressure of 160–180 mm. Hg before operation and a diastolic pressure which six months after adrenalectomy and subsequently lay between 130 and 160 mm. Hg, this threshold level must have been high. She alone after operation presented gross evidence of organic disease in the retinal arteries, presumably representing healed acute lesions; how far such healed lesions, which presumably healed during the period of low pressure following adrenalectomy, protected the vessels distally from raised arterial pressure is problematical.

Volhard (1931) originally suggested, and Wilson and Byrom (1941) produced experimental evidence for, the idea of a vicious circle in Bright's disease. According to this hypothesis ischæmia produced by acute arteriolar necroses in the kidney releases a renal substance which maintains and enhances hypertension. There is no direct evidence for this hypothesis in man, and the striking and maintained fall in arterial pressure following nephrectomy in case 1, with severe necroses in both kidney and adrenal, is against its being an important factor in the maintenance of hypertension. Even if a vicious circle exists it can clearly be broken.

The therapeutic implications of the hypothesis supported here are plain. Malignant hypertension is characterised by acute arteriolar necroses, and these necroses usually kill by producing renal failure. Sometimes they develop quickly, and the transition from intact renal function to death in uræmia may be a matter of a few weeks only. Once malignant hypertension is diagnosed—and it is diagnosed by the fundus oculi—treatment is urgent and is directed to one single end, the reduction of arterial pressure. Sometimes this may be achieved by removing the cause, a unilaterally diseased kidney or an adrenal medullary or adrenal cortical tumour. Sometimes it can be achieved only by a less direct approach—sympathectomy, salt-free diet, pyrogens, or hexamethonium compounds. Of these, sympathectomy, because it involves no prolonged restrictions and may have a persistent effect, will have a large place until something better is available. Hexamethonium compounds have the great virtue that they can be effective at once and in nearly all cases, except those too advanced for any therapy. Their chief disadvantage is the extent to which they interfere with the patient's way of life. Subtotal adrenalectomy was used in two of the cases reported here, combined with sympathectomy in one, and it was used in a similar case to be reported elsewhere (Pickering and Heptinstall 1952). It was, up to a point, effective. We have also used it in three adults in the malignant phase of essential hypertension, but with less success. Whether the success in the pyelonephritics was due to their youth, to the mechanism of hypertension, or to their being in a less advanced stage of the disease, is a question we leave without further comment.

SUMMARY

Three cases are reported in which the malignant was converted to the benign form of hypertension by operations persistently reducing arterial pressure. All three patients had pyelonephritis. Arterial pressure was reduced by nephrectomy in one, by subtotal adrenalectomy in another, and by sympathectomy and subtotal adrenalectomy in a third.

At operation all three patients had albuminuric retinitis, and acute arteriolar necroses in kidney and adrenal. All are alive and symptomatically well five or six years after operation, with less severe hypertension, a normal blood-urea level, and normal urea concentration.

These observations demonstrate conclusively that malignant hypertension is reversible, and support the hypothesis that the benign and malignant forms are simple consequences of the severity of the hypertension.

We wish to thank our colleagues for referring these cases to us and Dr. Martin Bodian for the kidney of case 3. Cases 1 and 3 are summarised as cases 11 and 3 in the article by Pickering and Heptinstall (1952).

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of the right heart is not materially increased, its work is augmented by the increased pulmonary arterial pressure. The circuit described, whereby blood from the right ventricle is returned to the right auricle without traversing the left side of the heart, may materially increase the volume of blood presented to the right ventricle and so impose an additional load on the right side of the heart. If such a circus movement is possible, it must challenge the validity of the concept that the output of the left ventricle is of necessity identical with the output of the right; for in mitral stenosis, and possibly in other causes of pulmonary venous hypertension, the right ventricle may put out more blood per unit of time than the left ventricle.

The tissues drained by the pleurohilar and true bronchial veins are enclosed by the peribronchial prolongations of the perivisceral fascia (Marchand 1951). Within the lung this area is drained by the true bronchial veins and is entirely separated from the alveoli by the peribronchial fascia. The true bronchial veins, by virtue of their free communication with the pulmonary veins, are subjected to any increase in pressure which may develop in the pulmonary venous system. The features of the stiff lung of mitral stenosis are those of an interstitial œdema. *Lungenstarre* or "stiff lung" was described by Schoen (1930) and Sylla (1935); but these workers held it to be due to congestion of the pulmonary veins and arteries, a pathology originally postulated by Vieussens (1715). Sylla (1935) described a macroscopic increase in the supporting tissues of the lung, and White (1947) states that in mitral stenosis there is a "tendency to bleeding or diffusion of serum (œdema) into the interstitial tissues of the lung." "This," he states, "develops into an extreme interstitial fibrosis which may in time resemble 'malignant pulmonary sclerosis' due to other causes." He also attributes this to engorgement of the pulmonary circulation, but it is difficult to envisage an interstitial œdema arising from a "leak in the pulmonary vein." An effusion originating from the capillaries of the true bronchial veins, however, would remain entirely interstitial. Ferguson et al. (1944) have shown that the intrabronchial tributaries of the bronchial vein are dilated in mitral stenosis. This is to be expected when it is realised that the bronchial veins drain into the pulmonary vein and not into the systemic veins as described by Miller (1947). Thus it is logical to presume that in mitral stenosis there is a rise in bronchial venous pressure, which in time may cause a transudation of œdema fluid into the supporting interstitial framework of the lung, and the development of a rigid or stiff lung without any intra-alveolar pulmonary œdema.

Apart from these considerations, it is possible that the pleurohilar and true bronchial veins play an important part in other aspects of the disease picture of mitral stenosis. Fig. 5 represents diagrammatically the possible functions of these veins in modifying the sequence of events leading to the end-results of mitral stenosis.

SUMMARY

Six cases of mitral stenosis have been studied anatomically at necropsy, and in thirty patients the condition of the lungs was observed at operation.

Striking engorgement of the pleurohilar veins was noted in all the cases in which they were exposed by dissection.

The possible function of the pleurohilar veins as a decompressive mechanism in patients with pulmonary venous hypertension is discussed, and the probable effects of this mechanism on the symptoms of mitral stenosis are considered.

Our thanks are due to Mr. L. Fatti for allowing us access to his operations; to Dr. A. C. Watt and Mr. A. Hughes for the photographs; and to Dr. M. Findlay, of the radiological department, for the X-ray investigations.

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ACUTE PELLAGRA DURING ISONIAZID THERAPY

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LIVERPOOL ROYAL INFIRMARY

Few serious toxic reactions have been reported during the use of isoniazid (isonicotinic acid hydrazide) in doses of 3 to 5 mg. per kg. body-weight per day. The Committee on Therapy of the American Trudeau Society (1952) summarise the preliminary clinical reports and quotes isolated instances of intractable asthma, persistent hypotension, and increased susceptibility to the effects of other drugs (but in this case the cause has not been clearly established). Less serious effects which have been reported are constipation, postural hypotension and dizziness, exaggerated reflexes, eosinophilia, difficulty in starting micturition, and the appearance of casts, albumin, and reducing substances in the urine. The first report of a symptom which suggested vitamin-B_2 deficiency during isoniazid therapy was by Pegum (1952), whose patient complained of "burning feet," a symptom which has been ascribed to deficiency of pantothenic acid.

In the following case severe symptoms and signs of pellagra developed within three weeks of starting treatment with isoniazid.

CASE-REPORT

A man, aged 22, had no family history of tuberculosis or mental disease, and had had no serious illness until two years ago. Occasional abdominal pains began in December, 1950, and the diagnosis of tuberculous peritonitis was confirmed by laparotomy and biopsy of the omentum in May, 1951. At first he responded to streptomycin and *p*-aminosalicylic acid (P.A.S.), but while in a sanatorium from July to December, 1951, his condition deteriorated. "The food did not agree with him," the abdominal pains returned, he lost his appetite, vomited often, and had diarrhœa, and his weight fell from 158 to 112 lb.

He returned home in December, 1951; his condition improved slightly and he stopped losing weight. He still had abdominal pain and loose stools (1 to 3 stools per day), but his appetite returned and he vomited only occasionally. In February, 1952, he had a further course of streptomycin at home but without benefit. During the four months before his admission to this hospital, his diet included plenty of eggs in milk and 1 lb. of a milk-protein preparation each week.

He was admitted on July 21, 1952. His weight was 112 lb., and he was emaciated. Abdominal examination was normal, except for several areas of tenderness. He was afebrile, his tongue was clean, and there were no abnormal signs in the respiratory or nervous systems. He had the introspection of the chronic tuberculous patient, but he was sensible and intelligent; his mood was rather depressed and resigned.

Hæmoglobin level was 9·8 g. per 100 ml and erythrocyte-sedimentation rate (Wintrobe) (corrected reading) 20 mm. in one hour. X-ray examination of the chest and abdomen and intravenous pyelograms were normal. The fæces and urine were repeatedly examined for tubercle bacilli, but none were found. However, treatment was started with isoniazid, 200 mg. twice daily (8 mg. per kg. body-weight per day), on July 28.

the pulmonary veins, whereas the pleurohilar veins empty into systemic veins, such as the azygos, hemiazygos, and intercostal veins (fig. 4).

The pleurohilar veins communicate freely with the pulmonary veins both at the hilum and in the subpleural plane (fig. 2).

Miller (1947) did not distinguish between these two systems of vessels. The veins which he describes as bronchial and which drain into systemic veins do not, in normal circumstances, drain more than the extrapulmonary bronchi, the hilar lymph-glands, and the other mediastinal structures at the hilum of the lung. These veins we have named the pleurohilar veins.

The true bronchial veins within the lung-substance course along a definite fascial plane which is an extension of the mediastinal perivisceral fascia (Marchand 1951). This fascia in the mediastinum encircles the trachea and œsophagus, and is prolonged into the lung as an investing layer of the bronchi and the pulmonary vessels. Situated within the plane between the bronchial wall and the peribronchial fascia lie the main trunks of the true bronchial veins, the true bronchial arteries, and the lymphatics of the lung. Venous tributaries from the intramural bronchial veins enter the venous trunks along the whole length of their course, particularly at the points of bronchial division. The peribronchial fascia is prolonged round the bronchi as far as the bronchioles and possibly may form the alveolar septum. The fascia therefore separates the respiratory portion of the lung from the interstitial framework, and the bronchial veins, which lie within the plane demarcated by this fascia, constitute the sole venous drainage of the supporting tissue of the lung.

FINDINGS IN MITRAL STENOSIS

At necropsy in all six cases of mitral stenosis congestion and dilatation of the pleurohilar veins in the mediastinum were observed. These normally insignificant veins were much distended and in two cases of tight mitral stenosis were tortuous and varicose (fig. 3). Injection of dye showed that they communicated freely with the pulmonary veins and drained directly into the azygos and hemiazygos veins.

The true bronchial veins lying within the peribronchial fascial planes have been found similarly dilated in patients who have died with mitral stenosis. The extrabronchial dilatation may be demonstrated by making a 'Vinylite' cast of the pulmonary venous tree (Marchand et al. 1950), and the intrabronchial dilatation of submucous and muscular tributaries of the bronchial veins can readily be demonstrated by injecting the pulmonary veins with a lead-gelatin mixture (Ferguson et al. 1944).

Recent developments in cardiac surgery have afforded the opportunity of more direct study of the pulmonary conditions in mitral stenosis. Dilatation of the subpleural veins over the costal surface of the lung has not been an obvious feature, but usually the veins close to the mediastinum have been prominent and thin walled. It has also been noted that the mediastinal veins at the hilum have appeared unduly congested. A feature often observed by surgeons performing mitral valvulotomy has been the difficulty experienced in collapsing the lungs after the chest has been opened. In the 30 cases observed, some degree of "stiffness of the lung" was encountered in 8. This slowness in collapsing is peculiar in that the lungs do not appear to be waterlogged, and pressure on them does not result in flooding of the trachea with expressed exudate. Once reduced in size by firm steady pressure, the lung can be reinflated without difficulty by the anæsthetist. The cause of the "stiffness" does not, therefore, seem to be within the alveoli or the lumina of the bronchi.

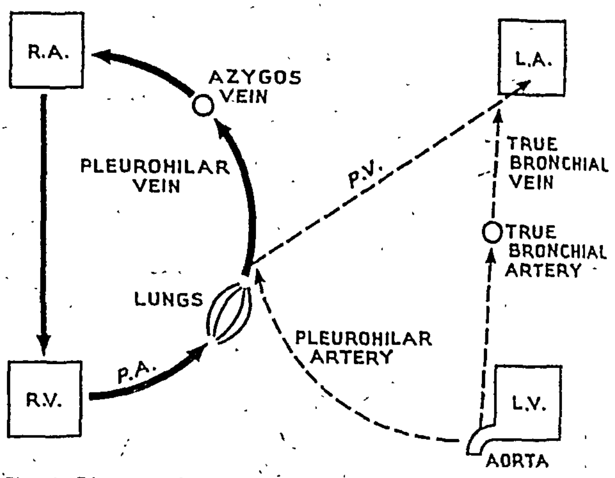

Fig. 4—Diagram of pulmonary and bronchial circulations. Circu movement described in mitral stenosis is shown in solid black.

DISCUSSION

The necropsy observation that the pleurohilar veins are dilated in advanced cases of mitral stenosis supports the belief that there is a natural decompressive arrangement within the pulmonary circulation. Even in normal circumstances the pressure in the pulmonary vein is slightly higher than that of the superior vena cava, and in mitral stenosis this pressure must be increased. The pleurohilar veins constitute a mechanism whereby the rise in pressure in the pulmonary veins may be modified. The degree of dilatation of the pleurohilar veins which has been found indicates that considerable amounts of blood may take part in a circus movement through them from right ventricle to right auricle (fig. 4).

Swan (1949) has pointed out that the pathogenesis of right-sided heart-failure consequent on mitral stenosis has never been established by adequate experimental or clinical data. He states that, although the output

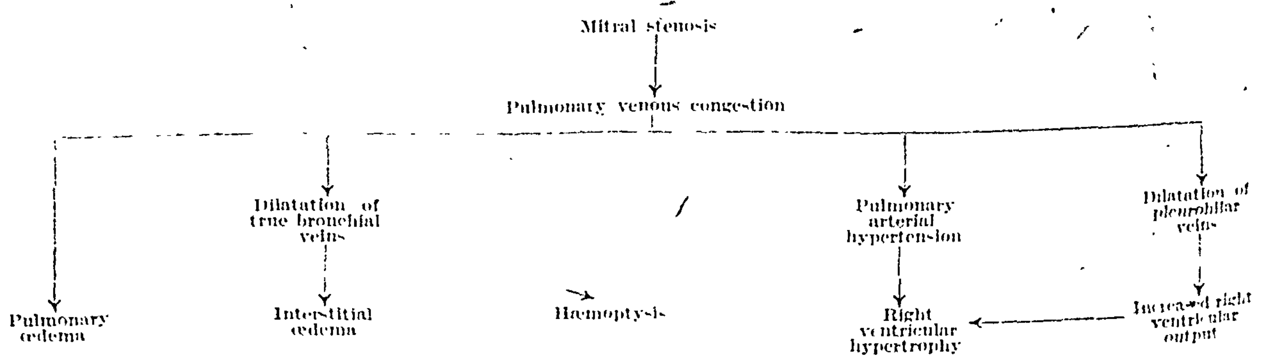
Mitral stenosis
Pulmonary venous congestion
Dilatation of true bronchial veins
Pulmonary arterial hypertension
Dilatation of pleurohilar veins
Pulmonary œdema
Interstitial œdema
Hæmoptysis
Right ventricular hypertrophy
Increased right ventricular output

Fig. 5—Sequence of events leading to end-results of mitral stenosis.

of the right heart is not materially increased; its work is augmented by the increased pulmonary arterial pressure. The circuit described, whereby blood from the right ventricle is returned to the right auricle without traversing the left side of the heart, may materially increase the volume of blood presented to the right ventricle and so impose an additional load on the right side of the heart. If such a circus movement is possible, it must challenge the validity of the concept that the output of the left ventricle is of necessity identical with the output of the right; for in mitral stenosis, and possibly in other causes of pulmonary venous hypertension, the right ventricle may put out more blood per unit of time than the left ventricle.

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Hæmoglobin level was 9·8 g. per 100 ml. and erythrocyte-sedimentation rate (Wintrobe) (corrected reading) 20 mm. in one hour. X-ray examination of the chest and abdomen and intravenous pyelograms were normal. The fæces and urine were repeatedly examined for tubercle bacilli, but none were found. However, treatment was started with isoniazid, 200 mg. twice daily (8 mg. per kg. body-weight per day), on July 28.

There was little change in his condition at first, but after a week the stools increased from 3 to 6 per day and became very offensive. By Aug. 10 he had become very depressed and slightly irrational, and it was noticed that the dorsum of each hand was red and roughened. His mental condition deteriorated rapidly and by Aug. 15 he was refusing to eat. The diarrhœa had become more frequent, and on Aug. 17 he became incontinent of urine and fæces.

The next day isoniazid was stopped, and a psychiatrist who saw him reported that he was suffering from a schizophrenic reaction which presented many catatonic features. He had marked thought-blocking, incongruity between emotion and stimulus, ambivalence, sudden impulsive movements, and possibly hallucinations. On Aug. 20 he was worse, being quite irrational and possibly suicidal.

By now the redness on the dorsum of his hands was typical of pellagra, and it had spread symmetrically to above the wrists, where there was a sharp line of demarcation with the healthy skin. He also had cheilosis, redness of the nasolabial folds, and was incontinent of frequent watery stools.

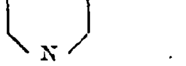
On Aug. 20 treatment was started with four-hourly doses of nicotinic acid, 40 mg. intramuscularly and 50 mg. by mouth, and vitamin-B complex intramuscularly twice daily. On Aug. 22 he was less disturbed mentally, he was able to take a high protein diet, and he was no longer incontinent, but still had much diarrhœa. By Aug. 24 his mental symptoms had all disappeared, the hand lesions were clearing, and the diarrhœa was less. By Sept. 1, the skin lesions had disappeared, and he was passing only 2 to 4 semiformed stools per day. His weight, which had remained at 112 lb. until Aug. 24, was now 120 lb. On Sept. 19 his weight was 131 lb. and he was only passing 1 or 2 semiformed stools per day, but the abdominal pains were still troubling him several times each day.

DISCUSSION

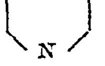
It is possible that on admission to hospital this patient was suffering from a deficiency of the B group of vitamins, though there were no symptoms or signs of this. His intake of vitamins was probably adequate, for his diet before admission, though not large, was not deficient in quality, and it was fortified by a milk-protein preparation rich in tryptophane, an amino-acid converted in the body to nicotinamide. Vitamin production in the intestine, however, may have been deficient owing to an alteration in the bacterial flora brought about by the courses of streptomycin; and there may have been inadequate absorption, for diarrhœa had been present since the early stages of the disease.

Within three weeks of starting a course of isoniazid he developed symptoms and signs of gross nicotinic-acid deficiency. During this time the only other drugs he was having were quinalbarbitone ('Seconal'), intravenous iron, and a vitamin preparation not containing the B_2 group. It thus seems likely that the isoniazid was the direct cause of the pellagra.

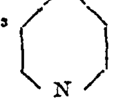
Pegum (1952) has suggested that isoniazid may block the action of nicotinamide by competitive inhibition. Other substances have been found which have this action (Woolley 1945, 1946). One of these, 3-acetylpyridine, and isoniazid are structurally similar to nicotinamide, differing from it in the side chain to the pyridine nucleus.



Nicotinamide



3-Acetylpyridine



Isoniazid

The amount of isoniazid which would compete successfully with nicotinamide in the formation of co-enzymes depends, by the law of mass equilibrium, on their relative concentration and their relative affinity for the co-enzyme residue.

As no previous case of fully developed pellagra has been reported during isoniazid therapy, its affinity is probably not great and its pellagra-producing effect depends on the patient's original nicotinamide level being low. Most patients develop a voracious appetite, and it may be that they are protected by the consequent high intake of B_2 vitamins. This patient was one of the minority whose appetite does not improve greatly. Exaggerated reflexes and difficulty in starting micturition are both found in some cases of pellagra, and it would be interesting to know whether the patients in whom these disorders developed during isoniazid therapy also had no improvement in appetite. Until further investigation has been carried out it may be advisable to give vitamin-B_2 complex to all patients taking isoniazid whose appetite remains poor.

SUMMARY

A man of 22 developed acute pellagra within three weeks of starting a course of isoniazid. It seems likely that the drug was directly responsible, and a theory of the mechanism is discussed.

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THE Medical Research Council report (1952) states that "isoniazid has shown little toxicity in the dosage used [200 mg. daily] over a three-months period," and that "toxicity with isoniazid has, so far, been a very minor problem." The side-effects reported in the M.R.C. trial were drowsiness in 8%, increase of deep reflexes in 13%, tremor of the limbs in 12%, twitching of the legs in 2 out of 173 patients, and difficulty in initiating micturition in another 2, with frequency in a 3rd. 9 patients suffered from constipation, 3 from transient flushing of the face, and 4 from skin disorders. There were 4 cases of "nervous reaction."

Robitzek and Selikoff (1952), using isoniazid in a dosage of 2–4 mg. per kg. and propyl isonicotinic acid hydrazide 2–10 mg. per kg. on 44 patients for up to fifteen weeks, found twitching of the extremities (37 cases) and increased deep reflexes (26 cases) to be the commonest signs of toxicity, followed by constipation, and vertigo associated with a fall in systolic blood-pressure. They concluded (Selikoff et al. 1952a) that the hydrazide of isonicotinic acid, and its glucoside and isopropyl derivatives, exert moderate "acute" side-effects related mainly to the central and autonomic nervous systems. Among the central-nervous-system effects they include hyperactive reflexes, involuntary twitching, insomnia, and drowsiness; the effect on the autonomic nervous system appeared to consist in sympathetic stimulation, as suggested by the constipation, bladder sphincter disturbance (delay of stream), and mouth dryness. Vertigo, when it occurred, was thought to be vasomotor in origin. Also noted were headache and disturbed vision. However, in a subsequent paper (Selikoff et al. 1952b) they attach little clinical importance to these manifestations of toxicity.

The higher incidence of toxicity reported by Robitzek and Selikoff (1952) may be explained in two ways.

1. Robitzek and Selikoff used doses up to 10 mg. per kg. body-weight, whereas the Medical Research Council employed a uniform dosage of 200 mg. per day. As 69% of the M.R.C. patients are described as being in fair or good condition, their average weight may be estimated at 8–10 st., and they were therefore receiving isoniazid in an estimated dose of 3–4 mg. per kg. daily, a rather lower amount than that employed by Robitzek and Selikoff.

2. All Robitzek and Selikoff's patients were suffering from acute progressive bilateral caseopneumonic tuberculosis, were losing weight, and were constantly pyrexial; the disease was considered far advanced and no longer suitable for any other standard accepted form of treatment. Of the M.R.C. series, only 31% of patients were in poor general condition, 44% being afebrile; only 29·5% had acute rapidly progressive pulmonary tuberculosis, 47·5% having "other forms of pulmonary tuberculosis suitable for chemotherapy."

The 4 cases of "nervous reaction" reported by the M.R.C. consisted in one patient of nausea and feeling nervy, in another of abdominal discomfort and a feeling of fright, and in a third merely of dizziness—these symptoms being limited to the first month of therapy. In the fourth patient showing a "nervous reaction," "isoniazid was stopped after two months because the patient was restless, irritable, had marked tremor of the hands and occasional spasmodic jerks and tics of the face and limbs, and finally had night wandering." No attempt was made to resume treatment, and "the symptoms gradually disappeared."

The following is an account of a case in which treatment with isoniazid for just over four months was followed by an acute toxic confusional psychosis, and by almost all the toxic manifestations previously reported. Eight weeks later the patient was left with residual organic cerebral impairment of the Korsakow type. The case is reported in detail because it seems to be the first in which such serious disturbances of the central nervous system have developed.

CASE-RECORD

Widow aged 41. Family history negative. No previous history of nervous or mental disease. Attacks of asthma during the summer for many years. She is described as having been bright, with a good memory, and a capable housewife; a non-smoker and teetotaller.

Pulmonary tuberculosis with positive sputum first diagnosed in 1938, when she received sanatorium treatment. She had a relapse in 1948 and since 1950 had lived quietly at home. Little improvement in 1951 after three months' treatment with *p*-aminosalicylic acid.

Treatment with Isoniazid

On April 28, 1952, she commenced treatment with isoniazid 50 mg. t.d.s., her weight being 7 st. (98 lb.). Two weeks later she had tingling in the arms and legs, which persisted throughout the time of taking the drug. By June she was losing weight and on July 28 the dose was doubled to 100 mg. t.d.s. In August she complained of insomnia and failing memory; later of feeling "funny in the head" and at times confused. These symptoms became worse and by Aug. 20 she could not remember the day of the week or write out a shopping-list.

Aug. 26 she spent crying, and the next day was agitated, used swear-words not previously her habit, and demanded that imaginary cats be removed. She continued to talk and behave strangely and by Aug. 29 she could no longer distinguish members of her family. On the following days she was more confused, would not be washed, and refused food and drink. She collapsed at midday and afterwards cried out for her mother who had been dead for many years. She appeared to be terrified and once rushed into the street saying she was frightened of strange men in the house.

On Aug. 31 she received the last dose of isoniazid. She no longer recognised anybody, was very agitated, got out of bed, and knocked on the walls; she still refused nourishment and no contact could be made with her. On Sept. 1 she complained that the light was too bright and insisted on curtains being kept drawn. She was removed to hospital, not having passed urine, opened her bowels, or slept for two days.

Condition on Admission to General Hospital

On admission, she did not answer questions, screamed as if in terror, and kept her eyes covered either with her hands or by burying her head under the bedclothes. She was disorientated for time, place, person, and situation. She was aurally hallucinated, conversing with imaginary people, and had visual hallucinations, seeing coloured lights, talking of "putting out the moon" and "sending the cats away." She was thin and pale with signs of bilateral pulmonary tuberculosis and clubbing of the fingers. No cardiovascular system abnormality apart from tachycardia. She showed irregular twitching of the face and extremities with jerky and exaggerated movements. No neck rigidity: Kernig's sign negative. Pupils equal, reactive to light. Cranial nerves appeared normal. Sensation could not be tested. Motor power seemed unimpaired; deep reflexes very brisk, plantar responses flexor. On Sept. 3 she was transferred on certificate to a mental hospital as she presented as a schizophrenic, catatonic type.

Observations in Mental Hospital

On admission her temperature was 99°F, her pulse-rate 94, and her respirations 22 per min. Heart sounds soft, blood-pressure 100/70. Bladder full to umbilicus, catheterisation producing 60 oz. urine. Weight 5 st. 12 lb. Findings in nervous system same as above plus a medium tremor of the extremities. She complained of headache and constipation, was totally disorientated, and could give no account of herself.

Laboratory investigations.—Hæmoglobin 10·0 g. per 100 ml. Red blood-cells 5,380,000 per c.mm.; marked microcytosis and hypochromia. White cells 16,650 (90% neutrophils, no eosinophils). Erythrocyte-sedimentation rate (Westergren) 7 mm. in one hour. Blood-urea 43 mg. per 100 ml. Wassermann and Kahn reactions negative. Cerebrospinal fluid normal. Sputum: tubercle bacilli present in large numbers. *Urine*: *light cloud of albumin. Radiography*: *skull, normal chest, multiple cavities and fibrosis both upper lobes.*

Course.—For the next eleven days she ran an irregular fever, up to 100°F, and the pulse, at times irregular, varied between 90 and 110, respiratory-rate between 28 and 34 per minute. She could not pass urine or open her bowels spontaneously and had to be catheterised daily.

She continued restless by day and night. She had to be spoon-fed. Her mouth was very dry and she developed sores at the corners. By Sept. 5 twitching of muscles was gross and resulted in head-banging and kicking movements which ceased in deep sleep and gradually subsided. She had visual hallucinations of cats and dogs on her bed and about the ward. She saw blood on the ceiling and similarly misinterpreted rust on water-pipes. At night she heard voices calling out.

By Sept. 10, one could have very brief periods of conversation with her. On the 16th she opened her bowels and passed urine spontaneously. She was much less restless, tremor and twitching had disappeared and reflexes were less brisk. By the 20th, though she felt exhausted, she was in fair contact with her environment, and no longer hallucinated, having sufficient insight to ask "Am I going mad?"

On Sept. 24 the hæmoglobin was 9·8 g. per 100 ml.; the red cells were 4,500,000 per c.mm., and the white cells 6200. E.S.R. 32 mm. in one hour. Blood-urea 32 mg. per 100 ml. A urinary infection which had developed was treated with sulphadimidine.

By the beginning of October her general condition had improved greatly despite unchanged chest signs. Temperature normal, pulse 75–95, respiration-rate 20–22 per min., blood-pressure 120/80. Eating and sleeping well. She remained quiet but complained of being confused and unable to remember. Progress was maintained and by Oct. 25 she had gained 7 lb. in weight.

Present Mental State

She is rather apathetic and does not speak unless addressed. She coöperates during examination, becomes anxious, but is easily reassured. She is fairly quick to answer questions, but frequently says "I don't know" and "Oh dear, I am so confused." She is emotionally facile, being easily moved from smiling to tearfulness. She is neither deluded nor hallucinated. She is orientated in so far as she knows the name of the hospital; but she cannot place it, nor does she know that it is a mental hospital. She does not know the time of day; she knows the day of the week and the year, but gives the date as March 7. She cannot distinguish the various nurses in the ward, and is not sure whether she has seen her regular doctor before. She gives a fair account of her early life, and knows her date of birth, but not the date of her marriage, nor her daughter's age. In describing events of the last ten years she loses the trend, cannot give them in consecutive order, and has no sense of time. Her memory for recent events is almost absent; she thought she had been in hospital for a day or two, could not tell how she got there, nor where she came from. She could not remember what she had read in the newspaper nor what she had eaten that day. Half an hour after her visitors had gone she complained of

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It is possible that on admission to hospital this patient was suffering from a deficiency of the B group of vitamins, though there were no symptoms or signs of this. His intake of vitamins was probably adequate, for his diet before admission, though not large, was not deficient in quality, and it was fortified by a milk-protein preparation rich in tryptophane, an amino-acid converted in the body to nicotinamide. Vitamin production in the intestine, however, may have been deficient owing to an alteration in the bacterial flora brought about by the courses of streptomycin; and there may have been inadequate absorption, for diarrhœa had been present since the early stages of the disease.

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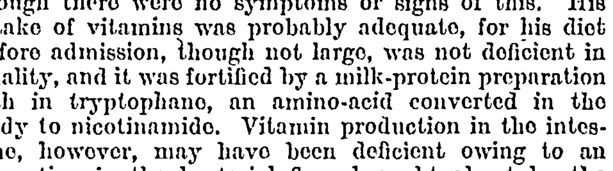

Nicotinamide 3-Acetylpyridine Isoniazid

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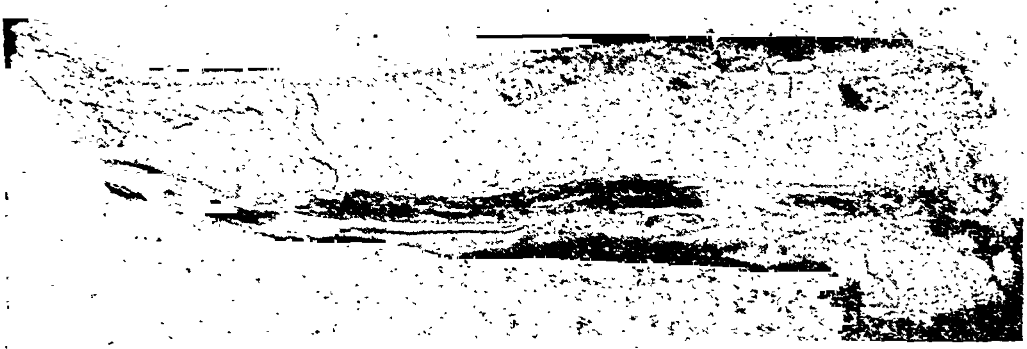

Fig. 1—Skin and subcutaneous fat from abdominal wall showing extensive fat-necrosis (× 1½).

he complained of severe pain in the region of the tendo Achillis and calf of the right leg. This was followed by the appearance on both legs of a crop of red-brown nodules which grew to a diameter of 2·5 cm. The differential diagnosis was then considered to lie between erythema nodosum and Bazin's disease, although the condition was typical of neither. Against erythema nodosum was the fact that the nodules were predominantly on the posterior aspects of the legs; against Bazin's disease was the absence of any tendency to ulceration.

A few weeks later the leg lesions were regressing, but a fresh crop of nodules appeared beneath the skin of the trunk and limbs. The patient's arms and legs felt stiff, and he complained of severe pains like toothache "deep in the bones of both legs." This caused him difficulty in walking. He had lost his appetite and a little weight but still did not look ill.

Condition on Admission

Admitted to hospital on Jan. 21, 1951, he was slightly pale and had bilateral palmar erythema, which he declared had been present as long as he could remember. Multiple subcutaneous nodules were present. In the skin of both calves their colours were those of fading bruises. On the trunk (anteriorly and posteriorly), thighs, upper arms, and scalp there was no discoloration except where the lesions had become attached to the skin, where they were dusky bluish red. The nodules varied from 0·5 to 2·5 cm. in diameter but gradually increased in size and a few were tender.

Biopsy

The nodule was broken in the course of removal, and its interior resembled pus. It proved to be a non-specific granuloma notable for the high degree of necrosis in contrast to the comparatively slight cell reaction. Samples of pus from the nodule, from a skin abscess, and from the right elbow-joint were all sterile on culture, but were remarkable for showing a paucity of cells in contrast to the large amount of necrotic material, and an excess of fat-globules which dissolved in ether.

Investigations

White-cell counts showed a gradually rising polymorph leucocytosis, with an eosinophilia in the first count which subsequently disappeared. Thus on Nov. 21 there were 10,900 white cells per c.mm. (polymorphs 65%, eosinophils 17%); on Nov. 29, 15,000 white cells per c.mm. (polymorphs 88%, eosinophils 0·5%); and on Feb. 13 20,800 white cells per c.mm. (polymorphs 89%, eosinophils 1·5%). A red-cell count showed 3,300,000 per c.mm., Hb 55%. The amount of alkaline phosphatase was increased (45 King-Armstrong units). Radiography showed only localised periosteal new-bone formation at the upper end of the left tibia.

Course of Illness

About ten days after admission the patient complained of pain in the right elbow, which restricted all its movements. There were nodules on the medial and lateral aspects of the joint, and it was difficult to tell whether a true arthritis was present. In the next few days these nodules became fluctuant, and could apparently be reduced into the joint; fluctuation could be elicited from one nodule through to another. The joint then became painless and the movements full except for slight limitation of extension. Meanwhile nodules elsewhere had grown larger, and most of them had gained attachment to the skin and become fluctuant. They were most numerous in areas of pressure, such as the back. A few on the left hip and heel came to resemble abscesses about to rupture through the skin. Most of them remained painless and not tender.

The patient had irregular pyrexia, up to 102°F, which did not respond to antibiotics. His urine occasionally contained small quantities of albumin. The fluctuating nodules, especially those on the back and over pressure points, showed a distinct tendency to coalesce. The patient perspired profusely. He finally developed acute dilatation of the stomach and died on Feb. 22, 1951.

NECROPSY

There was considerable general wasting. The subcutaneous fat formed nodular masses all over the body, especially on the back, where they were large, irregular, and firm in consistence. In some regions—notably the right costal margin, both elbow-joints, and the proximal interphalangeal joint of the left ring finger—the swellings were fluctuant and contained a creamy fluid, grey and granular from the costal margin, and green and smoother from the right elbow-joint.

The skin had a sallow almost icteric tinge, but the scleræ were not yellow. The lymph-nodes, except those in the mesentery, were not enlarged. On section the subcutaneous fat of the chest, abdomen (fig. 1), both legs, and the right arm was seen to be copiously flecked with fluffy white areas of fat-necrosis 3–5 mm. in diameter. Much less frequent, but still numerous, were small abscess-like collections of white, grey, or green creamy fluid: these varied in size from 5 mm. to several centimetres and were irregular in shape.

The calvarium was of normal average thickness and the diploë was pink. The meninges and venous sinuses were normal. The brain was pale but otherwise appeared normal. The cerebral vessels were slightly atheromatous.

Abdomen

There was no free fluid in the peritoneal sac, and the peritoneum was smooth and shiny. The stomach was dilated and empty except for a few ounces of bright-green fluid. There were a few calcified lymph-glands in the mesentery but no sign of fat necrosis in the mesenteric or retroperitoneal fat. The liver was enlarged, weighing 2830 g. On section it was generally brownish yellow and felt greasy, and it contained numerous tumours varying in appearance from white-solid masses to pink soft gelatinous ones. Round the smaller secondary deposits the liver tissue appeared to be compressed, but round the large pink areas it was gelatinous. There were numerous deposits under the capsule. Occasionally the secondary masses were completely necrotic. Here and there, remote from the tumour masses, the liver showed small grey flecks of necrosis. The biliary system appeared normal.

A large tumour occupied the centre portion of the pancreas; it was irregular in shape, fluctuant, and largest in the middle, tapering away towards the head and tail (fig. 2). The outer surface of the pancreas was smooth and covered by peritoneum. On section were found numerous thick-walled loculated cysts surrounded by considerable fibrosis; some contained serous fluid, some contained thick creamy fluid, and others were solid. Between the cysts the tumour tissue was white and soft, with necrotic areas green or pink in colour and usually gelatinous. The tumour was poorly demarcated from the pancreas, especially towards the tail. The head of the pancreas was moderately firm, and the pancreatic duct, though tortuous, could be traced through the tumour and was patent throughout. There was a considerable amount of adipose tissue in and around the gland, and in the region of the tail there were one or two very small foci of fat-necrosis.

Both kidneys (left 190 g., right 230 g.) showed one or more small congenital cysts but were otherwise normal. The prostate showed senile enlargement.

Other Findings

The bone-marrow, ribs, sternum, and vertebral bodies appeared normal. The right humerus, femur (fig. 3), and not having had any. Pressed to remember recent events, she confabulates to a marked degree and is readily led to enlarge on details. She could not remember a name and address for five minutes, but could repeat five digits forwards and three backwards. Told to repeat the substance of a short story she could only remember that the principal character was a cowboy and that a dog came into it. She subtracted 7 from 100 with only one mistake, but could not multiply 7 by 9 or 3 by 17 accurately. She could not remember the dates of the first world war and thought the Prime Minister was Mr. Attlee. She knew the Queen's name, but not that of her husband or children. Asked to name six large cities in England, she gave London, Swansea, Liverpool, Sunderland, Liverpool, and Swansea, with much hesitation. Her interpretation of proverbs was satisfactory, and she succeeded on a short list of similarities and differences.

Psychological Tests

On the Shipley Hartford Retreat Scale she scored 30 out of 40 in the vocabulary test, but only 4 out of 20 in the abstraction test. This gives a vocabulary age of 17 years, an abstraction age of 9·9 years; and a conceptual quotient of 58 which, on this scale, is to be regarded as definitely pathological and indicative of organic cerebral impairment.

On the Mill Hill Vocabulary Scale (form 1 senior) she scored a total of 61 out of 88, and on the Progressive Matrices Test 27 out of 60. She is therefore verbally of average ability, her score lying at the 60th percentile for people of her age. On the matrices her score only puts her in the 25th percentile.

These tests confirm the clinical finding of considerable organic cerebral damage.

DISCUSSION

Although Thomson (1952) mentions transient loss of memory as one of the toxic manifestations of isoniazid, the only confusional state reported is the mild one in the M.R.C. report, quoted in detail above. Their patient showed only restlessness, irritability, and night wandering, and these gradually disappeared when treatment was stopped after two months. Our patient showed the toxic manifestations previously reported to a marked degree. It is estimated that she received isoniazid in a dose of 3·5–5 mg. per kg. body-weight daily in the first three months, the only toxic manifestations being paræsthesia and loss of weight. The dose was then doubled and, in view of progressive weight loss, may be estimated at 8–10 mg. per kg. Two weeks later she developed insomnia, loss of appetite, confusion, and loss of memory; but treatment was continued for another fortnight during which she developed retention of urine, constipation, tachycardia, fever, photophobia, and a toxic confusional psychosis with tremor, twitching of muscles, and hyper-reflexia. On account of disorientation, bizarre behaviour, and hallucinations, she gave the impression of acute catatonic schizophrenia. Tuberculous meningitis was excluded by the absence of signs of meningitis and normal cerebrospinal fluid.

Increased sensitivity to light and colours as shown by this patient is similar to the experience given in a letter to THE LANCET (1952) which mentions being uncomfortably aware of physical surroundings: and "the trees seemed greener and the sky bluer." Visual disturbances were also noted by Selikoff et al. (1952a). Her present mental state also points to the diagnosis of an organic reaction. Although sensory disturbances could not be demonstrated objectively, the existence of paræsthesia, tremor, muscular twitching, and hyper-reflexia suggest a toxic neuropathy during the acute phase. Taken in conjunction with the acute mental symptoms and her present deficient memory for recent events, confabulation, and disorientation in time more completely than for place or person, as well as emotional deterioration shown by increased suggestibility and emotional facility, make the diagnosis of Korsakow's psychosis certain. Further proof is afforded by her performance on psychological tests.

Cases of Korsakow's psychosis may run a long course, with greater improvement physically than mentally. As the condition is the result of organic damage to the nervous system many cases never recover fully, particularly in regard to memory, affectivity, and judgment. Our patient showed most improvement in the first four weeks while emerging from the acute phase. There has been little improvement since then. Physically she may be considered as back to her original condition before the episode here reported; mentally she remains impaired.

Could cerebral damage have been avoided had the drug been omitted earlier at the first onset of severe symptoms? Rubin et al. (1952) conclude that the two outstanding manifestations of isoniazid toxicity in dogs—namely, damage to the liver and the nervous system—may be reversible "upon prompt cessation of drug administration." When isoniazid was eventually discontinued our patient failed to improve and her physical and mental condition deteriorated for another week.

The confusion and impairment of memory which appeared in this case before other gross signs of toxicity may, in retrospect, be taken as danger-signals of cerebral damage.

SUMMARY

A woman of 41 with chronic bilateral pulmonary tuberculosis received domiciliary treatment with isoniazid, in a dose of 3·5–5 mg. per kg. body-weight for three months. During this time she developed tingling feelings in the extremities and lost weight. The dose was then doubled to 8–10 mg. per kg. daily for another month. Early signs of involvement of the central nervous system were confusion and loss of memory, followed by insomnia and anorexia. She developed a toxic confusional psychosis and later dryness of the mouth, retention of urine, constipation, tremor, muscular twitching, hyper-reflexia, and a microcytic hypochromic anæmia. Eight weeks later she was left with signs of organic cerebral impairment of the Korsakow type.

I wish to thank Dr. J. H. Patterson for encouragement and Dr. James A. Robertson for his interest and advice.

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CARCINOMA OF THE PANCREAS ASSOCIATED WITH FAT-NECROSIS

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BIOCHEMIST

MANCHESTER ROYAL INFIRMARY

THIS case is reported because it presented a difficult diagnostic problem. A tumour of the pancreas and its secondaries in the liver retained some at least of the physiological activity of the normal pancreas and presented a pathological and clinical picture recorded in four other cases.

CASE-RECORD

A well-built man, aged 59, noticed in October, 1950, painless red firm flat nodules in the skin of both legs below the knees. After ten days these faded, but soon afterwards and the bone itself appeared unchanged. Outside the bone, next to the periosteum, there were scattered foci of fat-necrosis, some of which were surrounded by a few round cells indistinguishable from lymphocytes. There was no evidence of secondary tumour cells in serial sections of blocks taken from several areas. The red bone-marrow from the sternum appeared to be normal except for occasional isolated fat-cells showing early necrosis. No evidence of osteoporosis was obtained when the stripped femur was radiographed.

Other Organs

The *lungs* showed diffuse œdema, congestion, emphysema, purulent bronchitis, and a terminal bronchopneumonia. No evidence of secondary tumour was seen.

Frozen sections of the *brain*, stained by the methods of Loyez and Smith and Quigley, showed no evidence of demyelinisation in the many areas examined in this way. The *pituitary, suprarenals, thyroid, prostate, bladder, aorta,* and *heart muscle* were all normal. The *kidneys* were normal except for some œdema.

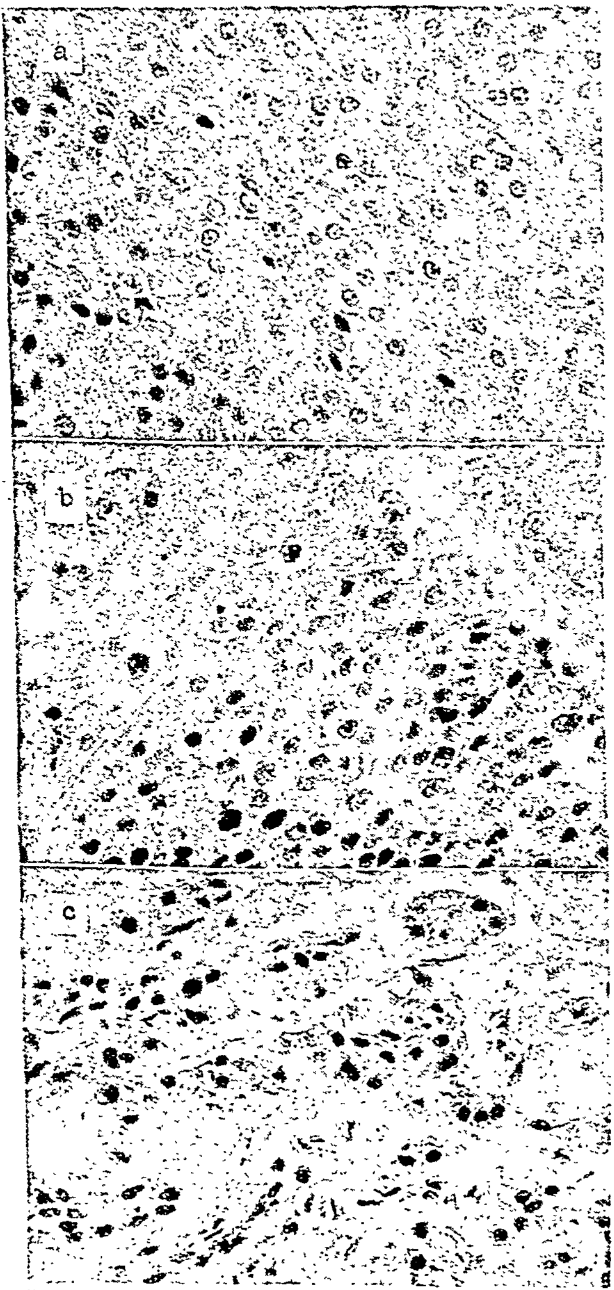

Fig. 4—Sections of tumour of pancreas showing various degrees of differentiation (× 480).

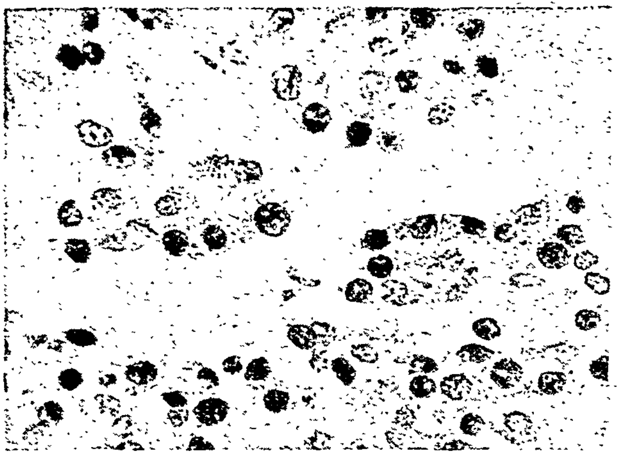

Fig. 5—Section of secondary deposits in liver, showing greater differentiation than in primary tumour shown in fig. 4*b*. Liver secondaries were producing much more lipase than was the primary tumour (× 480).

BIOCHEMISTRY

Semi-solid material from an "abscess cavity" contained neutral fat 21%, free fatty acid 19%, soaps 15%, cholesterol 1%, and debris 44% of dried weight. The serum-lipase level was 32 units per ml. Tissue lipase gave the following figures:

Pancreas:	tumour-free ..	*1200 units per g.
	tumour	1000 ,, ,,
Liver:	tumour-free ..	*300 ,, ,,
	tumour (secondary)	2400 ,, ,,

*As judged macroscopically.

Determination of Lipase

The method used for determining the lipase content of the tissues and blood was essentially that of Cherry and Crandall (1932). In this the substrate used is olive oil (triolein), digestion is for twenty-four hours, and the fatty acids produced are titrated with *N*/20 sodium hydroxide. Each unit corresponds to 1 ml. of *N*/20 sodium hydroxide required for this titration. The techniques used were:

Tissues.—About 3 or 4 g. of fresh tissue was cut up and ground with sand and about 50 ml. of physiological saline solution and then allowed to stand in the refrigerator overnight. The liquid extract was separated, and dilutions were put up so as to determine the volume of extract required to produce a final titration of about 3 ml. This is necessary to obtain comparable results, since enzyme activity does not increase in proportion to the amount of enzyme present. This effect is illustrated in the diagram (fig. 6). As a result, higher titrations do not adequately reflect the actual amount of enzyme present. The result was then expressed as the units per gramme of wet tissue calculated as follows:

$$\text{Units per gramme} = \frac{\text{ml. titration} \times \text{volume of extract} \times \text{dilution of extract}}{\text{weight of tissue used}}.$$

Normal post-mortem pancreases and livers were examined in the same way to determine the approximate normal range by the technique used. The results obtained were:

Pancreas:	1110–9000 (12 specimens) Average 4600 units per gramme.
Liver:	10–460 (10 specimens) Average 190 units per gramme.

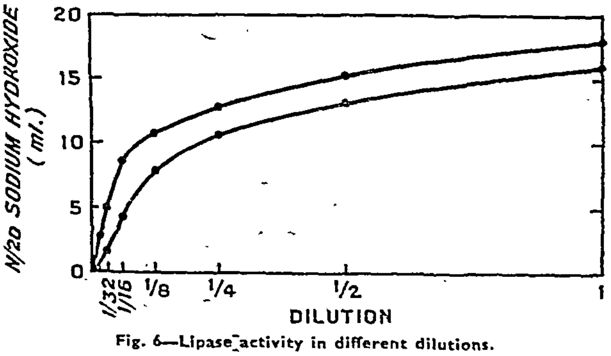

Fig. 6—Lipase activity in different dilutions.

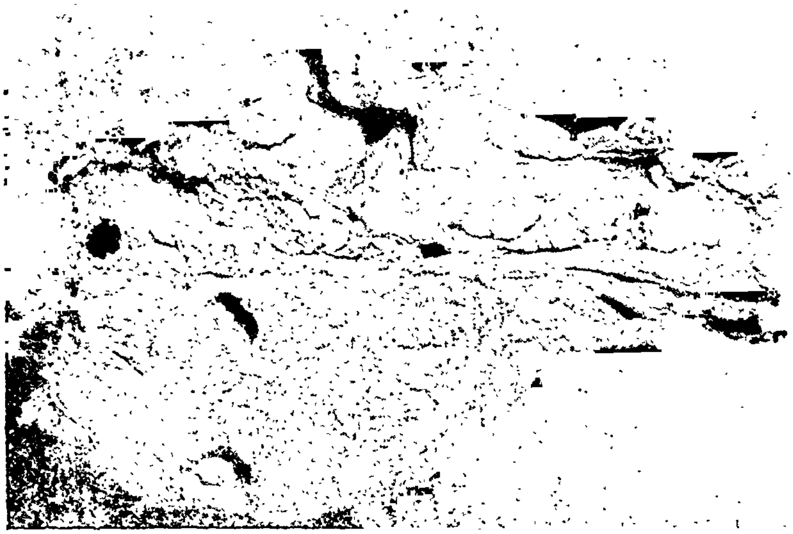

Fig. 2—Tumour in middle third of pancreas (about 4/5 of actual size).

tibia were sawn longitudinally and their marrow was uniformly grey and necrotic. The right elbow-joint was continuous with the subcutaneous abscess cavity already described, and the articular surfaces were roughened. The muscles, all other organs, and tissues appeared to be normal.

HISTOLOGY

Pancreas

The head and tail of the pancreas showed general patchy overgrowth of the connective tissue (fig. 4) and in some of the more fibrous areas there was evidence of duct proliferation. The parenchyma showed some patchy atrophy, with moderate infiltration by lymphocytes and plasma cells. The main ducts appeared to be normal, but the duct radicles in the head were slightly dilated. Many of the ducts contained eosinophilic material. Occasional areas of apparent necrosis were seen which showed no significant cell reaction, and some at least may have been due to post-mortem change. The islet tissue was normal. Adipose tissue in the tail region contained occasional areas of fat-necrosis. Here the fat-cells had a granular cytoplasm and looked opaque and the surrounding tissue was sparsely infiltrated with small round cells. No tumour tissue was seen in either head or tail. The body of the pancreas was wholly replaced by tumour tissue, which at its periphery sent thick finger-like projections of tumour into the surrounding pancreatic tissue and was surrounded by a dense fibrous reaction, which formed an imperfect capsule for the tumour. The tumour was made up of sheets of eosinophilic cells, divided by a delicate filamentous stroma into indistinct lobules. There was a fairly general differentiation into indefinite acini. Nuclear staining was variable and tended to be hyperchromic. The nuclei tended to be round, fairly uniform in size, and with one rather indistinct nucleolus. Occasionally the nuclei tended to elongate and the cells to form a palisade. The cells were polygonal, with a moderate amount of cytoplasm, and both nucleus and cytoplasm often showed vacuolation. Areas of necrosis occurred throughout the tumour. In the interstitial adipose tissue fat-necrosis was widespread.

Regional *lymph-nodes* showed mild subacute inflammation, with here and there occasional secondary deposits.

Liver

The metastatic deposits in the liver were better differentiated than in the primary growth (fig. 5). The cells were arranged in acinar circlets, though without a central aperture. Neither in the primary tumour nor in the metastases were zymogen granules seen.

There was marked perilobular fatty change in the liver cells, together with deposits of tumour tissue. Remote from the tumour deposits, scattered haphazardly, were small foci of necrotic liver cells surrounded by congestion and hæmorrhage. The cells in these foci and in the fatty areas showed masses of anisotropic crystals when viewed by polarised light. These areas took up copper acetate (Benda's stain) and were presumably areas of fat-necrosis.

Skin

The cutaneous lesions varied in appearance, shape, and size, but also showed fat-necrosis. They were mostly confined to the subcutaneous tissue, and only occasionally did they encroach on the dermis. The well-marked distinction into two types of lesion seen macroscopically was lost microscopically. The slightest lesion was a granular opacity of single or several contiguous cells.

Stained with hæmatoxylin and eosin, the cytoplasm was purple and appeared granular or faintly reticular in the adipose net. This change excited no response from the surrounding tissue. Occasionally in the region of these groups of cells small venous channels were thrombosed. In some of these small groups and in the larger lesions the altered fat-cells sometimes became smaller and crowded together, thus forming a more compact tissue, which might include some of the fibrous trabeculæ and vascular bundles. The limits of these areas were marked by a fairly vigorous fibroblastic and capillary extension, with a very slight infiltration with polymorphs, most of which showed necrosis. Scattered throughout these lesions were foci of disintegrating and disintegrated tissue, which might be basophilic or eosinophilic, reticulate or amorphous. The small arteries and veins present in some of these lesions showed necrosis; the walls of the arteries appeared hyaline and eosinophilic, and those of the veins, which usually contained thrombus, were sometimes infiltrated with polymorphs. Hæmorrhages from these necrotic vessels were only occasionally seen.

Although many blocks from the subcutaneous tissue of the chest and abdomen were sectioned serially and examined, nowhere was there any evidence of tumour cells or of any cells which might have been tumour cells but had disintegrated. All that could be seen were the lesions described above and scattered collections of lymphocytes, some round these lesions and others in the surrounding fat, often near to small vessels.

The semi-liquid material from the necrotic areas, when suspended in water, contained numerous needle-shaped crystals floating freely in the fluid, and heavier amorphous material. The crystalline material was anisotropic, but not the amorphous material. Material from the more solid areas of typical fat-necrosis emulsified badly, possibly owing to the absence of soaps, but had substantially the same constitution microscopically. The skin lesions appeared therefore to be areas of fatty and connective-tissue necrosis associated with venous thrombosis and vascular necrosis. There was no evidence of secondary deposits.

Bone

There was extensive necrosis of the bone-marrow of the long bones, essentially the same as that seen in the subcutaneous tissues. The fat-cells were granular and, when examined by polarised light, were seen to contain masses of anisotropic crystals. There was no inflammatory cell reaction

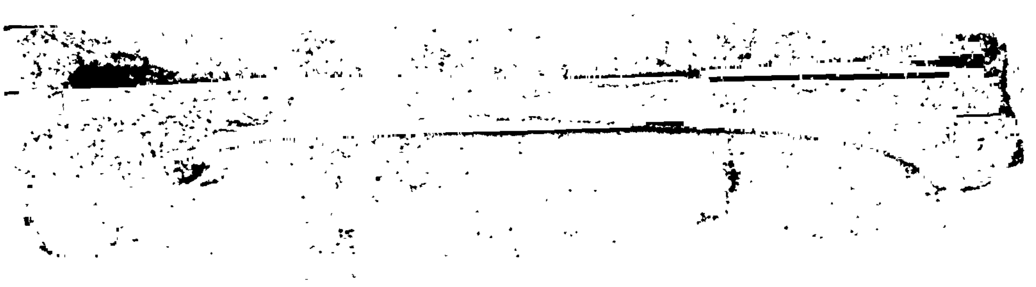

Fig. 3—Sawn femur showing fat necrosis.

and the bone itself appeared unchanged. Outside the bone, next to the periosteum, there were scattered foci of fat-necrosis, some of which were surrounded by a few round cells indistinguishable from lymphocytes. There was no evidence of secondary tumour cells in serial sections of blocks taken from several areas. The red bone-marrow from the sternum appeared to be normal except for occasional isolated fat-cells showing early necrosis. No evidence of osteoporosis was obtained when the stripped femur was radiographed.

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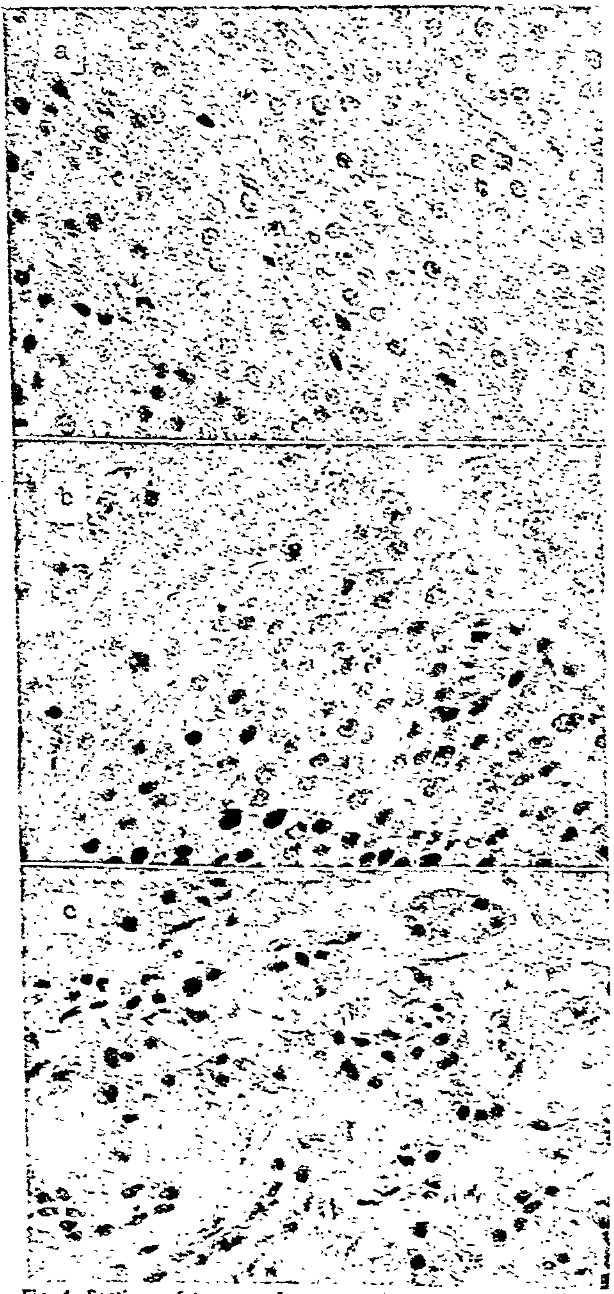
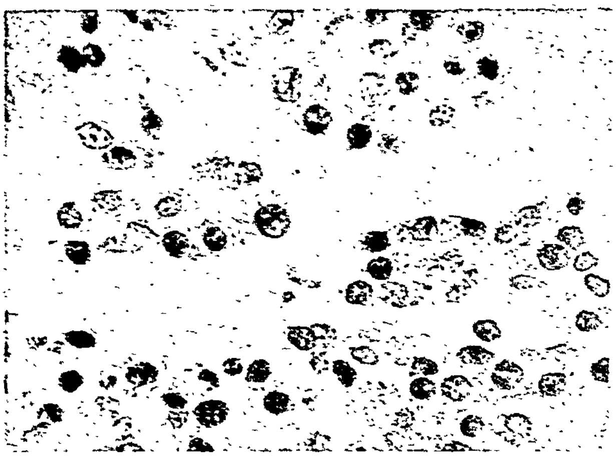


Fig. 4—Sections of tumour of pancreas showing various degrees of differentiation (× 450).



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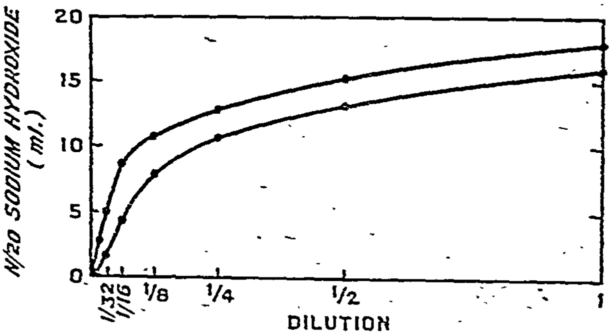

Fig. 6—Lipase activity in different dilutions.

Further work on the determination of the lipase activity of the pancreas is being done. These results must be regarded as provisional but suffice to show the relative degree of activity of the tissues from the present case.

Serum.—The lipase activity of the serum was also determined by the Cherry and Crandall method but modified so as to obtain a final titration of about 3 ml. With this a value of 32 units per ml. was obtained. This corresponds to a titration of approximately 11 ml. using 1 ml. of undiluted serum incubated for twenty-four hours. A series of post-mortem sera was also examined for lipase activity and these were found to be within the normal range for the Cherry and Crandall method, that is, less than 1·5 units.

DISCUSSION

Clinical Features

The present case and the four previously published present a clinical picture which is almost a definite entity. The features which tend to recur are:

1. Skin lesions, usually on the legs, which resemble erythema nodosum or Bazin's disease yet are typical of neither condition.
2. Subcutaneous nodules which later break down and become abscesses.
3. Limb pains and a tendency for the necrotic process to involve the joints.
4. A tendency to eosinophilia.
5. Sooner or later most of the patients develop malaise, high fever, and wasting, although they often remain in good condition for a time.
6. The duration of the illness is normally measured in months.

Pathology

The outstanding feature of this case was the occurrence of foci of typical fat-necrosis predominantly and strikingly in the subcutaneous tissue and in the yellow bone-marrow, with minor but similar changes in the tumour itself, the liver, the red bone-marrow, and the immediate locality of the long bones. Other workers have described a variable distribution. Auger (1947) found fat-necrosis of the renal capsule, the bladder, prostate, mesentery, heart, pancreas, subcutaneous tissue, and elsewhere, but did not record changes in the bone-marrow. Titone (1936) described necrosis in the subcutaneous tissue, lungs, muscle, and bone-marrow; Hegler and Wohlwill (1930) in the subcutaneous tissue and yellow bone-marrow; and Berner (1907) in the subcutaneous tissue as well as in the tumour. In all these cases the subcutaneous fat was involved, and the lesions there were widespread and histologically similar—namely, fat-necrosis of varying age accompanied by a variable cell reaction which increased with the age of the lesion. In no case was there positive evidence of the existence of secondary tumour cells related to the subcutaneous fat-necrosis. In three cases the bone-marrow was involved, and in one of these (Hegler and Wohlwill 1930) evidence of secondary deposits was found. Auger's (1947) case alone showed necrosis in most of the depot areas. Evidence of fat-necrosis in solid organs was found in Titone's (1936) case and in the present one. Here also it is notable that the liver showed fatty degeneration in areas remote from the tumour deposits, and it appeared to be the cells affected by this change that had undergone fat-necrosis. The histological appearance of these areas resembled that described by Schiller (1941). We feel justified, therefore, in concluding that the focal lesions described in the liver are areas of fat-necrosis. In Titone's case it is not clear that the necrosis was of fatty tissue. In our case the only evidence of fat-necrosis of the red bone-marrow was in the fat cells. The relationship of areas of fat-necrosis to necrotic vessels was emphasised by Auger, particularly in the mesentery, perirenal, pelvic, and other regions, but not in the skin. In the present case vascular necrosis and thrombosis were seen in association with the lesions in the subcutaneous fat.

Morphological evidence of functional activity of the tumour, shown by the presence of zymogen granules, was seen in Auger's case but not in ours and was not described in the others. It is well recognised that tumours and their secondary deposits when well differentiated may retain some or all of the functional activities of the parent tissues. This is particularly true of tumours of the endocrine system. It is also seen elsewhere, as in mucus-producing adenocarcinoma and bile-producing hepatomas. Ewing (1940) gives evidence of chemical function in tumours and notes that activity fades with increasing anaplasia. In the present case we found chemical evidence that the tumour and its secondaries were producing large amounts of lipase up to the time of death.

High serum-lipase levels were noted in 40·5% of cases of carcinoma of the pancreas reviewed by Comfort and Osterberg (1940). That this is not necessarily associated with tumour activity is shown in the experimental ligation of the pancreatic ducts in dogs and by the raised serum-lipase in acute pancreatitis in man (Comfort et al. 1943). The explanation given is that obstruction of the pancreatic ducts leads to rupture of their radicles under the stress of pent up secretion, which is released via lymphatics into the blood-stream. In these circumstances the effect is transient and disappears as the gland atrophies. The highest value for serum-lipase obtained by these workers was 15·8 ml. of *N*/20 sodium hydroxide per ml. of serum in a case of carcinoma of the pancreas. A level of 9·7 ml. recorded earlier in the same patient led them to suggest functional activity of the tumour, though there was possibly the complication of previous pancreatitis and duct obstruction. Chemical investigation of the tissues five days after death did not establish this activity but did not discount its possibility.

The problem in our case was to decide whether the remarkable fat-necrosis observed was due to small active secondaries which, by secreting lipase, underwent autodigestion and produced surrounding fat-necrosis, or whether it resulted from the high serum-lipase in combination with other factors, such as vascular thrombosis and trauma. There was also the problem of the distribution of the fat-necrosis—its peculiar tendency to occur predominantly in the subcutaneous fat and in the yellow bone-marrow. We do not know of any difference in the chemical constitution of the fat in these regions compared with that elsewhere which would make it especially susceptible to the action of lipase, and we can offer no explanation for this phenomenon.

Hegler and Wohlwill (1930) were satisfied that active secondaries were responsible for the fat-necrosis they described; Poičić (1920) suggested that this was also the explanation in Berner's patient, and Titone (1936) came to the same conclusion in his case but could not demonstrate such deposits. Auger (1947), however, could find no evidence of secondary deposits related to fat-necrosis, and we have had a similar experience. Thus in only one of the five cases reported so far has any evidence of secondary tumour in close relation to the fat-necrosis been found, and then only in the bone-marrow, where the association may well have been fortuitous.

We agree that, when secondary deposits of lipase-producing tissue occur in fatty regions, necrosis may be expected to develop, but we suggest that fat-necrosis can also occur from high serum-lipase levels alone in the absence of such metastases. Whether accessory factors, such as vascular thrombosis and trauma, must also be present we do not know.

Distant foci of fat necrosis have been found experimentally and in acute pancreatitis with duct obstruction (Perry 1947). His experimental work suggested that they were due to lymphatic spread of lipase. As the lymphatics drain ultimately into the blood-stream, generalised subcutaneous lesions could imply simply the further drainage of lipase into the general circulation. Lipase does not require very precise conditions for its activation; normal tissues have been shown to be adequate (Schiller 1941). The focal nature of the necrosis leads one to suspect some kind of directing influence, such as the vascular system. Auger showed that necrotic vessels were fairly constantly associated with the foci of necrosis, and in the present case necrosis of small vessels and thrombosis of venules were seen in association with the subcutaneous lesions, but we could not decide whether these antedated the necrosis or were a part of it. Multiple venous thromboses tend to occur in some types of neoplasia, especially in carcinoma of the pancreas (Sproul 1938). Possibly thromboses of this kind in association with high lipase values may initiate the foci of fat-necrosis.

The part played by trauma is difficult to assess. It might reasonably be thought to be a factor in the production of the subcutaneous lesions, but it is hard to believe that it could have played any part in the lesions of the bone-marrow, where one would have thought the fat was exceptionally well protected. Berner (1908), who thought that trauma did explain the skin lesions, advanced no evidence in support. In the present case, however, we noted that the lesions were much larger and more obvious over the pressure points and on the dorsum of the body, suggesting that it did contribute something to the genesis of the necrosis.

SUMMARY

A case is reported of adenocarcinoma of the body of the pancreas with secondary deposits in the liver only, associated with widely disseminated fat-necrosis in the subcutaneous tissues and bone-marrow.

This disseminated fat-necrosis produced a striking clinical picture constituting a difficult diagnostic problem.

The tumour and its secondaries were functionally active and were producing lipase in considerable quantities. The resulting high serum-lipase level seems to have been the cause of the disseminated fat-necrosis in the subcutaneous tissues and in the bone-marrow. Venous thrombosis, vascular necrosis, and trauma were possible accessory factors in the production of the necrotic lesions.

In cases presenting similar clinical features estimation of the levels of pancreatic enzymes in the serum during life may assist the diagnosis.

We are indebted to Dr. William Brockbank for his help and permission to publish the clinical records of this case; to Prof. A. C. P. Campbell for his encouragement and advice; to the steward and technicians of the department of pathology for their coöperation; and to Mr. F. W. Barnes for his assistance with the biochemistry. A special word of thanks is due to Dr. Sabina Strich for her considerable help with the translations from the German papers.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Effects of Intense Sound

ON Nov. 7 Air Vice-Marshal E. D. D. DICKSON was inducted as president of the section of otology of the Royal Society of Medicine. In a presidential address he discussed Effects of Intense Sound and Ultra-Sound on the Ear.

The human ear, he said, appreciates sounds of frequencies ranging from 20 to 20,000 cycles per second—from about the bottom note on a piano to more than two octaves above the top note. These are known as the sonic frequencies. Ultrasonic frequencies are those above 20,000 cycles per second; the term "supersonic" refers to speeds above those of sound. The sound-wave travels at about 760 miles per hour.

Intense sound can be defined as one that is strong enough to be perceived by structures other than the ear itself. In clinical audiology the normal unit of intensity is the decibel. The President gave some examples of noise in everyday life: a whisper has an intensity of up to 30 decibels; normal conversation, or a quiet motor-car, between 35 and 55 decibels; the raised voice, or a railway sleeping-car, between 60 and 75 decibels; and a shout about 100 decibels. At an intensity of 120 decibels the human ear experiences discomfort. It is already possible to measure intensities of noise at sonic levels, and equipment is now being developed in the Royal Air Force to measure the intensity of ultrasonic frequencies.

The sensation of loudness depends on the frequency and intensity of the sound. Acoustic trauma is influenced by many factors: the total time of exposure to noise, the duration of each exposure, the frequency of the noise, its volume, the use of protective devices, the age of the person exposed, and the presence or absence of previous aural disease.

A noise of more than 90 decibels' intensity may cause acoustic trauma. There are two types—the explosive and the chronic. The explosive type results from exposure to a sudden loud noise giving rise to acute concussion of the inner ear; there is permanent loss of hearing for sounds of all frequencies, and especially the higher ones. The chronic type of acoustic trauma is caused by long-continued exposure to noise, particularly from sounds of high frequency; interrupted sounds cause more damage than continuous ones, and the loss of hearing affects only frequencies above that of the damaging sound. This type of hearing loss is reversible if exposure is stopped, but with a loss of 60 decibels return to normal hearing may take four or five days.

Among flying personnel the tendency to deterioration in hearing is greater from multi-engined than from single-engined aeroplanes. In piston-engined aeroplanes the noise is mainly of low or middle frequencies, but in jet-engined aeroplanes, the high sonic frequencies predominate. The peak frequency of a jet engine is about 2000 cycles per second, and the intensity of its noise is about 145 decibels. Exposure to such an intense sound will cause a considerable hearing loss for higher tones, and extremely severe tinnitus; but the frequencies of ultra-sound have little or no effect on hearing—it is the intensity rather than the frequency of a sound that produces damage.

There is very little evidence from pathological changes in man on the effects of intense sound and ultra-sound, but in guineapigs degenerative changes have been noted in the cochlea; the greater the intensity of sound, the greater are these changes. Once the ear has been damaged by noise, its susceptibility to further damage is increased.

Noise as an industrial hazard has not received enough attention. Attempts should be made to protect the ears—for example, by wearing ear plugs or helmets. The President thought that any worker who was to be exposed continuously to a noise of more than 90 decibels' intensity should have his hearing tested by modern audiometric methods before starting work and at intervals afterwards. Only in this way could employers determine the susceptibility of individual workers to noise. Another possible improvement was insulation of machinery against noise.

There were no grounds for supposing that ultrasonic frequencies caused disturbances of vestibular function.

In the subsequent discussion Mr. J. F. SIMPSON cited the case of a business man who had become deafened in the left ear from use of the telephone. He began to use his right ear, but this too became deaf. Did we know, he asked, any of the factors responsible for the very wide individual variation in susceptibility to noise? In reply, the PRESIDENT said that he already had a programme in view to study this problem. He felt that some idea of susceptibility could be gained from knowing the rate at which hearing recovered after exposure.

Reviews of Books

Diabetes and Pregnancy

Blood Sugar of Newborn Infants during Fasting and Glucose Administration. JORGEN PEDERSEN, Blegdamshospitalet, Copenhagen. Copenhagen: Danish Science Press. 1952. Pp. 230.

Dr. Pedersen here presents both his own work and its general background; and the extent of the survey as well as his own contributions make it of real value to researchers in this field.

He has measured the blood-sugar four times daily of some 20 diabetic women for 32 to 80 days before delivery, and computed the average pregnancy blood-sugar level. This, he finds, is inversely related to the average blood-sugar level of the infant during the first 24 hours of its existence (the "24-hour level"), whereas the blood-sugar of the mother half an hour before delivery is directly related to the infant's "24-hour level." Furthermore infants of diabetics had a lower 24-hour blood-sugar level than infants of normal mothers, even where there was no difference in the maternal blood-sugar levels at delivery. Infants of diabetics also differed from those of non-diabetics in that their first 24-hour blood-sugar level varied inversely with their birth weight.

Unlike the Chicago school, he does not recommend feeding glucose to the infants of diabetics in the first 24 hours, since he found that the blood-sugar did not fall progressively in spite of fasting, and he is sceptical of explaining their increased neonatal mortality on a basis of hypoglycæmia. He states however that he still considers the hyperinsulinism theory for the infants of diabetics "plausible."

Although this work is in many ways a model of a full, if rather verbose, presentation of data, it is marred by a number of typographical errors.

Cellular Changes with Age

WARREN ANDREW, PH.D., M.D., professor of anatomy, George Washington School of Medicine, Washington, D.C. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 74. 18*s.*

THE level of this useful review of recent work on the histobiology of ageing is that of the monographs contributed to Cowdry's celebrated textbook. It touches on some of the recent studies in the ultramicroscopic structure of collagen fibres, the comparative anatomy of neurone degeneration, and the pointers—more numerous than the known facts about ageing processes—towards useful lines of research.

Hemifacial Spasm

A Clinical and Pathophysiological Study. ROBERT WARTENBERG, M.D. London: Oxford University Press. 1952. Pp. 86. 32*s.*

THIS clinical monograph on an obscure phenomenon is in many ways a model of its kind. Dr. Wartenberg has taken a tiny problem, analysed it with precision, illustrated it by lucid case-notes and excellent photographs, and submitted an explanatory hypothesis with modesty, clarity, and balance.

He sets out clearly the neurological relation between hemifacial spasm of unknown origin and spasm following facial paralysis, and he believes that they should both be regarded as release phenomena. The causes of this release are still obscure, and perhaps he overstates his case when he suggests that infection by the mouth is the likeliest cause both of spasm and of paralysis of the facial nerve. However, he admits that this cannot at present be considered proven or even susceptible of proof; but as he shrewdly affirms, "A fertile error is of more value than a sterile fact."

The only criticism that may arise is the brevity of the section on therapy. Neurologists are apt to be more preoccupied with diagnosis than treatment, and Dr. Wartenberg is a trifle summary with surgical methods. For instance, the recent work of Marino and Alurralde, who practise peripheral selective neurotomy, perhaps deserves mention.

Culdoscopy

A New Technic in Gynecologic and Obstetric Diagnosis. ALBERT A. DECKER, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders. 1952. Pp. 142. 17*s.* 6*d.*

THIS is a procedure which is gaining in popularity in the United States, and the time is ripe for a detailed description of its technique, scope, limitations, and risks. Only as regards the risks is Dr. Decker's book not quite satisfactory. A method that will often obviate laparotomy has obvious advantages, and many may be tempted to embark upon it because Dr. Decker emphasises the absence of complications and disasters. But in less practised hands unsuitable cases may be selected and accidents may well occur. He should perhaps have tempered his enthusiasm with warnings. Where bowel is adherent to the base of the pouch of Douglas—as a result of pelvic tuberculosis or endometriosis, for example—there is a real risk of injury, and only a high degree of clinical common sense and consistent luck will prevent such damage. In excluding tubal pregnancy the method is probably more valuable than for any other purpose. But there is always the danger that the general adoption of any new diagnostic or therapeutic measure will lead to abuses, and patients are hardly likely to find the experience a comfortable one, especially as the knee-chest position is essential.

The Medical Annual 1952 (Bristol: John Wright & Sons. London: Simpkin Marshall. 1952. Pp. 476. 27*s.* 6*d.*).—A year's medical news, distilled and condensed, makes strong drink: the annual is a little too potent perhaps for the student, who must risk a headache by sampling all the well-known vintages, but it is just the thing for those who need no longer keep so large a cellar. The editors, Sir Henry Tidy and Prof. A. Rendle Short, have again called for clear summaries of the more important publications of 1951, and their contributors have produced them by the score. The "literature," already unmanageable enough for most readers, gets more and more out of hand, and the annual has for many years been an excellent means of keeping it under control.

Spanish-English Chemical and Medical Dictionary (New York, Toronto, and London: McGraw-Hill Book Company. 1952. Pp. 610. £7 9*s.*).—The English-Spanish companion volume (reviewed in these columns on *Feb. 14*, 1948) has 692 pages and cost 50*s.*, its American price being $12. The volume now under review, compiled by the late Mr. Morris Goldberg, costs $17.50 in America, to which its English price of 149*s.* seems out of all proportion. Nor is it so superlatively good as to justify this enormous price; for, though it seems to include nearly all the words which, derived from Greek or from Latin, are almost the same in both English and Spanish, it omits many medical words of more Spanish character which could have been usefully included.

Textbook of Histology (6th ed. *Philadelphia and* London: W. B. Saunders. 1952. Pp. 616. 50*s.*).—Should anyone offer a prize for the best-illustrated textbook, "Maximow and Bloom" would be up there among the contenders—and the pictures of a pulmonary lobule and a section of the human pancreas would surely get a special mention. The book was originally planned in 1926 by the late Prof. A. A. Maximow, and the work was carried on after his death in 1928 by Prof. William Bloom, who has now directed another edition. Large parts of the book have been rewritten and many of the illustrations are new; an introductory chapter has been added which "correlates the submicroscopic, biochemical, and enzymatic constitution of cells with their structure and function" as seen through the optical microscope; and new accounts of the endocrine glands have been included.

THE LANCET

LONDON: SATURDAY, NOV. 15, 1952

Reversibility of Hypertension

The reversibility of hypertension is in no doubt when the causative disease is self-limited or can be cured. Thus in acute nephritis and toxæmia of pregnancy the blood-pressure returns to normal with resolution of the primary disease; removal of an adrenal tumour or a diseased kidney may likewise be followed by return of the blood-pressure to normal; and hypertension occurring in young adults during periods of stress may subside spontaneously. The real problem turns around the reversibility of chronic high blood-pressure. The change from a labile to a fixed level is a common sequence in both renal and essential hypertension, and in many cases fixation is followed by a progressive rise in pressure which may lead to a malignant termination, characterised by papillœdema and progressive renal failure. The mechanisms of fixation of the blood-pressure and of the transition from the benign to the malignant phase are unknown, as indeed are the mechanisms by which both renal and essential hypertension originate; and until these processes are understood it seems improbable that any reliable treatment of hypertension will be devised. Nevertheless certain facts have been established by clinical observation and animal experiment which must be taken into account both in the selection of cases for treatment and in the interpretation of results.

In the first place it is still of vital importance to make the distinction between essential hypertension and that due to primary renal disease. This distinction has been obscured in the past, and still is in some quarters, by two misconceptions—the first that essential hypertension is due to renal arteriosclerosis, and the second that the condition we now recognise as the malignant form of essential hypertension is a manifestation of chronic nephritis. Both these concepts found a place in the classification of Bright's disease by Volhard and Fahr,[1] who attributed hypertension in nephrosclerosis to degenerative lesions of the renal arteries and described malignant nephrosclerosis as a combination of the benign form and nephritis. Kimmelstiel and Wilson[2] first clearly showed that nephrosclerosis was a progressive development during the course of both benign and malignant hypertension and that, in the latter, renal lesions were slight in the early stages. These observations were strikingly confirmed when Wilson and Byrom[3] demonstrated by experiment on animals that hypertension could produce arterial and parenchymatous lesions in the kidney closely resembling those of malignant hypertension. This work presented an admirable opportunity to dispense with the two misconceptions which had previously obscured the relationship of essential hypertension with the kidney. Unfortunately, however, Goldblatt[4] dismissed the lesions described by Wilson and Byrom as artefacts and persisted in the view that his experiments provided unequivocal evidence on the one hand that essential hypertension is due to renal arteriosclerosis and on the other that uræmia is an essential factor in producing the lesions of malignant hypertension. Byrom and Dodson[5] refuted this argument when they produced arteriolar necroses in the rat kidney after forcibly raising renal blood-pressure by intra-arterial saline injection. Wilson and Byrom justifiably concluded that malignant hypertension, with its histological counterpart malignant nephrosclerosis, was a syndrome which might complicate any form of hypertensive disease. The value of these experimental studies in the interpretation of the natural history of various forms of hypertensive Bright's disease was emphasised by Ellis in his Croonian lectures.[6]

It is now common experience that papillœdema, the diagnostic sign of malignant hypertension, usually subsides if the blood-pressure can be reduced by sympathectomy or hexamethonium drugs, and this is true whether the underlying disorder is essential hypertension or primary renal disease. Elsewhere in this issue Professor Pickering and his colleagues describe such a reversal of papillœdema in three cases of pyelonephritis severally treated by nephrectomy, subtotal adrenalectomy, or sympathectomy. In all three, acute vascular necroses were found in the adrenals and in sections of kidney removed at operation, but the writers had no opportunity to observe the reversal of these lesions. They present the thesis that therapeutic reduction of blood-pressure can change malignant hypertension to benign and that the benign and malignant courses are merely expressive of the severity of the hypertensive process irrespective of the underlying lesion. While this thesis is broadly acceptable there is nevertheless considerable evidence that the level of high blood-pressure cannot alone account for the malignant change. Women may sustain for half a lifetime a degree of hypertension which in men would almost certainly change to the malignant form in a few years. Similar qualitative differences in response to high blood-pressures have been observed in animals. It seems likely that there is some individual susceptibility of the arteries and arterioles which produces an exaggerated vasoconstrictor response to rise in intra-arterial tension. The reversibility or otherwise of the process may then well be determined by the resulting damage to the renal vessels. Pickering and his colleagues regard the successful reduction of blood-pressure in their three cases as evidence against the concept of a vicious circle (put forward by Wilson and Byrom[7]) in which hypertensive renal vascular lesions perpetuate and aggravate the hypertension. They agree that alternatively a vicious circle may exist which apparently can be broken in the early stages. One cannot overlook the fact that many cases of unilateral renal disease continue with sustained hypertension after nephrectomy, and the clinical features of the malignant phase may return after an apparent reversal. In essential hypertension, moreover, a change from the malignant to the benign type for more than a few years is uncommon and even so the blood-pressure usually

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1. Volhard, F., Fahr, T. Die Brightsche Nierenkrankheit. Berlin, 1914
2. Kimmelstiel, P., Wilson, C. *Amer. J. Path.* 1936, 12, 45.
3. Wilson, C., Byrom, F. B. *Lancet*, 1939, i, 136.
4. Goldblatt, H. The Renal Origin of Hypertension. Springfield, Ill., 1948.
5. Byrom, F. B., Dodson, L. F. *J. Path. Bact.* 1948, 60, 357.
6. Ellis, A. *Lancet*, 1942, i, 72.
7. Wilson, C., Byrom, F. B. *Quart. J. Med.* 1941, 10, 65.

remains at a high level; in benign hypertension, on the other hand, restoration of blood-pressure to normal by sympathectomy is often successful. It is hard to avoid the conclusion that the comparative irreversibility of malignant hypertension, whether essential or renal, is due to secondary renal vascular lesions—i.e., arterial necrosis and endarteritis which produce irreversible renal ischæmia.

The experiments of BYROM and DODSON[8] and FLOYER[9] have confirmed WILSON and BYROM's conclusion that persistent hypertension after removal of the ischæmic kidney is attributable to secondary changes in the opposite kidney. That similar lesions occur in the opposite kidney in patients with hypertension due to unilateral renal disease is now well recognised.[10] It is possibly hazardous therefore to claim reversibility of malignant hypertension without full reference to the underlying cause of the hypertension and the possible influence of secondary renal lesions. Much confusion still derives from the use of "malignant hypertension" as a diagnostic label in primary renal disease. In view of the terminological obscurantism which Bright's disease produces in most of its devotees it would be better to speak (though not in the hearing of the patient) of benign and malignant essential hypertension, and in primary renal disease to follow the time-honoured tradition of choosing a name which indicates the primary disorder rather than a late and still somewhat uncertain complication.

Preventing Poliomyelitis

EXCITING news of poliomyelitis was given at the annual meeting of the American Public Health Association.[11] Dr. W. McD. HAMMON described the results which he and his colleagues have had in a carefully conducted trial of the protective effect of gamma-globulin in poliomyelitis.[12] Extensive field tests were made during poliomyelitis epidemics in Utah, Texas, Iowa, and Nebraska in 1951 and 1952. Of nearly 55,000 children, aged from one to eleven years, half received an intramuscular injection of gamma-globulin, while the remainder were injected with gelatin solution. The solutions looked exactly alike and strict precautions were taken to ensure that until all assessments had been made no-one concerned with the trial knew which children received the gamma-globulin. There were 64 cases of paralytic poliomyelitis among the control children, compared with 26 among those receiving gamma-globulin. In the first week following the injection of gamma-globulin the degree of protection was barely significant, but HAMMON et al. think that in the late stages of the incubation period gamma-globulin may modify the severity of the paralysis without preventing it altogether. During the second week the degree of protection increased greatly, for only 3 children who had had gamma-globulin got poliomyelitis, compared with 23 who had had gelatin. This increased protection was maintained until the end of the fifth week; thus, between the second and fifth weeks 6 cases occurred in the gamma-globulin group and 38 in the controls. True, protection was short-lived, in spite of the fact that large amounts of gamma-globulin were given: on the basis of body-weight, an average five-year-old child received 7 ml. Nevertheless, this is the first prophylactic measure which has significantly reduced the incidence of paralytic poliomyelitis. STOKES et al.[13] have suggested that gamma-globulin, given to children who have been exposed to the virus of *infective hepatitis*, may, instead of preventing the disease, modify it in such a way that a subclinical infection with lasting immunity results. It may be that a similar effect in this poliomyelitis trial will prolong the period of protection in certain individuals; alternatively gamma-globulin may prevent subclinical infections, so that its action would be less favourable in the long run; but it is too early to assess these possibilities. Of course, gamma-globulin has been used before in attempts to protect children exposed to poliomyelitis; but this is the first evidence to suggest that poliomyelitis may take its place beside measles and infective hepatitis as a disease in which those at risk can be protected in this way.

At the same meeting,[14] Dr. H. A. HOWE described the use of an inactivated poliomyelitis vaccine in children. It has been well established that monkeys can be protected against large doses of poliomyelitis virus by intramuscular injections of an inactive vaccine, and HOWE's experiments are the clinical application of these findings. The vaccine was prepared from the brain of an infected monkey, and the brain was treated with formaldehyde to inactivate the virus. Strains of all three serological types of poliomyelitis virus were incorporated in the vaccine, for injection with one strain gives little protection against heterologous types. These polyvalent vaccines produced no untoward reactions in 6 children to whom they were given, and significant levels of antibody to the three serological types of virus developed in the children's sera. Serum antibody is known to be effective against experimental poliomyelitis, and there is also evidence that after invading the gastro-intestinal tract the virus reaches the nervous system by way of the blood-stream[15]; it is therefore reasonable to suggest that these children may be protected against paralytic poliomyelitis. HOWE pointed out, however, that the vaccine might still require many modifications in order to increase its effectiveness and abolish the risk of allergic encephalomyelitis.

These are clearly important steps towards the prevention of poliomyelitis, but it is probably best to regard them, for the time being only, as pointers to further research. To protect a large number of people in this way gamma-globulin would be required in such enormous amounts that we may be faced with the possibility of exsanguinating half the population to protect the rest. The use of inactivated vaccines on a large scale may raise a similar problem, for one monkey might be needed to provide enough virus to vaccinate a single child successfully. The only clear way out of this impasse is to use live attenuated virus vaccines; here two difficulties arise—the preparation of attenuated strains of poliomyelitis virus and their testing in human beings—

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[8] Byrom, F. B., Dodson, L. F. *Clin. Sci.*, 1949, 8, 1.
[9] Floyer, M. A. *Ibid*, 1951, 10, 405.
[10] Allen, A. C. The Kidney. New York, 1951.
[11] *New York Times*, Oct. 23, 1952.
[12] Hammon, W. M., Coriell, L. L., Stokes, J. jun. *J. Amer. med. Ass.* 1952, 150, 739; Hammon, W. M., Coriell, L. L., Wehrle, P. F., Klimt, C. R. Stokes, J. jun. *Ibid*, p. 757.
[13] Stokes, J. jun., Farquhar, J. A., Drake, M. E., Capps, R. B., Ward, C. S., Mills, O., Kitts, A. W. *Ibid*, 1951, 147, 714.
[14] *New York Times*, Oct. 21, 1952.
[15] Bodian, D. *Amer. J. Hyg.* 1952, 55, 414.

and some progress has already been made towards overcoming them. The successful cultivation of poliomyelitis viruses in tissue cultures by Enders and his colleagues,[16] and the subsequent confirmation and extension of this work in many American laboratories, has given a strong stimulus to the search for attenuated variants. Underlying much of this work is the belief that the poliomyelitis viruses are not strictly neurotropic; and here Scherer and Syverton[17] have lately shown that poliomyelitis viruses can multiply in microscopically "pure" cultures of fibroblasts in vitro. Arguing on the analogy of other virus diseases, it may be possible to select in this way variants of poliomyelitis virus which have a low virulence for nerve-cells. Another report[18] from the United States says that Dr. H. R. Cox has grown the Lansing strain of virus in the chick embryo; and if the method can be extended to other strains, this may help to provide enough tissue to grow the virus cheaply and abundantly. The second problem, that of testing the vaccine in human beings, has already been tackled by Koprowski et al.,[19] who fed 20 volunteers with an attenuated variant of the Lansing strain without mishap. The risks of this sort of experiment are considerable, but it can reasonably be argued that urgent methods are justified. Many technical difficulties have yet to be overcome, but the progress of poliomyelitis research during the past ten years gives us good reason to hope that success, if not yet in sight, will surely come.

Tubercle Bacilli in the Tissues

There is still much to be learnt about the behaviour of tubercle bacilli in the tissues. Why, for instance, are the bacilli so scarce in the centre of caseous masses and so abundant in the cavities formed by their excavation? It has been suggested that in caseous material low oxygen tension and organic acids do not favour bacterial multiplication. Sometimes the bacilli are so altered that, although they have the usual morphology and staining properties in direct smears, they fail to grow on culture-media and do not cause disease in animals.[20–22] Such bacilli may be dead; on the other hand they may have lost only temporarily the ability to reproduce, and alteration of the environment may restore them to normal activity. The fate of tubercle bacilli in the tissues does not seem to depend simply on the recognised immune processes. Certain extracts of animal tissue are now known to retard the growth of tubercle bacilli in vitro. Hirsch and Dubos[23] have isolated from these extracts a crystalline inhibitory substance, spermine. This is present in many animal tissues, and especially the prostate and pancreas; and in cases of pneumonia, tuberculosis, and cancer the diseased tissue consistently contains more spermine than a normal portion of the same organ. The tuberculostatic action of spermine can only be demonstrated in vitro when a certain fraction of bovine serum-albumin is present. Its action in the body may, therefore, depend on the environment provided by a particular tissue. An inhibitory substance has also been found in extracts of tuberculous lymph-nodes[24]; this has not been isolated or identified, and its relation to spermine is unknown, but extracts of healthy lymph-nodes do not have an inhibitory action.

Knowledge of the behaviour of tubercle bacilli in the tissues has been extended by direct observation of the bacilli within living cells. Mackaness[25] in this country and Suter[26] in the U.S.A. have investigated the interaction of tubercle bacilli and macrophages in tissue culture. The bacilli were readily ingested by the macrophages, and if enough bacilli were present the cells disintegrated. The bacilli could also multiply within the cells and eventually kill them. Mackaness investigated the action of several substances on this intracellular growth. Streptomycin inhibited such growth only when its concentration in the culture-medium was many times that required to inhibit extracellular growth of the same strain. *p*-Aminosalicylic acid (P.A.S.) had hardly any effect even in high concentrations, but isoniazid was equally active against intracellular bacilli and those grown in a liquid medium.[27, 28] With fully bacteriostatic concentrations of both streptomycin and isoniazid the intracellular bacilli remained viable for at least seven days. Even double this concentration of streptomycin (a level most unlikely to be reached in the body) did not kill all the bacilli. The bactericidal activity of isoniazid in high concentrations has yet to be investigated.

The effect on tubercle bacilli of a substance in an artificial culture-medium can give only a hint of what happens in the body. To speak of an effective serum-concentration of an antibacterial agent is meaningless, unless clinical trials have shown that a response is obtained only when such a concentration is reached. The inhibitory concentration observed in the laboratory may vary with the strain of bacillus, the composition of the culture-medium, the size of the inoculum, and the period of incubation; and to these factors must now be added the intracellular or extracellular position of the bacilli. It is not possible to reproduce exactly the condition within each type of tuberculous lesion; and even if this were possible, it would also be necessary to estimate the concentration of the antibacterial agent within the lesions during treatment, and to relate this to the concentration in the blood-stream, before deducing the clinical effect of particular serum-levels and schemes of dosage. Streptomycin was first used in doses of 0·5 g. every six hours, to maintain a constant high level in the blood. It was then found that 1 g. daily was no less effective, and that this could be given in a single dose. Now it is claimed that 1 g. can be administered twice weekly together with P.A.S. daily without much, if any, loss of therapeutic effect. The observations of the physician are not easily reconciled with the findings of the bacteriologist; but then the tubercle bacillus behaves very differently in the test-tube and in the tissues.

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[16] Enders, J. F., Weller, T. H., Robbins, F. C. *Science*, 1949, 109, 85.
[17] Scherer, W. F., Syverton, J. T. *J. exp. Med.* 1952, 96, 389.
[18] *New York Times*, Oct. 26, 1952.
[19] Koprowski, H., Jervis, G. A., Norton, T. W. *Amer. J. Hyg.* 1952, 55, 108.
[20] Canetti, G. Le bacille de Koch dans la lesion tuberculeuse du poumon. Paris, 1946; p. 82.
[21] Medlar, E. M., Bernstein, S., Steward, D. M. *Amer. Rev. Tuberc.* 1952, 66, 36.
[22] Beck, F., Yegian, D. *Ibid*, p. 44.
[23] Hirsch, J. G., Dubos, R. J. *J. exp. Med.* 1952, 95, 191.
[24] Soltys, M. A. *Nature, Lond.* 1952, 169, 1095.
[25] Mackaness, G. B. *J. Path. Bact.* 1952, 64, 429.
[26] Suter, E. *J. exp. Med.* 1952, 96, 137.
[27] Mackaness, G. B., Smith, N. *Amer. Rev. Tuberc.* 1952, 66, 125.
[28] Suter, E. *Ibid*, 65, 775.

Annotations

THE UNWILLING PATIENT

THE Royal Medico-Psychological Association's Maudsley lecture for this year was given on Nov. 6 by Dr. W. Rees Thomas, senior medical commissioner of the Board of Control, who spoke about the changing public attitude towards the incarceration of the insane, and in particular about the progress of British legislation on insanity since the 18th century. From ancient times, he said, the popular idea of the insane equated lunacy with violence. The madman was often believed to be possessed by spirits or to have exchanged his soul for that of another, and his treatment might consist in a religious ceremony or in close confinement and neglect —" the dark house and the whip " of Shakespeare, and very often the restraint of chains. This was quite consistent with a belief in love towards all men, for the lunatic was thought to have lost his humanity. It was above all the French physician Pinel who led the way to the modern view. Writing in 1806, for instance, he denied that it was necessary or advantageous to bind or chain the insane. Control could be achieved by producing a balance between their passions, and the ideal psychiatrist was he who concealed from the patient any restraint he might have to use.

The incidence of mental disorder in the past was difficult to compute, though after 1840 note was kept of the number of patients shut up. Continental writers in the 18th century referred to attacks of the vapours, nerves, and distemper as the " English malady," and said that a third of the people of condition in England were affected—an estimate not unlike that for neurosis today. Two hundred years ago, however, mental illness got little official notice. An act of 1744 merely empowered any two justices of the peace to lock up and chain any poor man they judged insane, while the well-to-do could be imprisoned by relatives or friends without any check whatsoever. The improved handling of the unwilling patient since those days could be regarded as the development of external control over the conduct of mental homes and hospitals, and also as the amelioration of the conditions within them, particularly the abandoning of chaining. It was long thought that a period of restraint by chaining was necessary to induce the patient to submit to the authority of the physician, just as later there were some who claimed that the dark house was of therapeutic value. Under Dr. Charlesworth the hospital at Lincoln now called The Lawn was a pioneer in freeing the patients. In 1829 over half were under restraint : eight years later less than 2% were still so controlled. At first there was no segregation of the sexes, and no separate rooms for the excited ; patients sometimes came to blows and injured one another. This led to criticism of the new policy which was really criticism of the inadequacy of the old building. But public feeling was changing. Advertisements of licensed private mental homes in the 1840s promised " no restraint," though they sometimes used it on the quiet. Lord Shaftesbury, who was chairman of the Commissioners in Lunacy for forty years from 1845, was very active in promoting the new humanity in all the hospitals within his jurisdiction. Colney Hatch, in particular, seems to have given trouble, the medical staff claiming that chaining and other forms of physical restraint were less disagreeable to the insane than to normal people, that they were better than surveillance by a bad attendant, and that they were more economical of staff and bedding. In 1866, when it was found that the same hospital was shutting up patients naked, with only bare boards to lie on day and night for weeks on end, the plea was that this was the patients' own choice.

Gradually buildings were improved, and more money provided for attendants, who were better selected and trained. Records came to be kept of what each patient did each day, and seclusion, instead of being ordered on the authority of the nurse, was reserved to the doctor and used only for purposes of treatment. Finally today's regulations were established by the Lunacy Act of 1890.

In the 18th century a man could rid himself of an inconvenient wife, or a relative who stood between him and a fortune, by placing them in a private mental home. This imprisonment of the sane caused many scandals and led in 1744 to the licensing of all such houses by a commission of five physicians in the Metropolitan area and by magistrates elsewhere. Such homes had to be inspected at least once a year. The act of 1828 enlarged the commission by the addition of ten laymen, and insisted that each licensed house caring for more than 120 patients must have a resident physician. It also for the first time made a doctor's certificate necessary before the insane poor (but not the well-to-do) could be committed to an asylum, though it was not till 1853 that the diagnosis of unsound mind had to be supported by facts. Another step forward came in 1842 when the Metropolitan commission was given power over the whole of England and Wales in place of the justices. Although a mid-19th-century Lord Chief Justice had expressed the view that patients should only be confined if they endangered themselves or others, the way in which opinion was moving was shown by an incident in 1862 when a Member of Parliament who was a patient in a private mental home was allowed out from 8 P.M. to 2 A.M. to record his vote in the House. The doctor responsible for this permission was forced to resign. Finally in 1877 a Select Committee of the House of Commons considered what should be the relation of law on lunacy to the laws guaranteeing individual liberty, and the present regulations governing certification were codified in the Act of 1890.

Voluntary patients were first heard of after 1854, when licensed houses were allowed to keep patients after discharge if they wished to stay, and also to take relatives and friends as boarders. In each individual case, however, permission had to be given by two commissioners, who might call at any time to see the person in question. Later, anyone who had been a mental patient some time in the preceding five years was also made eligible for voluntary admission in this way. It was not till as recently as 1930 that voluntary patients were at last admitted to hospital without the central authority's consent in each instance. Today the extent of voluntary admissions varies from hospital to hospital, being anything from 45 to 94% of the total admissions in different parts of the country. Dr. Rees Thomas looked forward to the time when admissions for mental illness will be regarded no differently from those for other causes. He hoped also that temporary detention will be extended to those patients who are opposed to admission only by reason of their illness, so that certification will fall altogether into disuse.

DENTAL TREATMENT OF CHILDREN

LETTERS in our last issue suggest that the only factor preventing a large increase in the number of qualified dentists is the lack of facilities for training them, and that the introduction of dental ancillaries would further impede expansion of the profession, because the ancillaries would occupy places in the dental schools which might be filled by dental students. Our correspondents contend that, were it only possible to enlarge existing schools and found new training establishments, there would be, or could be, enough suitable applicants for admission as dental students to the dental schools to permit a rapid expansion of the profession to a size commensurate with its responsibilities. We, on the other hand, believe that this view is quite unrealistic and that the number of suitable candidates is limited. At the present moment, of the students who satisfy the scholastic and other conditions of entry to the schools, far too many fail to complete their training at all or take longer to qualify than the prescribed number of years of study, because they are unable to pass one or more of their qualifying examinations. The result is a considerable waste of training facilities, which would become even greater were the intake into the schools to be increased threefold, as the Teviot Committee estimated would be essential in order to double the size of the dental profession over the next twenty years. At present, we understand, no candidate with the necessary entrance qualifications is unable to find a place as a dental student in one or other of the schools. If that is so, trebling of the annual intake would almost certainly entail lowering of the conditions of entry, in order to admit into the schools a large number of students who would be considered unsuitable by present criteria. As a corollary, to enable these additional students to complete their course of study, it would be necessary to lower the standards of training and of the qualifying examinations. We are quite sure that most dentists would reject the idea that, in future, students should enter the profession after a training inferior to that now demanded by the licensing bodies. The price of lowered standards of training would be too great to pay, especially as the efficiency of the profession at its present size could be greatly raised if it were supplemented by ancillaries specially trained to relieve the dental surgeon of many of the simple routine tasks of children's dentistry.

In New Zealand, the training establishment for dental nurses is separate from and independent of the dental school, and there is thus no question of dental nurse trainees occupying places which might otherwise have been filled by dental students. The school dental nurses scheme is far from having had a deleterious effect on the general dental service to the community, for there are in New Zealand twice as many dentists in proportion to the size of population as there are over here. In that country, professional and public opinion share a confidence in the scheme and a belief that it must continue in being.

The fear expressed that the Dentists Bill did not provide for sufficiently close supervision of the work of the dental ancillaries appears exaggerated. The Bill proposed no more than a three-year experiment in training and employing ancillaries, under the direction of the General Dental Council. This body, which was also to be set up when the Bill's proposals became law, would consist of 40 members, of whom at least 30 would be dentists, and only 4 of the 7 Crown nominees would be laymen. According to the relevant clauses of the Bill, it was this council that was to frame the regulations governing the experiment and would ensure " that dental work . . . is carried out by an ancillary dental worker only under the supervision of a registered dentist." It is inconceivable that a body so overwhelmingly composed of dentists and doctors should not be able to ensure close personal supervision by dentists of the work of the ancillaries during the period of the experiment. Moreover, the General Dental Council was to be the judge of the success of the experiment and to advise the Government whether the employment of ancillaries had been justified or should be abandoned. Neither the public interest nor that of the dental profession could have more complete safeguards than these.

When Dr. MacGregor uses the phrase " panic legislation," we can only wonder whether he is talking about the same Bill. This issue has now been debated for many years, during which the lack of proper care for children's teeth has been a blot on our health services. In the long run, the only practicable way of providing that care is to enlarge the dental schools, or build new ones, so as to produce more dental surgeons (if suitable candidates are available) or to produce ancillaries. If the course for ancillaries were half as long as the course for dental surgeons, a given school could presumably produce ancillaries a great deal faster than it could produce dentists. Naturally training in a new school (whether for dentists or ancillaries) would be far more expensive than training in an old one, built and equipped when things were cheaper; but if training for ancillaries lasted half as long as training for dentists, it is hard to see why, in a given school, it should cost much more than half as much per head. Let us at any rate try the experiment.

A NEW ANTISEPTIC

A REPORT[1] from a large maternity hospital in France describes the successful results obtained with a saponium, one of the quaternary ammonium compounds, which was used in place of all other chemical disinfectants in the surgical and obstetric routine of the hospital. The antiseptic (methyl-phenyl-dodecyl-trimethyl ammonium methosulphate) was used for the hands of the attendants, for the skin and vaginal toilet of the patient, for finger-stalls, and for sterilisation of forceps and other instruments. Dilute solutions (0·4–0·5%) in warm, not hot, water were used, and it was important to avoid the presence of the ordinary anionic soaps which inactivate these cationic agents. Other advantages claimed for this new antiseptic are its low cost, its small bulk for transport, and its value in disinfecting the many light plastic pieces of apparatus that do not stand heat sterilisation. These properties suggest that this antiseptic would be valuable when large numbers of people are being immunised or treated by injection, particularly in places with few facilities for heat sterilisation. Instruments could be treated with the antiseptic after degreasing with ether—or a mixture of the antiseptic with water, alcohol, and amyl acetate could be used.

Although earlier work on this group of chemicals had been done in the United States, the great possibilities of these compounds as antiseptics were first noted in 1935 by Domagk,[2] who demonstrated germicidal properties in all quaternary ammonium salts in which at least one radical was a long-chain aliphatic group. These compounds are available under various official or trade names—e.g., cetrimide, 'Zephiran,' 'Phemerol,' 'Roccal,' and 'Bradosol.' Their properties have been reviewed by Rahn and Van Eseltine,[3] and by Berry.[4] They are surface-wetting agents and their bacteriostatic action is probably due to reversible interference with the mechanism of synthesis or cell division. Their mode of action as lethal agents is not certain; they may disrupt the bacterial cell membrane or inactivate enzymes or indispensable proteins. They are neutralised by soaps and by phospholipids, and, as they are adsorbed not only by bacteria but by precipitated proteins, they are less effective in vivo or in the presence of serum. They are most active in the alkaline range of pH, and they are ineffective in an acid environment. They are non-toxic to animals in the concentrations in which they are commonly applied. A wide range of bacterial species are susceptible to their action, but they have no appreciable effect on the pseudomonas group, the tubercle bacillus, or bacterial spores.

Assessment of the quaternary ammonium salts as bactericidal agents is fraught with certain technical difficulties. Tests for sterility are invalidated by the bacteriostatic action of small amounts of the agent carried over with the transferred bacteria, and specific antidotes must be used. The determination of phenol

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1. Lévy-Solal, E., Choukroun, J., Badin, J. *Sem. Hôp. Paris*, 1952, 28, 3011.
2. Domagk, G. *Dtsch. med. Wschr.* 1935, 61, 829.
3. Rahn, O., Van Eseltine, W. P. *Ann. Rev. Microbiol.* 1947, 1, 173.
4. Berry, H. *J. Pharm., Lond.* 1951, 3, 689.

coefficients is of little value, especially for purposes such as the sterilisation of surgical instruments, where absolute sterility, including the killing of spores, is demanded. For hospital purposes, and particularly for the disinfection of the skin before operation, good results have been obtained by a number of workers. Kramer and Sedwitz,[5] used 'Ceepryn' in about 18,000 cases and they had no infections or irritation of the skin. However, Miller and his colleagues[6] have given a warning that the peculiar orientation of the antiseptic molecule on the skin surface may result in the retention of living bacteria on the under layer of an invisible film formed on the skin. We have already mentioned[7] some other difficulties which arise when judging the merits of various methods of skin disinfection. The quaternary ammonium salts certainly offer great possibilities, but it would be a help to have more information about their activity and suitability for surgical practice.

NUTRITION IN INDIA

WIDESPREAD malnutrition among the peoples of India unhappily offers considerable opportunities for research into the metabolic disorders to which it gives rise. It is clear from the latest report[8] of the Nutrition Research Laboratories at Coonoor, South India, that the Indian Council of Medical Research are making full use of these opportunities, and they are encouraging both field studies and fundamental research. Among the work of the institute during the past year, that of greatest general interest deals with nutritional œdema in adults and children—probably the commonest nutritional disease in India. The condition in adults is considered separately from that in children; but the disease is fundamentally the same at all ages, and the cause is certainly the same—a severe deficiency of calories and protein in the diet. The brief but excellent account of the clinical picture given in the report shows the close resemblance to what is called kwashiorkor in Africa.

The cause of the œdema has received particular attention. The plasma-protein level was appreciably reduced in all cases in which it was measured; the main fall was in the albumin, and usually the globulin level was correspondingly raised. The incidence and severity of œdema, however, showed only a poor correlation with the plasma-protein values; perhaps closer correlation may exist between œdema and the osmotic pressure of the plasma proteins, but this point does not seem to have been investigated. The importance of increased capillary permeability is also discounted, for the protein content of the œdema fluid is extremely low. The œdema differs therefore from the ascites of hepatic cirrhosis, with which it seems at first sight to have much in common, because the protein content of ascitic fluid usually exceeds 3%. An interesting observation was the excretion in the urine of an antidiuretic substance, demonstrable in the concentrated non-dialysable fraction. The Indian workers are particularly impressed with this evidence of hormonal imbalance, and they attribute it, as others have done, to impaired hepatic function, which is now well known to be associated with hypolipotropic protein-deficient diets. Loss of libido and gynæcomastia in adult males provided further evidence of hormonal disturbances. The sequence of events leading from malnutrition to œdema is still far from clear, and it is rather doubtful whether the antidiuretic substance in the urine is of much importance. Little attention has been paid in the last few years to changes in the water-binding capacity of the connective tissue, yet it is a change of this kind that might well be brought about by both nutritional and hormonal influences. The effects of the adrenal cortical-hormones on connective-tissue ground-substance may well be of significance in this respect. Moreover, signs suggestive of hypothyroidism are present in many of these cases; definite bradycardia, "thick" speech, sparse hair, and subnormal temperature may lead to a mistaken diagnosis of myxœdema. The relatively low specific-gravity of the urine (1013–1018), despite pronounced oliguria of 200–400 ml. per day, also suggests a considerable reduction in catabolic activity.

A technique for distinguishing between the lipase and esterase activity of the plasma is also described in the report, and the results of their estimation in nutritional œdema are of some interest.[9] There is reason to believe that the plasma lipase is normally produced by the pancreas and the plasma esterase by the liver. A distinct fall in the plasma level of these enzymes therefore suggests pancreatic and hepatic damage respectively. A fall in the level of both these enzymes has been reported in nutritional œdema and this could be explained by the damage to the liver and pancreas which has been demonstrated in this disease.

PAPILLŒDEMA

THE papillœdema of raised intracranial pressure is usually easy to recognise but occasionally it may be difficult. Discussing this question, Chamlin and Davidoff[10] emphasise the importance of measuring the size of the blind-spot when the diagnosis of papillœdema is in doubt on the ophthalmoscopic appearance alone. The blind-spot should be plotted on a Bjerrum screen at a distance of 2 m.; and, with a white test object of 10 mm. diameter, its normal size is reasonably constant, the width being 5·5° and the length 7·5°. This absolute blind-spot is surrounded by a 1° pericæcal amblyopic zone, which is best plotted with a 2 mm. white test object; this zone corresponds to the area around the optic disc where the rods and cones are less sensitive than in other parts of the retina. The authors say that they have never seen papillœdema with a completely normal blind-spot and pericæcal amblyopic zone when its size is plotted with a 2 mm. test object. On the other hand, they have found enlargement of the blind-spot before there is ophthalmoscopic evidence of papillœdema.

Enlargement of the blind-spot may also be found with myopic degeneration around the disc, with medullated nerve-fibres, and with juxtapapillary choroiditis, but the ophthalmoscopic appearances of these conditions are not likely to be confused with papillœdema. The three conditions which are most likely to cause difficulty are pseudopapillœdema, hyaline bodies in the disc, and occasional cases of retrobulbar neuritis. Pseudopapillœdema is the name given to a congenital condition in which the optic discs may appear to be swollen and may actually be elevated several diopters, but in which there is no œdema and no disturbance of the retinal neuroepithelium. The condition is most often seen in association with hypermetropia, and it is of no serious pathological significance. No enlargement of the blind-spot is found in pseudopapillœdema,[11] and this fact is of considerable value in distinguishing it from true papillœdema—a distinction which may at times be difficult on the ophthalmoscopic appearances alone. Moreover, in pseudopapillœdema the appearances remain unchanged, in contrast to the usual sequel of events in true papillœdema. Hyaline bodies in the optic nerve-head are also a developmental abnormality in which whitish or yellowish tissue accumulates in front of the lamina cribrosa. This accumulation may push aside the rods

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5. Kramer, G. B., Sedwitz, S. H. *Amer. J. Surg.* 1944, 63, 240.
6. Miller, B. F., Abrams, R., Huber, D. A., Klein, M. *Proc. Soc. exp. Biol., N.Y.* 1943, 54, 174.
7. *Lancet*, 1952, i, 250.
8. Annual Report of the Nutrition Research Laboratories, Coonoor, South India, 1951–52. Indian Council of Medical Research. 1952. Pp. 30.
9. Srinivasan, P. R., Patwardhan, V. N. *Lancet*, Nov. 1, 1952, p. 864.
10. Chamlin, M., Davidoff, L. M. *Arch. Neurol. Psychiat.* 1952, 68, 213.
11. Lambert, R. K., Weiss, H. *Ibid*, 1933, 30, 580.

and cones, and thus cause enlargement of the blind-spot, so this point is not helpful in the differentiation from papillœdema. Retinal hæmorrhages do not occur with this abnormality. In many cases the hyaline tissue forms rounded refractile excrescences (*Drusen*), and if the edge of one of these can be distinguished the diagnosis can usually be made. If, however, they are buried beneath the surface of the disc, the appearance may be very similar to true papillœdema. In the absence of other symptoms or signs indicating the need for pneumo-encephalography or cerebral angiography, the best course is to examine the patient at regular intervals, for the appearance of hyaline bodies will remain unchanged.

In a few patients suffering from retrobulbar neuritis, gross swelling of the optic disc, congestion of the retinal veins, hæmorrhages, and exudate may be seen, and the diagnosis from papillœdema due to raised intracranial pressure by the ophthalmoscopic appearance alone may be impossible. The diagnosis is often made clear by the sudden onset of visual impairment in retrobulbar neuritis, and by the fact that usually one eye only is affected, but the changes in the visual field are the most important differential point. In retrobulbar neuritis the pathological process, usually disseminated sclerosis, involves the papillomacular bundle, resulting in a centrocæcal scotoma. Less commonly there is a paracentral scotoma or a nerve-fibre bundle defect—findings quite distinct from the enlargement of the blind-spot which is found with the papillœdema of raised intracranial pressure.

CONCEPTION CONTROL

There is still a good deal of prudery in our attitude to contraception. When the Medical Women's Federation in 1949 asked medical schools whether they gave their students any guidance on this subject[1] only 4 out of 27 said that they did; and such a defect in the training of general practitioners is really indefensible, unless on religious grounds. In a valuable lecture[2] Mr. N. W. Pirie, F.R.S., points out that, for successful use, the present contraceptive methods often require skill and intelligence, and that many of the 50,000 or more illegal abortions believed to be performed every year in this country must be the sequel to a contraceptive failure. Yet little research is going forward to find better methods, although bull semen from artificial-insemination centres and human semen from subfertility clinics is often available for experiment. Part of the reason, he thinks, must be a taboo on the study of this kind of physiology; otherwise pharmaceutical manufacturers would routinely test their new antibacterial products on spermatozoa "just in case," and biochemists would study the metabolism of the gametes with the enthusiasm they have devoted to yeast and muscle.

To get away from the limited aim of finding more effective spermicides and better diaphragms, Pirie wants the problem viewed against a background of more fundamental research on sexual function—a change which is marked by talking no longer of "contraception" but of "conception control." Each stage in the production, maturation, and union of ovum and sperm can be analysed to see what the chances are of preventing it. Perhaps the cervical mucus can be rendered impenetrable to motile sperm; perhaps the maturation of the ovum in its follicle can be delayed; perhaps the union of the gametes in the fallopian tube can be prevented—as seems to have been achieved in the rat by inhibiting its sperm hyaluronidase with phosphorylated hesperidin.[3] Implantation of the fertilised ovum could probably be stopped by something much less drastic than a Grafenberg ring in the uterus, and the possibility is worth investigation with the aid of all the new biochemical knowledge of the last twenty years. The factors controlling fertility, fertilisation, and viability are of general biological interest in their own right. Knowledge of them is likely to be valuable clinically in treating involuntary sterility. If in addition contraception can be simplified and perfected, the majority of laymen will be thankful. The case for more research is unassailable, and it is to be hoped that Pirie's original appeal[4] for it has not fallen on deaf ears.

But how far a new simple contraceptive will help to avert the threat of world overpopulation is another matter. It is not merely that the most warlike nations are the least interested in limiting births, or that the giving of contraceptive advice to backward peoples is fraught with political difficulties, as a debate at the last World Health Assembly showed. Many of these backward peoples already practise contraception of a kind—e.g., with intravaginal bark pads in some parts of Africa, and oral plant extracts in the Pacific[5]—but the practice has a prescribed place in their culture and may only be used on certain defined occasions—for instance, before marriage. It must be recognised that in some societies to have few children is to court social ostracism or to be enfeebled economically.[6] These social and psychological factors cannot be ignored or disregarded, and very much more study of them will be needed before Western European ideas can replace the tribal taboos.

One other kind of conception control is also possible. It removes all responsibility from the individual and gives it to the government. This is the possibility of diminishing fertility by means of substances added to the national diet—for instance, mixing some long-acting contraceptive in the national loaf. So far, perhaps fortunately, such a substance is not known, and the large funds probably needed for the successful prosecution of such research are not forthcoming. But they no doubt would be if someone saw that reduction of an opponent's fertility was a practicable method of biological warfare. The prospect of man's complete control over reproductive processes, which science promises him, is a frightening one indeed.

ELECTRON MICROSCOPY AND SMALLPOX

The electron microscope has been directed on viruses mainly as a research tool. However, in confirmation of an earlier paper,[7] Lépine and Croissant[8] now suggest that it may be of assistance in the laboratory diagnosis of smallpox. One or two drops of blood-free fluid from fresh vesicles are suspended in distilled water, the mixture is allowed to settle in a fine tube, and the supernatant liquid is then dried and shadowed. The authors claim that, by examining electron micrographs of material prepared in this way, it is possible to differentiate smallpox from chickenpox. The elementary bodies of smallpox and vaccinia are on the average slightly larger and more rectangular than those of chickenpox. However, the largest of the chickenpox elementary bodies are much the same size as the smallest of the vaccinia and smallpox ones, so that a careful statistical evaluation would be required before size could be accepted as a reliable differential feature in any given case. Rake et al.[9] described the elementary bodies of chickenpox as brick-shaped, but Lépine and Croissant do not agree; differences in technique or in the material examined may account for these discrepancies. However, it is difficult to see the point of the new technique, when there are much simpler

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1. *Brit. med. J.* 1952, i, 595.
2. Pirie, N. W. *Eugen. Rev.* 1952, 44, 129.
3. Martin, G. J., Beiler, J. M. *Science*, 1952, 115, 402.
4. *Lancet*, 1952, i, 54.
5. Ford, C. S. *Ann. N.Y. Acad. Sci.* 1952, 54, 763.
6. Banks, A. L. *Lancet*, 1951, ii, 258.
7. Nagler, F. P. O., Rake, G. *J. Bact.* 1948, 55, 45.
8. Lépine, P., Croissant, O. *Pr. méd.* 1952, 60, 1427.
9. Rake, G., Blank, H., Coriell, L. L., Nagler, F. P. O., Scott, T. F. McN. *J. Bact.* 1948, 56, 293.

and more reliable methods, such as those advocated by Downie,[10] for the differential diagnosis of smallpox. Downie claimed that direct microscopic examination of vesicle fluid and direct complement-fixation tests of crusts often give a quick and reliable answer, and that egg culture will bring early confirmation. These are well-tried diagnostic methods which appeal as much to the public-health authorities as to the laboratory worker. On the other hand, if electron microscopy could be combined with serological techniques—e.g., in a direct serum-agglutination test—it would add greatly to the precision of such methods.

THE END OF AN INSTITUTE

THE Oxford Institute of Social Medicine, as conceived by John Ryle, its first director, had not reached maturity when he died; and it will disappoint many who shared his belief in its potentialities that it is now to be brought to an end—anyhow in its present form; for the final report, prepared by his successor Dr. Alice Stewart, describes many promising projects which are still incomplete. But at all events the institute has gathered experience which will be valuable to others, and particularly, as Sir Ernest Rock Carling, chairman of the institute's committee, points out in a foreword, has established the value of the "combined" no less than the self-contained survey. The combined survey takes advantage of material already accessible, or anyhow easy of access. There are many competent people—clinicians, health visitors, overseers in factories, Government officials, and others—working in jobs which enable them to collect data of importance to social medicine; and, given straightforward instructions, they willingly coöperate.

Examples of such combined surveys mentioned in the report include studies of tuberculosis in Northamptonshire, begun in the boot-and-shoe industry, and later extended to other populations. The findings strengthen the view that infection at work is an important factor in the tuberculosis morbidity of adults, and that the chronic active case is the chief source of danger to workers in light industries. Studies, in two factories, of absenteeism from all causes showed that voluntary absences were positively correlated with the numbers in the working group; which reinforces the common belief that morale is better in small than in large working units. An influenza study showed that, as far as transmission of this disease goes, every worker is "in effective contact" with every other regular occupant of his workshop, no matter how the machines or benches are arranged. In 1947, the Royal College of Physicians initiated a survey of the social factors in the incidence and course of acute rheumatism in children, and in 1951 it sent the institute records collected in various parts of the country during three and a half years. Analyses of these records show that in the areas selected there was more disease in towns than in the country, and more among the children of working-class people than among the children of professional and administrative workers. Opportunity for infection, however, appears to be the important factor determining incidence, and there was no evidence that disease was directly associated with either bad housing or poverty. The incidence in blue-eyed children was 50% below expectation; and in children who had had tonsillitis the risk of developing rheumatism was thought to be considerably reduced if the tonsils were removed—a conclusion which has been criticised in our correspondence columns.[11] Another copious source of information has been tapped in the records of the civilian medical boards. From a sample of 23,322 men between the ages of 17 and 45, it appears that bronchitis is the special risk of lorry-drivers, tuberculosis of boot-and-shoe workers, and peptic ulcer of unskilled labourers. Asthma is relatively common in the upper social groups, particularly in youth, but other respiratory diseases tend to concentrate in the lower social groups. A study of old people in Dorset suggests that of the 37,000 living in private houses, 7400 are permanently incapacitated, and an equal number are likely soon to have major breakdowns. About 60% of the permanently incapacitated are being adequately looked after by relations or others, and it is estimated that the home-help service could supply all that is needed for half the remainder.

Self-contained surveys have proved more difficult to complete. This method, which entails the repeated examination of the same persons, accurate recording of detail, and strict observance of the rules of procedure, has in practice demanded more resources than a small institute could command. Clinical work on the student health survey ended in 1950, and by the end of this year 8 papers will have been published on this study. The child-health survey is the only other self-contained study still on hand, and is now in its eighth year. If the original plan is followed the collection of clinical, social, and radiological data will be continued until September, 1953. Some new standards for assessing weight in infancy have been devised which take account of parental size in normal expectations. These standards reduce to negligible proportions the effect on weight gain of low social status, lack of household amenities, and poor mothercraft, and enhance the weight differences of bottle-fed and breast-fed babies. New standards of skeletal maturity, based on serial radiographs of the hands and knees, have shown that several features which have hitherto been regarded as evidence of disease are in fact normal variants. Such findings are good evidence that the candle lighted at the institute by Ryle had a penetrating beam. It is to be hoped that the flame will not be quite extinguished.

NOBEL LAUREATE

THE Nobel prize for chemistry for 1952 has been awarded to Mr. A. J. P. Martin, PH.D., F.R.S., and Mr. R. L. M. Synge, SC.D., F.R.S., for the work on chromatography which they carried out together at Cambridge University and at the Wool Industries Research Association's laboratories. Dr. Martin is now a member of the scientific staff of the National Institute for Medical Research, Mill Hill, and Dr. Synge, who was formerly biochemist to the Lister Institute in London, now holds the same post at the Rowett Research Institute, Aberdeenshire. Their invention of partition chromatography, which has made possible the separation and identification of amino-acids, has been of special value to protein chemistry, for the method can be used not only to recognise and isolate the new amino-acids from natural sources but also to investigate the amino-acid constitution of complete proteins.

Air Vice-Marshal Sir DAVID MUNRO died at Halton, Bucks, on Nov. 8, at the age of 74. A former director of the R.A.F. Medical Services, he was also for twelve years secretary to the Industrial Health Research Board.

Mr. J. E. STACEY, a former vice-president of the Royal College of Obstetricians and Gynæcologists and senior surgeon to the Jessop Hospital for Women, Sheffield, died on Nov. 9.

Mr. J. T. EDWARDS, D.SC., who died on Nov. 6, was from 1921 to 1929 director of the Imperial Bacteriological Laboratory (Indian Institute of Veterinary Research) where his studies on the immunisation of cattle against rinderpest were begun. Later in this country as a member of the Foot and Mouth Disease Committee he worked at the Lister Institute and at the Pirbright Research Station.

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[10] Downie, A. W. *Proc. R. Soc. Med.* 1947, 40, 657.

[11] *Lancet*, July 19, 1952, p. 143; July 26, p. 198; Aug. 9, p. 291.

Points of View

WISDOM IS NOT ENOUGH

REFLECTIONS ON THE ART AND SCIENCE OF MEDICINE *

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Some clinical problems can be solved by knowledge, some by experience, and some by understanding. The application of these three qualities has come to be known as clinical instinct or clinical wisdom.

Coarctation of the aorta is an example of a disorder which is frequently undiagnosed. In other words, knowledgeable physicians of all ages delight to make the diagnosis for the first time in patients who have already been seen by a number of other doctors, some of them highly qualified and experienced. In most cases the diagnosis presents no difficulty. Only *knowledge* is really required. Knowledge that such a condition may occur, of the type of person in whom coarctation may be found, of its physical signs, and of the means by which the diagnosis, once suspected, may be confirmed. The diagnosis is as likely to be made by a young enthusiast as by an older man of long training.

Experience tells more in the assessment of a clinical problem, and the weighing of clinical evidence. It is not a quality confined to the elderly, however; for what we mean by experience in this sense is really the ability to profit by experience, and that is a thing which some men never achieve.

As an example of a clinical problem in which experience rather than knowledge was brought to bear I will cite a case about which a doctor telephoned to me one evening many years ago. He would not, by ordinary standards be considered a good doctor, if only because his devotion to alcohol was often more evident than his devotion to his patients. On this particular occasion I did not wish to be called out, and as he had given me very little information about the patient I suggested that I might meet him the following morning. Then he said in a rather thick voice "you please yourself, but he is cold and he is sweating"; and I said "I'll come." The voice was that of an alcoholic but the wisdom was that of a clinician. (For those who like to know the end of a story I may say that the patient had cardiac infarction.)

The antithesis of the good clinician, the man who has not profited by his experience, is to me exemplified by the physician who is obsessed by the tangible in medicine—a radiograph showing gallstones, or a high blood-pressure, or an enlarged liver, to the neglect of the subtle indications of a clinical history. Leaving aside all the facts which with a little patience he can learn from the invalid himself, he seizes upon the evidence of the physical signs or of the radiologist or the laboratory, ignoring the discrepancy between them. He is right of course, in diagnosing gallstones, but they do not happen to be the cause of the patient's symptoms.

Physical signs can tell us only about the patient's body. The clue to his mind is the history: and since symptoms, being subjective, exist only in his mind, and it is usually symptoms not physical signs for which he seeks a cure, it is a pity to direct attention prematurely into channels which can give us only indirect information as to his state of disease.

The association of headache with high blood-pressure is a common one, but the fact of their association does not prove their dependence upon one another. Quite often it is the husband or the neighbours that are the cause of the headache. One would perhaps expect that a highly trained scientific mind, used to the interpretation of evidence, would be helpful in this process of assessing a clinical problem, but I have reluctantly to admit that such is not always the case. I have known more than one medical scientist fall repeatedly into errors of the kind that I have illustrated, though he would not tolerate the same logical fallacy in the laboratory. Perhaps it is the forensic rather than the scientific mind, because of its familiarity with the human element, which excels in this aspect of clinical medicine. F. M. R. Walshe[1] in fact makes a good point when he infers that it is perhaps logic rather than science that we should teach at the bedside, and in his unrivalled phraseology speaks of "the barren triumphs of technique over reason."

The third quality which is required of the clinician is that of *understanding*. This is probably more an inborn quality than the other two, for I refer to a true and sympathetic understanding and not (to quote Walshe[1] again) "the hollow formulæ of false solicitude which masquerade as humanity."

It is often required particularly at the beginning, when we are trying to assess the nature or essence of the problem, and again at the final summing-up when diagnosis, investigation, and treatment (in its restricted sense) are completed and we have to agree upon a way of life for the patient. I use the words "agree upon" deliberately, because such advice must always be the result of consultation and discussion. Rarely if ever should it be authoritarian, didactic, or given as an order. It is often our duty to point out to a patient the risk that he is taking—for instance by making a journey or by remaining at his work. It is never really within our competence to forbid him to take it. Some doctors seem to delight in ordering patients to give up all that they find most satisfying, be it work or alcohol; "be it of virtue or of mischief," as Francis Bacon would have said.

While we are on the subject of virtue and mischief in our patients' lives I would say that it is not our business as doctors to moralise, except perhaps about ourselves. It is not our duty to advise a burglar to give up burglary unless we feel that his particular occupational hazards are acting to the detriment of his health. (I have known one or two street bookmakers and tic-tac men who have developed an anxiety state clearly related to their occupations.) Our duties as citizens and as doctors often overlap and sometimes conflict, but we should at least try to distinguish between them.

SCIENTIFIC AIDS AND SCIENTIFIC METHOD

I have omitted from consideration, you may say, the clinical problem which can only be solved by medical science; but here we get into difficulties, for it has to be admitted that many men practise good medicine with little scientific knowledge. Science puts tools into the hands of the clinician; it is not necessary to understand optical theory to use an ophthalmoscope, or to be a physicist in order to interpret an X-ray photograph. Even laboratory reports may be intelligently used with little or no knowledge of how the tests have been performed. These refinements, essential to modern medical practice, are given to us by scientific discovery but are used by the clinician as an extension of what he can discover by his unaided senses. Moreover they must be so used; for if considered in isolation from the problem of the patient as a whole they can be misleading. Indeed it is one of the difficulties of the medical teacher, who hopes to inculcate scientific ways of thought into his students, that so much of the everyday work of medical practice can be done without any pretence to scientific thinking. The less interested student very soon begins to believe that a good deal of his scientific background is unnecessary—a belief which may even be encouraged by some of his teachers.

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* From an address to the Manchester Medico-ethical Association on Oct. 9, 1952.

[1] *Lancet*, 1951, ii, 895.

There remain perhaps a few cases in which the diagnostic problem can be solved only by the use of the scientific method at the bedside—cases in which we must observe and record *the response of the patient to conditions* imposed upon him experimentally.

THE PSYCHIATRIST

Before leaving the subject of the practical art of medicine we might here make a short digression on the rôle of the psychiatrist. Truly it is his business to investigate human relationships and emotions, which form much of the material with which the art of medicine is intimately concerned; but like all specialists he is ill equipped to deal with the patient as a whole, and in my experience he is generally no better as a humanist, and no more skilful in the art of medicine than is the General Physician or Practitioner. It is his business to develop new techniques in the investigation and treatment of mental and emotional disorder, and to teach what he has learnt; but it would be a bad day indeed if he came to be regarded as the only person capable of dealing with human feeling; for the art which above all includes the ability to handle human beings must pervade all branches of our subject. It is as necessary in the aurist whose patients dread the threat of deafness as it is in the cardiologist whose patients fear for their lives.

TRAINING IN SCIENCE

Those who love the art and fear the science of medicine will no doubt approve of what I have said so far. Wherein then lies the need for training physicians in science to the extent which some of us try to do today?

First, I would say, the training is needed because scientific discipline is the antidote to a surfeit of the art of medicine, which, carried too far, degenerates into medical lifemanship. It is said that all power corrupts, and the power which a physician has to influence the lives of his patients is formidable indeed. Ideally, no antidote should be required, but the clinician who knows only the art and is unversed in scientific thought and method may end by deceiving not only his patients but himself. If he does so unwittingly he will soon become satisfied with standards which are less than the best, if wittingly he becomes a quack, albeit a highly qualified and experienced one. Self-deception is the sin against which scientific discipline protects. I have illustrated some of the pitfalls which beset the scientist at the bedside through neglect of appreciation of the human element, but his occasional ineptitudes are not to be compared with the pompous stupidity which neglect of scientific thinking makes possible in the clinician.

Secondly it is necessary to teach scientific methods in order that the efficient weapons against disease that are now in our hands shall not be misused. The means to solve most clinical problems are now available. It is a major error, for instance, to treat a patient suspected of pernicious anæmia without first establishing the diagnosis, if only because the diagnosis is thereby obscured and the answer, all-important to the patient, to the question of how long he must continue the treatment will not be known. The inculcation of more scientific thinking into the clinical student should prevent some of these misdemeanours which at present are being daily committed by our profession, and would in time greatly improve standards of medical practice. Moreover the new remedies are often themselves dangerous. To use them empirically without establishing a diagnosis is usually to run an unnecessary risk as well as to conceal the truth both from patient and doctor. Sometimes it is a risk which must be taken, but if so it should be *done deliberately after a full appreciation of the position.*

Thirdly, science is necessary for the advance of medicine. Some advances are still possible from the use of clinical methods alone, as the recent brilliant work on the surgery of mitral stenosis has shown; but these are subject to the law of diminishing returns, and we must look to the scientists for most of the major advances of the future. Unless clinicians *are prepared themselves* to engage in scientific investigation and experiment these advances cannot come. Only the clinician can appreciate the problem which disease presents, though he may require the help of an army of scientists to disclose its secrets. Surely he should be *a collaborator with them*, and will be a better man for taking part in the adventure.

Finally there is the satisfaction which scientific honesty, truth, logic, and method give, which can be an object in itself; and the thrill of discovery, however trivial and unimportant may be its *immediate implications.* It is fundamental to a university education that we should try to teach not only what to do and how to act, but the reasons for doing so. This is the essential distinction between such an education and a technical training. It is further *fundamental to a university that its teachers* should themselves be engaged in the advancement of knowledge and that its students should be in contact with the frontiers of knowledge, should learn the limitations of knowledge at the present day and should have *some contact, even though it be secondhand*, with research and discovery.

In the days of Osler there were still plenty of opportunities for the advancement of medical knowledge by the clinical methods of experience, observation, and record. Those *opportunities have narrowed very greatly* and pure clinical observation is no longer enough. It is fairly true to say that except in surgery, the great advances of the last thirty years have come from the science rather than the art, and even in surgery they have largely been made possible by the scientists, who have given surgery the benefit of antibiotics and modern anæsthesia.

CLINICAL RESEARCH

In a recent address Sir Cecil Wakeley *spoke of clinical* research as if it were simply a matter of keeping accurate records. If he has done this himself I am sure he has found his records very disappointing. Occasionally matters of great importance will come from them, but more often there is *little to be learnt which is not already* known—unless the records have been kept with an end in view, as part of a planned experiment. Records should be kept for purposes of record. They are useful if the patient returns, and they may be of historical interest. But neither clinical records nor *logic by themselves* can replace the experimental method in *clinical investigation* as Harvey knew a long time ago. Twenty years of record are useless in determining the importance (or otherwise) of potassium therapy in diabetic coma; for, until someone realises *that it may be of* interest, the serum-potassium is never estimated and therefore never recorded. Clinical experiment need not mean the subjection of patients to uncomfortable procedures of *doubtful* value or benefit. It means the planning of a line of action and the *recording of observations* designed to withstand critical analysis and give the answer to a clinical problem. It is an attitude of mind, and it includes the investigation of disordered function in disease *as well as the response* to therapy.

The practice of medicine is probably of as high a quality in this country as anywhere in the world, but in the advancement of medical knowledge we have been falling behind America and Scandinavia. In my view the honorary system has had a great deal to do with this slow rate of progress, and its recent abolition has come thirty years too late. British physicians have been too long content with a system which put all its emphasis on the art and practice and almost none upon the science. The result has been that some of our best men have never had time to make an adequate contribution to knowledge. And so when we hear voices raised against the inroad of science and stressing the need throughout to teach the art, we have first to ask whose voice it is that we hear and whether the plea is not partly one of self-justification. Who then should be the teachers of medicine? Should they be these whole-time professors who are sometimes thought to be lacking in the art or should they be drawn from those who have a rich experience of the practice of medicine? Obviously it is to the benefit of the medical student and of the school that there should be teachers of various kinds. As to whether the professor himself should be whole-time or engage in private practice, the answer is easy. There are only 24 hours in a day. A professor of medicine has four separate tasks and could quite easily spend his whole time on any one of them—teaching, research, administration, and hospital practice. It follows that he cannot possibly have time for private practice in addition, and that even without it, if he has a conscience, he is bound to feel continually inadequate to his task.

As to what kind of a man he should be the answer is also quite obvious. Medicine being a synthesis of art and science, he must be a man who is supremely competent at both. The only difficulty is that no such man exists, and so we have to make do with the best compromise that we can find. If he is primarily a clinician he must have a staff which is particularly strong on the scientific side; if primarily a researcher he must have strong clinical backing. Of one thing I am quite certain, that he must be a man whose opinion as a clinician his colleagues can respect, and that in the conflict of loyalties to which he will be daily exposed he must in the final issue put the welfare of his patients before anything else, because he has a fifth duty, which is to set a standard of doctoring.

I have the notion that ideally he should be a man whose father was a Fellow of the Royal Society and whose mother was on the stage—a synthesis of science and art. (Of course, he might inherit the wrong qualities from either side—the story of Bernard Shaw and Isadora Duncan is not unknown to me.)

THE DOCTOR'S GROWING RESPONSIBILITY

Before leaving the place of science in medicine I would like to touch upon a theme on which I have written before. It is that the responsibility which we shoulder increases with every new discovery. When there was no efficient treatment for meningitis it did not matter whether we made the diagnosis on the first day or the fifth. Today it may literally be of vital importance. The same responsibility concerns us in all that we do, with chronic illness as well as with acute. Advances in surgery are not solely the concern of the surgeon, but place a new responsibility on the practitioner to recognise the early stages of disease which may be amenable to the surgeon's newer skills. Advances in social services bring with them a responsibility again that they shall be properly and freely used by those in need of them.

THE NEW MEDICINE

It seems fantastic that one should today spend time in justifying the place of science in medicine, but it is clear from the writings of a few and the talk of many that such a justification is still required. Among the few I emphatically do not include Dr. Walshe, whose warning of the encroachment of technology on the Arts of Medicine is well warranted, and from whose Lloyd-Roberts lecture I have already quoted.

I was fortunate myself in being brought up in a university in which such a justification of the place of science in medicine would, in 1920, have been considered already unnecessary. By an act of Providence, the elderly purveyors of polypharmacy had all been recently eliminated by the operation of time from the medical staff of the Royal Infirmary at Sheffield, and when I qualified and later became a registrar my most senior colleagues were less than 20 years older than I. I realise now that the clinicians who influenced me most as a student and a young man were between 35 and 45. They had clinical wisdom in plenty, but they were also clearly conscious of the fact that the new medicine was something different from that which had been taught by their predecessors.

This is not to say that older men, if they keep in touch with young minds, cannot be at least equally inspiring; but with a subject advancing as rapidly as medicine it is increasingly difficult to keep pace as the years go on. Wisdom and experience increase and are valuable. I know that I can now talk on equal terms with some patients on whom for all my young man's knowledge I would have made little impression 20 years ago; but I know that it is at the sacrifice of something else, and something very important. Even if we try to keep up to date and learn the new electrocardiography and the biochemical intricacies of metabolic medicine, our knowledge of the basic sciences on which the medicine of today is built becomes more and more outdated. I will cast discretion to the winds and say that I doubt if any professor of medicine should be more than 55. Allow him as an act of grace a few more years to reap something of what he may have sown, and for the sake of continuity and for the benefit of any wisdom which may have come with maturity; but if he shows signs of believing that only those of maturer years can have sound judgment or practise good medicine, or if he begins to think that he is indispensable, or becomes too highly respected for anyone to dare to tell him the truth, and above all if he begins to think that his wisdom and experience more than compensate for his inability to grasp the significance of new discovery and to keep up with new knowledge, get rid of him. It is possible to practise good medicine at a considerable age, but not to be an efficient teacher and trainer of the coming generation, or the leader of a team of medical investigators.

ARTIST AND RATIONALIST

In the title of this address and throughout its substance I have laid myself wide open to attack from those who like definitions and semantic niceties. I have avoided defining wisdom, art, and science, and in a subject like medicine it is quite impossible to set exact boundaries between them. Logic is the basis of science, but so it is also of good clinical skill: it is the link between the two. You may say also that I am being illogical or unscientific in discussing matters in terms which I have not defined, but I am not discussing the material of science. It is a good deal easier to define sodium than it is to define wisdom. I can only say that I hope that the sense in which I have used my terms has been clear from the context.

If there seems to me to be no essential conflict between the art and science of medicine, then equally there seems no conflict in trying to be at the same time both artist and rationalist in one's personal outlook in and out of medicine. Bertrand Russell in his recent defence of rationality[2] points out that reason signifies a choice of the right means to an end that you wish to achieve. Reason does not dictate the end itself. Reason is not the driving force which is supplied we know not whence—the inspiration of the artist. I would personally go a little further. While I accept the fact that emotional and irrational forces are the main determinants of our aims, both good and bad, I think reason should and can influence the choice of the ends towards which our endeavour is directed. Rationalism to me means above all the attempt to avoid self-deception, an attitude of mind which compels one to ask equally of oneself or another "what are the reasons for your belief?" and expect a logical answer, whether we are discussing psychiatry, theology, or the treatment of pneumonia; and in questions where as yet no logical answer is possible the rationalist is much happier with an honest agnosticism than with a statement of faith; for the former leaves the whole matter open for further investigation and research whereas the latter closes the door to inquiry and erects an emotional barrier between believer and unbeliever.

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[2] *Listener*, Sept. 25, 1952, p. 495.

Five years ago I was stimulated by hearing Bertrand Russell broadcast in a series entitled "What I Believe."[3] Most of his opinions spring ultimately, he said, from admiration for two qualities: kindly feeling and veracity. To cultivate them it is not necessary to appeal to supernatural authority but only to have a general wish for happiness. It is surely not irrational to believe that the world would be a better place if these two virtues were more generally practised. In them I saw again the art and science of medicine, in kindness and veracity. The wish to help and above all to understand the human being in distress, the discipline to withstand all temptation to depart from scientific accuracy, and the determination to advance knowledge by the methods of science which are ultimately concerned only with the search for truth.

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It is dangerous for a man to speak in public upon his aims and ideals, for he soon finds himself only too vulnerable. If occasionally he dares to do so it is not to be inferred that he has any conviction that he has lived up to them.

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[3] *Ibid*, May 29, 1947, p. 826.

Special Articles

EPIDEMIC HÆMORRHAGIC FEVER

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BEFORE June, 1950, when epidemic hæmorrhagic fever (E.H.F.) was first encountered by United Nations forces in Korea, this disease was unknown to the Western world. The only references to it in English were a few paragraphs in two official reports based on information collected from the Japanese in 1946 (Mayer 1952a).

When the first cases occurred among United Nations troops in Korea, the disease was thought to be one never before recorded, but investigations by the Americans indicated that it was similar to a hæmorrhagic disease known to the Japanese during their occupation of Manchuria. It was later established that the condition described by the Japanese was exactly the same as the disease in Korea (Beard 1952, Mayer 1952a). Further studies by Mayer (1951) showed a striking similarity between E.H.F. and a disease known to the Russians as hæmorrhagic nephrosonephritis.

HISTORY

Little is known about outbreaks of E.H.F. before those recorded by the Japanese and Russians, but Mayer quotes inhabitants of Manchuria (including doctors) who said that the disease has been endemic there for many years. The first Japanese account, written in 1939, tells of an outbreak in the Songo district of Northern Manchuria. Many different names were given to the disease depending on the district involved—e.g. Songo fever, Kokka disease, and Korin fever. Various workers in Japan showed that all these diseases were identical, and in 1942 the disease was renamed febris hæmorrhagica epidemica, the anglicised version of which has now been adopted in this country and the United States. Ibuki (quoted by Beard 1952) later established that E.H.F. had broken out among Japanese troops serving in Northern Manchuria in 1935, the illness having been diagnosed at the time as purpura, hæmorrhagic typhus, or scarlet fever. All the Japanese cases were found in swampy areas or near rivers, and it was in this type of country that the disease first attacked United Nations troops.

Mayer has drawn attention to certain communicable diseases described by the Russians. Several types of hæmorrhagic communicable disease (presumed to be virus infections) are known in Russia—e.g., Omsk hæmorrhagic fever, Crimean hæmorrhagic fever, and the hæmorrhagic fever described by Katsenovich and Itskovich (1950)—but the true E.H.F. seems to be limited to Far Eastern Russia. It was first described in 1934 under the name Churilov's disease, but this title was later changed to hæmorrhagic nephrosonephritis. Further accounts of hæmorrhagic nephrosonephritis have been given by Bilibin (1950) and Viskovsky (1951).

ÆTIOLOGY

The ætiology of E.H.F. is uncertain. Clinically there is some resemblance between it and Weil's disease, and some early workers reported thread-like objects in the blood, suggesting that a leptospira was possibly the cause. Tsygankov (1941), discussing infectious nephrosonephritis, also thought that it was a leptospiral infection.

The Japanese, on the other hand, regarded the disease as either viral or rickettsial in origin, and certainly the bulk of the evidence seems to be in favour of a virus. Kitano (1944) (quoted by Mayer 1952a and Beard 1952) reported that the virus of the Far Eastern type of E.H.F. could be isolated in the febrile stage of the disease, and that it passed through L_5, L_6, and L_9 Chamberland candles and through the EK Seitz filter. The disease has been reproduced in monkeys and human volunteers by inoculation of virus-containing material (Smorodintsev et al. 1944, quoted by Mayer 1952b). Viskovsky (1951) said that Smorodintsev had identified a virus as the cause of hæmorrhagic nephrosonephirtis in 1940.

Others have suggested that the mite, *Lælaps jettmari* Vitzthum, which is a parasite on the field-mouse, *Apodemus agrarius*, is responsible for transmitting the disease to man. *A. agrarius* usually lives in swampy areas and in the long grass on river banks, but it is not confined to damp places and may be found in forests. In Russia the Eastern vole, *Microtus michnoi*, may also carry the virus (Viskovsky 1951). Mayer (1952a) mentions some interesting experimental work with emulsions prepared from infected mites or from infected organs. Although inoculation of this material into monkeys and man will reproduce the disease, the Manchurian field-mouse and house-mouse show no visible effects from such inoculation. The Eastern vole, however, develops enlargement of the spleen and hæmorrhagic changes in various organs, although there is no selective involvement of the kidneys (Leibin 1947).

Although the disease is present all the year round in Manchuria, Korea, and Far Eastern Russia, there are some seasonal changes; in Korea the number of cases reaches a peak in the spring and the autumn, and Viskovsky (1951) records a similar seasonal distribution of hæmorrhagic nephrosonephritis.

DISTRIBUTION

E.H.F. does not seem to have spread throughout Manchuria and Far Eastern Russia. The southern and western parts of Manchuria are thought to be free of the disease, though endemic foci exist along the Korea-

Manchurian border. The Russians have reported it as far north as latitude 50° (Mayer 1952a and Viskovsky 1951). In Korea E.H.F. is mainly, but not entirely, confined to swampy ground and areas near rivers. Kater (1951) suggested that it was introduced into Korea from Manchuria by the Chinese Communist forces. Mayer (1952a) gives a detailed account of the distribution of E.H.F.

CLINICAL COURSE

The incubation period is from one to three weeks. Prodromal symptoms are not common, but fatigue, general malaise, and slight myalgia with "lumbago," mild fever (Nancekivell and Macdonald 1952), and diarrhœa (Beard 1952) may occur at this stage. However, the onset is usually abrupt, with high fever, chills, tremor, frontal headache, anorexia, nausea, and vomiting.

Mayer (1952a) describes three stages: (1) a febrile stage; (2) an afebrile stage, in which the hæmorrhagic tendency and signs of toxæmia appear; and (3) the convalescent stage. Nancekivell and Macdonald (1952) prefer four phases: (1) febrile; (2) shock; (3) oliguric; and (4) convalescent.

In the febrile stage the temperature may rise to 104°–105°F. The pyrexia usually persists for five to seven days, reaching its maximum after about forty-eight hours (in Siberia, one of the names given to E.H.F. is "six-day fever"). The temperature falls suddenly, but the severity of the symptoms does not diminish as the temperature falls—lysis paradoxicus (Kater 1951). During the febrile stage, nausea and vomiting are severe and may last about a week. The hæmorrhagic tendency gradually makes its appearance, and from about the third day onwards, morbilliform or linear petechiæ may be seen, especially in the skin of the neck and face. Hæmatemesis, bloody diarrhœa, hæmoptysis, and hæmaturia may appear as the hæmorrhagic state becomes more pronounced (Nancekivell and Macdonald 1952).

Hæmaturia is one of the most important symptoms and is a great help in differentiating E.H.F. from other similar hæmorrhagic infectious diseases. There is some degree of renal involvement in nearly all cases, and the urinary symptoms are one of the most characteristic features of this disease.

Another characteristic sign is the appearance of the face. From about the third day onwards the face becomes flushed, and by the seventh or eighth day subconjunctival hæmorrhages are common. The conjunctivæ may appear uniformly cherry-red in colour, and vision becomes blurred. Petechiæ are often present on the palate and pharynx (Nancekivell and Macdonald 1952).

By the time the second or "shock" phase has developed, the hæmorrhagic tendency is well established. In this stage the patient is afebrile; the pulse, which during the febrile stage often shows a relative bradycardia, becomes rapid and thready; and the systolic blood-pressure is low. The skin, which is dry in the first stage of the disease, becomes cold and sweaty. This phase lasts four to five days, and during this time oliguria develops and urine of low specific gravity is excreted. This phase ends with a sudden diuresis and the production of large volumes of urine of low specific gravity, or it may progress to anuria.

Among other symptoms, backache is sometimes quite severe and may persist for several weeks; Beard (1952) mentions a peculiar characteristic odour about these patients; and hiccup may be very troublesome and persistent. The central nervous system can be affected and symptoms such as restlessness, insomnia, photophobia, and mania may develop. The Russians describe a meningo-encephalitic form of E.H.F. which usually ends in coma and death (Mayer 1952a, Tsygankov 1941). The liver and spleen are sometimes slightly enlarged and tender. but jaundice is rare (Kater 1951). Ruptured spleen has been recorded by Monroe (1952). The lymph-glands may be enlarged and tender, especially those of the cervical and axillary regions. Gastro-intestinal symptoms are emphasised by the Russians (Viskovsky 1951).

Recovery usually begins towards the end of the second week. After the sudden diuresis, the concentrating power of the kidneys recovers with consequent increase in the specific gravity of the urine. In fatal cases, death usually occurs within forty-eight hours of the fall of temperature.

Complications include bronchopneumonia, orchitis, pancreatitis, hepatitis, and encephalitis, but the commonest is parotitis, which, it has been estimated, occurs in 3–4% of cases.

Convalescence is usually rapid, except in the severe cases where renal symptoms and failure to gain weight may continue for some time. The Japanese report recurrent bouts of temperature and a mild hæmorrhagic tendency A follow-up of British cases for periods up to nine months has shown that most of the urinary symptoms resolve completely. In a series of 9 cases only 2 showed any evidence of diminution in renal function after six and nine months respectively, and in both cases there was continued improvement.

LABORATORY INVESTIGATIONS

Occasionally there is an initial leucopenia, although the white-cell count is usually normal early in the disease. The count rises fairly rapidly to 30,000–50,000 cells per c.mm., and occasionally much higher. There is always a shift to the left, mainly in the granulocyte series. This leucocytosis of E.H.F. and hæmorrhagic nephrosonephritis is in striking contrast to the leucopenia found in the other Russian hæmorrhagic fevers already mentioned (Bilibin 1950).

The platelet-count falls to 40,000–100,000 per c.mm. during the hæmorrhagic period. but rapidly returns to normal on recovery. The capillary fragility test becomes positive early in the disease and the prothrombin-time is sometimes prolonged, but the bleeding-time is usually normal.

The red-cell count and the hæmoglobin level are normal unless there is severe hæmorrhage. Albuminuria, which may be very heavy, occurs early in the disease, and is accompanied by granular casts and red cells. Microscopic hæmaturia is a constant feature of E.H.F.

The cerebrospinal fluid is usually normal. The Takata-Ara test is usually positive at the height of the fever (Mayer 1952a), but such serological tests as the Weil-Felix, Widal, and Wassermann are negative.

The level of non-protein nitrogen in the blood is raised during the disease, and falls with improvement in renal function. The level of reduced vitamin C is below normal, and the Thorne test (A.C.T.H.) may produce no response (Nancekivell and Macdonald 1952).

TREATMENT

Treatment is almost entirely symptomatic; antibiotics and chemotherapeutic agents have been tried, but they are of value only if secondary infection occurs. Convalescent serum has been used, and is said to help if given during the first two or three days. Otherwise treatment consists in intravenous infusion to maintain fluid and electrolyte balance, vitamin K, vitamin C, and blood-transfusion where necessary.

PATHOLOGY

Accounts of the morbid anatomy of E.H.F. are given by Kater, Beard, and Mayer. The most important pathological finding is the widespread involvement of the capillary circulation; the peripheral vessels all over the body are dilated and there is hyperæmia with purpuric hæmorrhages. Perivascular cuffing is found in several organs (Mayer 1952a), and Viskovsky (1951) mentions specific changes in the endothelial layers of the capillaries. The outstanding changes are found in the kidneys, which may swell to twice their normal size; rupture from severe hæmorrhage has been recorded (Beard 1952). Macroscopically the medulla is bright red, and the cortex pale and cloudy. Microscopically, hæmorrhage is greatest at the corticomedullary junction, and is quite severe in the rest of the medulla.

As well as hæmorrhage in the heart muscle, hyaline degeneration may be found, and Beard records dilatation of the right auricle of the heart. The liver and spleen are less enlarged than the kidney, but they may show albuminous degeneration and hæmorrhages. Reactive hyperplasia of the reticulo-endothelial system may develop in the spleen. In the brain, both parenchymatous and meningeal capillaries are affected, and hæmorrhage into the parenchyma, particularly in the region of the pituitary gland, sometimes occurs. Pituitary hæmorrhage has been a common post-mortem finding and is regarded by some as highly significant; sometimes the nerve-cells show degenerative changes. Hæmorrhage into the suprarenals has been recorded.

Examination of necropsy material from 2 British cases showed no specific lesions other than those associated with a hæmorrhagic diathesis. In one case pituitary hæmorrhage was very marked, and in both cases the medulla of the kidney was grossly disorganised by hæmorrhage. The glomeruli, however, showed few signs of hæmorrhage.

PROGNOSIS

It is difficult to give a prognosis in the early stages of E.H.F.; for, although the temperature may fall, the disease may become more severe and collapse can occur at any time. The Japanese record a mortality-rate of 30%, but the mortality-rate in the United Nations series varied from 8 to 16%.

DIFFERENTIAL DIAGNOSIS

This disease has been incorrectly diagnosed as Weil's disease, epidemic typhus, scrub typhus, purpura, and hæmorrhagic smallpox. In Russia the group of hæmorrhagic diseases referred to above, such as Crimean fever, have also to be excluded.

I wish to thank the Director-General, Army Medical Services, for permission to publish this paper, and Brigadier A. Sachs, Director of Pathology to the Army, for his encouragement. My thanks are also due to Major J. B. Neal, R.A.M.C., for providing access to histological material initially submitted to the Army Tumour Registry by Captain A. Knudsen, R.A.M.C.; and also to Major J. Kilner, R.A.M.C.

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FELLOWSHIP FOR FREEDOM IN MEDICINE

THE third annual meeting of the Fellowship for Freedom in Medicine was held in London on Nov. 8, under the chairmanship of Lord Horder.

Dr. E. C. WARNER, the hon. secretary, said that the membership of 3293 was almost the same as in the previous year. Publicity had included the printing of four bulletins and of two broadsheets entitled "How to improve the hospital service" and "Why private patients should be entitled to receive essential drugs on the same terms as N.H.S. patients." The fellowship had also conducted an inquiry which showed that there was wide support for returning the right of buying and selling the goodwill of medical practices to those who wished to regain this right.

The reports of five subcommittees of the fellowship were discussed and adopted. Arising out of this, two resolutions were passed, nem con.: "That this meeting deplores the method by which the G.M.S. Committee of the B.M.A. presented the findings of the Working Party, which has led to misunderstanding and disagreement in the profession"; and "That this meeting calls for a re-examination of the unsatisfactory method of distribution of the Central Pool, with particular reference to the position of the small-list doctor."

Mr. E. J. R. BURROUGH presented the proposed terms of reference of the lay associate members, and gave an account of how they could best further the interests of the fellowship. The terms of reference were approved by the meeting.

Lord HORDER, speaking as chairman, said that the most outstanding fact about the fellowship's work was its influence on current thought about the National Health Service. Criticisms of the N.H.S. which the fellowship was making three or even four years ago, and which seemed at the time to go unheeded, were now quoted by the press as commonplace. The fellowship had been criticised for not producing spectacular results: it had never set out to do this, but aimed at changing the climate of opinion. Who could doubt that the climate of opinion had changed—and not only among the public? "Perhaps it would be egregious to suggest we have influenced the Minister, and yet is it only an accident that, if you read the speech of the Minister which we print in our current bulletin, you will be struck by the close resemblance between the aims and objects of the fellowship and the present declared policy of the Government?" In the counsels of the B.M.A. the fellowship had been the first to press for the principles of arbitration in settling the vexed matter of the general practitioners' long-delayed remuneration betterment factor: even the rider to the Working Party's report, which secured some measure of justice for the small-list doctor, was the result of pressure by the fellowship. There remained a great deal to do—expressed simply this meant lifting the health services of the nation right out of the political field. The administrator was essential to our purpose: the politician was not only unessential, he was an incubus. When the fellowship started four years ago, it had set out to achieve what to many in the profession seemed wholly unattainable. "They said that Mr. Bevan's travesty of a National Health Service was an accomplished fact and that we must hug our chains. But we believed that the freedom of our profession was something worth fighting for; and our faith is being justified. One by one we are casting off our fetters." Lord Horder concluded by appealing to all who recognised the work of the fellowship to join: doubling the present membership would double its influence and double the amount of work that could be done and was crying out to be done.

Reconstruction

DO'S AND DON'TS FOR HOSPITAL PLANNERS

IN his recent book, *Background to Hospital Planning*[1] Prof. H. W. C. Vines shares with his readers the experience he has gained in studying hospital design and in helping to plan the new Charing Cross Hospital. His musings on and around the purpose and function of a hospital cover such topics as the work, size, patients, and staff of acute general hospitals; the care of outpatients; inpatients and the planning of the main special departments and services; the special problems of teaching hospitals; and the changes the next hundred years will bring. But he has written a book to stimulate thought and further investigation of hospital planning in its wider aspects rather than to serve as a vade-mecum for the architect on hospital architecture.

One of the important problems he considers is whether all specialties, except mental illness, should be included within the general hospital, so that every sick person may have at his disposal the full range of facilities of a general hospital. The evolution of the medical services in this country has led to the building of a considerable number of special hospitals, particularly by the local authorities; but as Professor Vines points out, some of these have been closed, and others are ceasing to be special hospitals. The training of nurses and the difficulties of staffing have speeded the process of including special beds, such as those for tuberculosis and chronic patients, within the ambit of the general hospital, and also of bringing acute general cases into the larger special hospitals, more particularly those designed, but no longer needed to the same extent, for the treatment of communicable diseases.

THE RIGHT SIZE

Professor Vines also discusses what is the best size for an acute general hospital. His own opinion is that 800 beds is a reasonable maximum, with a lower limit of 200 for acute general work. But he believes that there is also a place for the smaller hospital, down to fewer than 100 beds, staffed by general practitioners with visiting consultants. He advises that in chronic wards the beds should be spaced more widely than in acute wards, giving as one reason the fact that the patient is generally encouraged to get up as much as possible. But might it not be preferable to meet this need, even when adapting existing buildings, by providing more day accommodation—warm, comfortable, and homely—even at cost of economies in bed space?

In planning general hospitals the question always arises what provisions should be made for future expansion. Professor Vines leaves this as a moot point, but on the whole he is in favour of building a hospital only slightly larger than the immediate need demands, and then, if necessary in the more distant future, building a second hospital when natural shifts of population may show a different site to be more suitable.

THE PATIENT

Professor Vines has so many sensible things to say about the patient's place in the hospital that one is tempted to quote him at length.

> "The patient, the doctor and the nurse together form the elemental unit of medical care in the hospital, the home, or on the battlefield; like peace, they are 'one and indivisible,' for if there is no patient, the other two have no function. In the home, the patient lives in his own house and is fed and generally serviced by his own family; the nurse may sometimes stay in the house or may come in daily, and the doctor, too, may visit daily or less often. This unit requires the minimum of services, the State is put to a minimum of expenditure, and if the patient is not too seriously ill, this arrangement of the unit is satisfactory to his well-being. But both doctor and nurse can serve more than one patient, and if for any reason it is thought desirable to assemble a number of these simple units into one place, a building is erected or adapted for the purpose and the hospital is born. The patients are now separated from their homes and families so that integrated services become immediately necessary to provide food, treatment and hygiene for them and to light, heat and clean the building. In order to arrange these services efficiently and with economy, it has been usual to set up an administrative body, which is therefore but indirectly concerned with patient-care.
>
> "In such a way the patient becomes the most important person in the hospital, for he is the *raison d'être* of the institution and everyone else is there to serve him. When it comes to planning a hospital, everything should be made to centre around the patient, but quite often one finds that the convenience of the staff creeps into first place, and sometimes indeed it seems as though the patients had been put in as an afterthought. Rationally, the first element of the hospital should be patient-care, and next to that will come services, which provide all those things necessary, not only for the patient, but also for the staff in whose care the patient is. These two elements are linked together by a third, communications, used in the broadest sense of the routes and means of providing services. . . . I propose to regard the hospital as being built up on these three foundation stones, patient-care, services, and communications."

He argues that the mistake of planning for administrative tidiness rather than for the care of patients leads not only to difficulties in administration but also to unsatisfactory conditions for patients and staff.

> "It is reasonable for the patient entering the hospital to assume that all the facilities of the hospital will be at his disposal with a minimum of inconvenience, or even discomfort, to himself and that they will be adequate to deal with any eventuality which may arise in his case. If the buildings are well-sited and the departments have easy access to each other, the patient, being disturbed the less, will have the greater confidence in the hospital and it will be to him. a member of the public, a 'good' hospital."

This leads Professor Vines to a consideration of communications, which he defines as all those methods by which information, materials, and people move from one part of the hospital to another. In discussing their rôle in saving time and reducing the use of labour he justly points out that they require more study than they have yet had in this country. In particular, lifts have not yet been fully recognised as vertical corridors, but are still deprecated at times as an expensive way of pandering to laziness. Is there some vestigial puritanism here? There should be separate lifts for the patient in bed, for personnel (including patients in wheel-chairs) and for service; Professor Vines would provide a fourth to be reserved for food, with openings into the kitchen and the ward-kitchen only. If this lift were large enough to accommodate a food trolley, it would involve radical replanning of many existing ward-kitchens.

He also thinks that we have not given enough thought to the lighting of sickrooms and service rooms:

> "While we are beginning to take some care to place the patients' beds parallel with the windows and to provide night lamps at skirting-board level so that the patients shall not be worried by glare, it is curious that so little has been done, in this country or abroad, to improve the almost invariable system of lighting rooms from one or more central points in the ceiling. In the darker wards of city hospitals, as for instance in London, these lights shine down on the patients' faces for hours on end in the winter months; by contrast, in the service rooms where equipment, sinks, benches, and so forth are usually sited round the walls, the nurses and assistants work perpetually in their own shadows. It is time that we sublimated the chandelier-complex from which we have suffered so long and devised room-lighting so as to give a service of maximum efficiency and to bear a positive relationship to the work for which it is needed. There is still room for a good deal of research on the general lighting of sickrooms and

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[1] London: Faber & Faber. 1952. Pp. 188. 30s.

service rooms, on reading lamps for patients at the bed-head and on the diffuse lighting of the whole bed without any distortion of colour, so necessary for the medical examination of the patient."

For the planner other people's mistakes may be almost as valuable as their successes, and the following warning list which Professor Vines has compiled is worthy of study:

"Inadequate provision of w.c.s for ward patients, to cater for the practice of getting patients out of bed earlier.
Insufficient or absent air-conditioning in operating suites.
The omission of piped oxygen and suction services.
The omission of the pneumatic tube services.
The scattering of lifts.
Insufficient cupboard space for storage in theatre suites and ward units.
Planning the entrance to the hospital for emergency cases too far from the main theatres and administrative offices.
Absence of an 'interview' room for relatives' use in the ward areas.
Planning linen and rubbish chutes too close so that confusion of their use arose."

HOSPITAL AS TEACHER

Looking into the future, Professor Vines says that, with the continuing improvement of the health of the people, thanks to better social conditions and proper education, there will not be the same call upon large general hospitals. In their place he sees a group of consultant outpatient clinics with a small number of beds. These outpatient clinics should be designed so as to be easily refitted internally; if the demand for beds decreases, or the advance in medical treatment necessitates the use of bedrooms as technical rooms, it should be possible to adapt the accommodation without major structural alteration.

But if in the future the hospital's responsibility for the practice of curative medicine decreases, Professor Vines believes that its responsibility for preventive medicine will increase.

"Apart from the curative treatment of the already ill, the acute hospital, as part of the local community, should now be developing a functional part in the prevention of disease, as in the more distant future its activities in this field may have to be considerable. Modern methods of treatment demand increasingly early diagnosis of illness in order to be fully effective and it is in the hospitals that methods of early diagnosis are likely to be developed and applied. There is then an increasing approach towards real preventive medicine as applied to the individual in contrast to sanitary preventive medicine, which applies rather to the masses. The hospital should be a centre of education of the local practitioners in this aspect of medicine, which is going to become increasingly important.' Indeed, the hospital has a large educative function to play in any community. Some hospitals are specifically concerned with the training of medical students or doctors; a far larger number are schools for the training of nurses or midwives; and others act as technical training centres for radiographers, almoners, dietitians, physiotherapists and so on. Intimately mixed with the daily routine of the hospital, there is the simple education of the patient in how to keep healthy, of the young mother in how to manage her baby or what she should do with her difficult child, a thousand problems dealt with by the nursing and medical staffs every day. And this leads on even to the teaching of the staff itself in what are called 'human relations' composed so largely of toleration, forbearance, and good sense. So the educative function of the hospital is wide, *ranging from professional technicalities almost to a philosophy* of life."

Medicine and the Law

Matrimonial Desertion and Mental Capacity

DIFFICULTIES arise in the Divorce Court when a petitioning spouse alleges desertion and the respondent spouse is a patient in a mental hospital. Desertion presupposes the *animus deserendi*, the intention to desert; if a party is of unsound mind, how can he or she form that intention?

In Keeley *v.* Keeley[1] it appeared that a wife had entered a mental hospital as a voluntary patient in 1941 and had remained there ever since. She was said to have suffered from the delusion that her husband was unfaithful and was poisoning her. During one of his visits to her, the husband had in 1943 asked her to return home, thinking that she had recovered. She refused, saying that she was quite happy where she was. He did not renew his request. In 1951 his solicitors invited the opinion of the medical superintendent of the hospital as to her capacity to form the intention to desert. The reply was that she was capable of making a reasonable decision to desert if she wished. At the trial he testified that though, as a voluntary patient, she was entitled to leave the hospital after 72 hours' notice, her condition was such that, if she did so, she would almost certainly be certified insane either on discharge or soon after. The Divorce Commissioner thereupon dismissed the husband's petition, on the ground that the wife was not, at the material time, capable of forming the intention to desert.

The Court of Appeal has allowed the husband's appeal and has granted him his decree, though with the caution that the case must be regarded as having depended on its own special facts. Reference was made to a decision of the House of Lords in May, 1951, in Crowther *v.* Crowther, where the husband had for the statutory period of three years been an inmate of a mental home under a reception order. It was there held that the court was not entitled to infer continued desertion from an intention shown in the pre-certification and post-certification periods, if the petitioner did not establish that the respondent spouse retained the mental capacity requisite for an intention to desert, or if no evidence was offered. The trial judge and the Court of Appeal had refused the wife her decree on the ground that the husband had been incapable of having an *animus deserendi* during the three years of the reception order. The House of Lords took a different view. There was, they said, no irrebuttable presumption that the desertion had been terminated by the mental incapacity; the petitioner was entitled to produce evidence that the respondent remained mentally capable of an intention to desert. Lord Oaksey went so far as to say that, once the original desertion was proved, the onus was transferred to the deserting spouse to prove an intention to resume cohabitation. Applying the Crowther decision to the Keeley case, the Court of Appeal held that the husband had succeeded; the evidence of the medical superintendent and other witnesses showed that the wife was perfectly capable, despite her hallucinations (which seemed in part to have disappeared), of making a reasonable decision about returning to her husband.

Desertion as a ground of divorce must be, under the Herbert Act of 1937 (now consolidated in the Matrimonial Causes Act, 1950), not only for three years but also "without cause." The Court of Appeal in the Keeley case seemed to think that "without cause" could hardly be established where a party was affected by illness which compelled residence in hospital for the three-year period. The position would be the same whether the illness was heart-disease or insanity. In any future litigation, if that question arose, the material allegations would have to be specifically pleaded and argued and the evidence considered. If, for instance, a wife remained in a mental hospital as a voluntary patient on medical advice in the interests of her health, the court might have to consider evidence whether that was the reason for her not returning to her husband or whether she remained there because she did not wish to return to him. It might even be argued in some future case that the patient was remaining in an institution in the public interest. That kind of speculation, however, the Court of Appeal left to be dealt with when the point arises.

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[1] *Times*, Oct. 29, 1952.

Suicide and Temporary Insanity

Two coroners have lately been referring to the form of verdict which associates suicide with unsound mind. The Birmingham city coroner, discussing "fictitious verdicts" before a lay audience,[1] expressed the view that people who take their lives are not of unsound mind. "They are simply suffering from a sick mind in the same way that people have a sick heart or a sick lung." Coroners, he said, hated this question of suicide verdicts, but had no alternative. A finding of felo-de-se (suicide while of sound mind) left the dead man's family with the stigma of criminality; a finding of "suicide while of unsound mind" left it with the stigma of insanity. This was quite wrong; the speaker wished some other verdict could be substituted, such as the simple word "suicide." On the other hand the Bath coroner,[2] recording a finding that a 65-year-old man had died from coal-gas poisoning self-inflicted "while the balance of his mind was disturbed," denied that such verdicts were fictitious. They were, he declared, of respectable antiquity; he recalled the conversation of the grave-diggers about the death of Ophelia in the fifth Act of *Hamlet*.

The 1910 report of the Departmental Committee on Coroners might have been quoted in support of the Birmingham coroner's view. It recommended the abolition of the verdict of felo-de-se. "The only effect of retaining this verdict," said the committee, "is to induce juries to find a verdict of temporary insanity without any evidence to justify it." When the same committee, reconstituted with Lord Wright as chairman, reported in 1936, they recommended that where the deceased had died by his own hand there should be no inquiry into the state of his mind (except so far as it might throw light on the question whether he took his own life) and the verdict should make no reference to his state of mind. The official forms appended to the Coroners Rules of 1927 continue to use the formula (associated in the statute-book with the Infanticide Act) "while the balance of his mind was disturbed." If fresh legislation be needed to carry out the recommendations of the Wright Committee, perhaps some member of Parliament will bear the matter in mind if he is lucky in the ballot for private members' Bills.

According to the Criminal Statistics for 1951, the suicide figures are dropping: there were 4282 in 1951 as against 4324 in 1950. There were more male suicides than female (2675 men and 1607 women); but more women took their lives in 1951 than in the previous year (1607 against 1555). If the statistics show a decrease, the latest total is still amply sufficient to make the form of verdict important. As the Wright Committee's report reminded its readers, the felony of self-murder involved forfeiture of the dead man's property to the Crown down to the year 1870 when the Forfeiture Act was passed. And as recently as 1882 Parliament was formally and finally forbidding coroners to direct that the body of a suicide should be interred in a public highway or have a stake driven through it. Thenceforth a suicide's remains could be buried in the parish churchyard as if there had been no verdict of felo-de-se against him; they could at last be assured of what the Second Grave-digger called "Christian burial." These are comparatively recent dates and folk memory is tenacious. Has the time arrived for a third Departmental Committee on Coroners, to persuade the Legislature to abolish an embarrassing verdict?

In England Now

A Running Commentary by Peripatetic Correspondents

EMPIRE-BUILDING we call it in these parts, when one specialty enlarges its territory at the expense of its neighbours. Thoracic surgeon and neurosurgeon must carve out their domains from the body of general surgery. That is understood, but they are less easily forgiven when they do it by snaffling the beds that the potential gerontologist had his eye on. In pædiatrics we know all about this cut-and-thrust. Have we not made splendid gains in the debatable land of the newborn period, and even, here and there, got our hooks on the children with infectious fevers? Of course we have not always been able to defend our own borders against acquisitive moss-troopers such as the covetous cardiologist. A year or two ago I read with foreboding an article called "A Psychiatrist looks at the Newborn." Imagine then my elation when I found last week a reference to a paper on Neonatal Morality. Is this the counterblast of the pædiatrician? "Hands off the newborn! We can deal with his twisted psyche." I have yet to look it up, but I fear a misprint.

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When the World Conference on Medical Education opens in London next year I hope that evidence will be taken from ageing and aged practitioners and specialists who have made a success of their profession despite the many important facts and theories they have forgotten.

Speaking for myself, I am regarded as a successful man, with a well-balanced judgment, a good manner, and the ability to inspire confidence. Yet if ever I knew the origin and insertion of the peroneus longus or the puzzling components of the brachial plexus, I have long forgotten them. Though I remember the mnemonics with which I sailed through my examinations, I cannot recall what they stood for. Weird and wonderful things they were—works of genius, forged in lonely lodgings, and handed down from generation to generation, like the ancient ballads. In my youth I studied with courage and avidity the motley crowd of medical curiosities I found in the wards. But I have never met them since, and I take comfort in the thought that with the rapid advance in living they have disappeared.

In this nostalgic concern for the student I speak as a specialist, and as such I must affirm that it is easier to become a specialist than it is to graduate in medicine. After all, the budding specialist knows what to jettison and usually he does it in truck-loads, but the poor student doesn't know what to get rid of. If I am asked to give evidence at the World Conference, I shall advise that students should be taught how to consult a Bradshaw. Then they will be able to pick out the principal trains for immediate attention, and leave the branch lines for intensive study when their journey there is really necessary.

* * *

First impressions are often important, and in my wanderings in recent months I have noted the words or inscriptions which caught my eye first at various hospitals. At one a notice in large letters proclaimed "Children under 14 years are not allowed to pass through the gates." I felt more comfortable at the hospital above whose door was carved in the stone "I was sick and ye visited me."

At another a quotation from William Blake's *Songs of Innocence* reminded me that "Where mercy, love and pity dwell there God is dwelling too."

* * *

"But darling it's a research job! But of course we're thrilled! Well, she is our only daughter. No, I'm not quite sure what she is going to work on. One can never tell, she might get a brainwave and discover something any minute. No, darling not too hard. They don't mind about the hours as long as the work is done. Of course, when she gets her brainwave then it will be quite different. Surely you remember the film about Mme. Curie? Well, that gives you some idea of research. Yes darling, just some idea . . ."

"Clarice? Oh darling, I've such a terrible disappointment, Binksie says she can't come to dinner. Work darling, gets back terribly late and often brings things home. Not a particular idea of hers. Old Bluebeard—no, darling, not his real name—well he's got to write an article for one of those medical magazines. Yes, terribly important. Well, Binksie has to find all the articles that other people have written on the same subject and pick out the important points. At the R.S.M. darling. Don't you know! It's the Royal Society of Medicine. Binksie goes there every day. Of course, it isn't always easy. Sometimes old Bluebeard asks for things he thinks he's read and hasn't really. Well you know the sort of thing. Says there's a certain article on a certain subject, by a certain man, in a certain paper and then, after Binksie has moved heaven and earth—or rather the R.S.M.—to find it, it turns out to be on a different subject—and often by a different man, and in a different paper. Oh yes, quite often. By the time she's got it old Bluebeard usually says he doesn't want it anyhow. Passion spent, you know. Yes darling, but that's why they call him Bluebeard."

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[1] *Manchester Guardian*, Nov. 5.
[2] *Daily Mail*, Nov. 7.

"Clarice, but darling, hello! Its ages since I spoke to you. But of course I'll call Binksie. Yes I'm sure she'd love to come to dinner. No, not so hard now. No, no real brainwaves. Research isn't like that at all really. Old Bluebeard gets an occasional ripple and then Binksie goes through the files—to look up the statistics—and crystallises it out. I'll give her a call. Oh no darling not too busy at all. Just working out a scheme on how to spend £500. My money? No darling, of course not. It's hospital money. Well naturally it's important. No it's not how to make it go round, it's how to spend it all up. Well, if they don't get it all spent up by the end of the year then they lose it. Surely you remember that show *Zip Goes a Million?* Well, that gives you some idea of research. Yes darling, just some idea . . ."

* * *

What fine fellows the pioneers and research-workers are, whose names appear on the pages of our textbooks—inventors of anæsthetics, microscopes, syringes, antibiotics, and all the paraphernalia of modern medicine. How wonderful. So I mused this morning, while shaving. Suddenly I realised that ordinary life, too, is nurtured by countless friendly ghosts—inventors of brushes and combs, loofahs, towels, and soap, beds and pyjamas. It was then that I nearly cut myself with my safety razor when my face puckered the wrong way in a smile.

* * *

I drove up to the branch surgery to take my second session, and started taking my things out of the car under the interested eyes of Michael, aged 7, and Teresa, aged 5, the caretaker's children. With quiet professional pride I overheard Michael telling Teresa that I was the new doctor. She conceded one scornful glance in my direction. "That's not a doctor," she said, "that's a lady." I gave myself the benefit of the doubt and took this as a compliment—only to be dashed by her explanation: "She's got lipstick on."

* * *

Advertisement from the Bath Chronicle, Thursday, March, 20, 1777.

WANTED, for a family who have bad health, a sober, steady person, in the capacity of doctor, surgeon, apothecary, and man-midwife: He must occasionally act in the capacity of butler, and dress hair and wigs: He will be required to read prayers occasionally, and a sermon every Sunday evening. The reason of this advertisement is, that the family cannot any longer afford the expences of the physical tribe, and wish to be at a certain expence. A good salary will be given. N.B. He will have liberty to turn a penny in any branch of his profession when not wanted in the family.

* * *

My daughter, aged 8, was failing to respond, as doctors' children do, to the application of a parent's skill. Thinking to prepare her for an ordeal I suggested that we might ask a specialist to see her. She remarked with great calm and earnestness: "I am so glad, Mother; after all, you are only practising."

Letters to the Editor

DENTAL TREATMENT OF CHILDREN

SIR,—One wonders whether the argument that it is an uneconomical proposition to train dental ancillaries, because the experience of the New Zealand school dental nurses scheme has shown that a proportion of dental nurses leave the service when they marry, is to be carried to its logical conclusion. The argument applies with even greater weight to the training of women dental surgeons, since many of them also retire on marriage and most others carry on their professional work afterwards only on a part-time basis. The economic loss is substantial, since their training has been much more costly than would be that of an ancillary, and during their course of study they have monopolised facilities which could have been used to train a man who would have given the community many more years of service after qualifying as a dentist. Logically, we should expect the dental schools to be closed to women so that the greatest benefit could be derived from limited accommodation and teaching staffs, in the interest of increasing the number of dentists actually practising as distinct from an increase in the number of names on the Dental Register. Actually, the proportion of women students following the dental course increases steadily with the years and apparently no-one feels that this is an economically wasteful development. It would, of course, be a great pity if women were debarred from the dental profession, for they have an important part to play; but this retrograde step would be the logical conclusion of the argument about "wastage."

There is no valid reason why this "wastage" factor should not be reduced in importance by recruiting men as well as women for training as dental ancillaries.

Mr. Rosenstiel (Nov. 8) is surely wrong if he believes that children's dentistry can be learnt by gaining skill and experience in treating adults. No amount of experience of adult dentistry will, by itself, enable a dentist to treat satisfactorily his child patients. A serious shortcoming of dental education has been the absence from curricula of courses in children's dentistry. Not all schools have, even now, introduced such courses, and the result is that the newly qualified dentist may have little or no experience of treating children, no instruction in the different techniques involved, and little practice in gaining the confidence of small children. Most of us have had to acquire this experience after qualification, much of it simply by means of "trial and error." The dental nurse, on the other hand, would receive, at the hands of experienced practitioners, a training exclusively in the treatment of children and would thereby become something of a specialist in the techniques of fillings and extracting children's teeth. The wider experience necessary for diagnosis and treatment planning would be provided by the dental surgeon supervising the team of ancillaries, and he would also perform all the more difficult operations encountered.

I quite agree with Mr. Wookey that orthodontic work is a more interesting aspect of children's dentistry. Unfortunately we school dentists are morally obliged to devote the greater part of our time and energy to the urgent task of combating dental disease. Until we can pass on to ancillaries the less skilled routine operations, we shall be unable to make full use of our expensively acquired skill in other directions; and orthodontics, though important, must take a secondary place in our activities. Our skill and knowledge are at present largely wasted because we must spend so much of our time on work which could be equally well performed by an ancillary with a purely technical training.

SENIOR SCHOOL DENTAL OFFICER.

GRADING REVIEWS AND THE CHEST PHYSICIAN

SIR,—In 1949, in response to protests against the decisions of the original grading committees, the Ministry of Health promised that these decisions would be reviewed in two years' time; and, although mention was made of the opportunity offered for the attainment meanwhile of further qualifications, the Ministry promised that all cases would be reviewed. When the review committees were set up in 1951, however, the Ministry issued a circular which was in effect a directive emphasising higher qualifications or additional responsibilities since 1949 as the criteria for decisions. Most of the review committees acted upon this advice and refused to consider any appeal based on a claim of injustice in the original decisions. This was a contravention of the Ministry's promise.

There is still widespread dissatisfaction with the later gradings, and representations are being made. In this letter I want to draw your readers' attention to the particular case of the tuberculosis service.

Before 1948 the tuberculosis service was largely isolated from other branches of medicine. Even now, the work of an efficient chest clinic not yet within the curtilage of a hospital seldom comes to the notice of general physicians, surgeons, and gynæcologists, or even of many chest consultants serving at teaching hospitals, who have little conception of the nature or volume of the work done, the problems to be faced, and the standards attained. Only the few inefficient clinics draw attention to themselves.

The review committees, composed mainly of consultants in general medicine or surgery with only one direct representative of the whole-time tuberculosis service, had therefore little or no personal knowledge of the work of individual appellants; and they not infrequently rejected the advice of the specialist members of the committees. It is not surprising therefore that there were inequalities and injustices in the decisions arrived at both within the various regions and between them. The disparities within the regions sometimes gave rise to suspicions of prejudice but were perhaps due rather to varying degrees of knowledge of the particular clinics concerned. Between the regions, no uniform standard of judgment was possible without well-defined criteria.

There is a special case for reconsideration of the status of chest physicians in general apart from their individual claims. Most if not all of them are transferred officers, already doing consultant work for general practitioners and Government departments; and often they are of considerable seniority, well established in posts to which they were appointed in competition with others on the basis of medical and personal qualifications and experience. The majority of their posts are on the establishment as consultant posts and would be advertised as such if they resigned.

Most of these men, by reason of their age and responsibilities in whole-time posts, would find it impossible to seek further qualifications in general medicine; and in the opinion of their colleagues in the service they already fulfil the conditions laid down in the Ministry's original directives of 1949. Many of them hold the higher qualification previously required by the Ministry for senior posts in the tuberculosis service (D.P.H.). They have all acquired specialised experience in fields of work presenting greater complexity than many other branches of medicine; for example, the rehabilitation of the tuberculous which calls for a high standard of clinical judgment, and the problems associated with chronic infectious disease. Though this work is of great importance to the community, there has been a tendency to decry it as of less value than purely clinical work.

There is little chance of their obtaining consultant posts elsewhere in competition with younger men straight from training hospitals and with higher academic distinctions; nor should they be expected to give up the posts to which they have contributed many years' work in order to seek similar posts in other districts. They are therefore condemned to spend the rest of their professional careers as senior hospital medical officers—perhaps fifteen or twenty years or more—with inferior status in the eyes of their colleagues in other specialties and little heart to give of their best.

This is a non-recurring problem, particularly in the chest service, for the status of all new posts is now fixed before appointment, and new officers will not be expected to do consultant work without consultant status. The principle should be established that all S.H.M.O.s doing consultant work and/or in charge of chest units should be upgraded to consultant status if not already graded as such. There are less than 200 doctors involved: the cost would be comparatively small but the gain a satisfied service. The principle has already been accepted in the Welsh region with happy results.

If, however, this principle is not accepted for all regions, certain provisos should be insisted upon in any further review. The review committees for each specialty should consist predominantly of assessors who have first-hand knowledge of the work of the specialty: in the case of chest physicians, this means practical experience in or close association with chest clinics. Secondly, full weight should be given to the opinion of those practitioners, general and consultant, and local authorities who have direct knowledge of the work being done at the particular clinic.

London, N.1.   C. K. CULLEN.

CLIMATE AND INFECTION

SIR,—I was very interested to read in Dr. Waddy's article (Oct. 4) that he considered that drying of the respiratory mucosa might predispose to infections of the respiratory tract as well as to cerebrospinal meningitis.

I have plotted graphs of the incidence of respiratory infections occurring in Africans employed by the Magadi Soda Co. Ltd. over a period of nearly two years, and also graphs of various meteorological data. Among the latter I have included the actual evaporation-rate (in inches of water per month), which I think is a fair indication of the drying-power of inspired air. So far, peaks have occurred in the disease-incidence curve each time the evaporation-rate has fallen to an unusually low level. That is to say, when there is *less* tendency to drying of the mucosa, respiratory diseases are more common. My figures do not include cerebrospinal meningitis, for there have been no cases of this disease here in recent years.

I hope to publish the results of this investigation at the end of the two years.

Magadi, Kenya.   T. H. WHITE.

THE CORRECT SPELLING OF MEDICAL TERMS

SIR,—Spelling is a curious blend of phonetics, etymology, tradition, and nonsense; we should take care not to let the last preponderate. Dr. Napier (Nov. 1) is to be congratulated on his attack on the absurd *o* which it is customary now to insert into *fetus*. I would like to raise support for a similar attack on the *ph* with which we generally mis-spell *sulfur* and the other words derived from it.

Sulfur comes from a Latin word. Undeniably some Latin authors used the *ph* form, but there is good reason to think that this was a blunder, and most of the European languages that use the Latin root have not followed the erroneous spelling. The spelling *sulfur* was common in Britain from the 14th to 18th centuries, and this presumably explains its present day use in the U.S.A. It is in no sense an American innovation.

To adapt Dr. Napier's phrase, the *ph* crept in nearly 2000 years ago, but it is time that it too was gently eased out again.

Rothamsted Experimental Station,
Harpenden, Herts.
N. W. PIRIE.

WITHDRAWAL OF TEACHING

SIR,—I would like to underline and elaborate on Dr. Mac Keith's closing remarks last week about the need for better records of clinical conditions.

We are at the moment being asked by the Ministry of Health, through the daily press, to watch out for a visitor to this country thought to be incubating rabies. Has the Ministry taken any step to ensure that an adequate teaching record is made of this case, should it develop into frank disease? I know of only one film record of rabies existing in Britain, and that has been withdrawn from circulation. Similarly with smallpox: I have custody of one small collection of colour slides, taken recently through the beneficence of Messrs. Dalmas, of Leicester, and available on free loan to teaching centres. The only other series I know of is the excellent mass of material recorded at the turn of the century at Joyce Green Hospital—but even that is not lent out, nor is it in colour.

Again, recognised authorities have been written to, asking access to cases of anthrax, cowpox, and leprosy, amongst others: but these diseases are now so rare that when a case does turn up the physician has usually lost the letter, and begins treatment at once.

There is indeed need, as Dr. Mac Keith points out, for a ward specifically designed for recording the progress of patients under treatment. And what is more, there is a need to ensure that these records, once made, are readily available to all medical schools. The closing of the activities of the C.O.I. mobile projection units will prove to have been a severe blow to medical teaching.

London, W.1.
BRIAN STANFORD.

WHITHER MEDICINE?

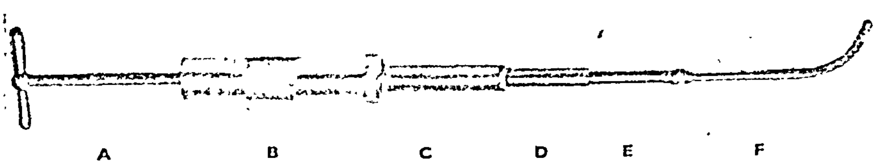
SIR,—One has always assumed that members of the profession entrusted with the task of grading their colleagues would recognise an obligation of strict confidence.

Sir Heneage Ogilvie (Oct. 25), however, sees fit in a public oration not only to express his contempt for certain individuals who, in his opinion, fail to attain consultant grade, but in two cases to give sufficient details to make the victims of his derision nearly certainly identifiable to many of their colleagues. One may well repeat with Sir Heneage "Whither Medicine?"

Horley, Surrey.
T. W. PRESTON.

MANAGEMENT OF A GASTROSTOMY AT HOME

SIR,—In general practice it is unusual to have a patient with a disease requiring gastrostomy, and a still rarer event to have the care of such a patient after operation. However, while hospital beds are scarce, the practitioner may be called on to do what he can, and to advise on home nursing.



Care of the Skin

The skin round the gastrostomy opening becomes fired by the action of escaping gastric juice, and some form of application should be used to protect the skin. The skin should be smeared for 3 in. around the gastrostomy with hydrous wool-fat, and then dusted thickly with a talc powder laced with bicarbonate of soda. A gastrostomy plug of the appropriate size should minimise leakage.

Pressure points require careful attention owing to the extreme emaciation of these patients. A time-table of bed postures should be followed so that the patient is not too long in one position.

Care of the Mouth

This is very important. Dentures are better left out, and the mouth frequently cleaned with a fragrant mouthwash, such as Glycer. Thymol Co. *B.P.C.*, or half a tablet of 'Sotol' in half a tumbler of warm water. Neglect of these precautions may lead to severe stomatitis or even to a fatal parotitis. Penicillin chewing-gum may be a help, for it stimulates the flow of saliva, and supplies a topical application of penicillin to the growth in the gullet.

Control of Pain and Infection

Pain in the chest and neck is often severe. 'Nepenthe' minims 20, diluted and passed through the gastrostomy tube, should give relief, and can be repeated when required. Constipation is often induced, and this is corrected by liquid paraffin, for a purge is not well tolerated.

Antibiotics have their place in keeping the growth clean. 'Crystopen,' a penicillin preparation containing 200,000 units per tablet, may be crushed up and given with a little fluid through the gastrostomy tube every two hours.

Diet

Most gastrostomy patients have a cancer of the gullet, so their activities are curtailed and they require only a low caloric intake, which is usually provided by nourishing fluids given by catheter through the gastrostomy. There are also those patients who have had a gastrostomy because of œsophageal damage by corrosive fluids, and they often need a fuller diet.

It would clearly be an advantage to be able to give other than liquid food, and the apparatus shown in the accompanying figure enables this to be done.

The assembled components A to E are those of an ordinary grease-gun used to lubricate motor-cars; and the end-piece F is a metal catheter about size 12 (English) with a large lateral eye. The screw ram A works in the loading barrel B, which is attached to the pressure chamber C by a screw thread. Next to C is the sleeve D into which E slides when the gun is in the feeding position. When E is in the extended position, as shown, nothing can pass.

Anything which can be made into a purée will go through this gastrostomy gun. Fine mince, boiled grated carrot, mashed potato and gravy, sieved green vegetables, and so on, will all go through it. There is no point in putting fluids through because the usual gravity method can be used.

To load the gun, detach the loading barrel and see that the screw ram is fully out. Air-bubbles in the food are dispersed by stirring with a fine rigid rod. When full, reassemble, slide E up into D, and screw the ram down into B until food appears at the eye of the catheter. Now detach B, screw A back into the empty position, top up with more food, and reassemble. The gun is now ready for use. When the point of the catheter has been greased with 'Vaseline,' it will slide easily into the gastrostomy opening. Theoretically the whole of a meal could be mixed up in one dish, but it is obviously better to serve it in courses.

Cleaning the apparatus is of the greatest importance. Detach the barrel, remove the surplus food, and screw back the ram to the empty position. The barrel is then cleaned with a bottle brush and a domestic detergent, scalded, and put on the hob or hot-plate to dry. The distal part of the apparatus is more difficult to clean, for there is a tightly packed residue of food to be forced out. This is done by fitting an inch of rubber tubing over the end of a cold-water tap so that it acts as a watertight seating when the pressure chamber C is forced tightly up against it, and the water turned on. Be sure that section E is telescoped into the sleeve D, otherwise the result will be a shower-bath. When this part is clear, boiling water can be flushed through it, provided E is in the up position.

Care of the gastrostomy patient is chiefly a matter of adequate diet, and this method is an attempt to provide a fuller diet. It has proved satisfactory in the 2 cases in which I have used it.

Longtown, Cumberland.
ROBERT RUTHERFORD.

A TECHNIQUE FOR SAVING THE VEIN

SIR,—The article by Dr. Aronson (Nov. 1) prompts me to record the following simple technique:

A transverse incision is made, the vein is exposed, and two sutures are placed round it. The ends of the proximal suture are sewn loosely through the proximal skin edge, one on each side of the vein; the distal suture is similarly sewn through the distal edge of the cut.

The vein is snicked and the cannula introduced in the normal way. The proximal suture is tied tightly over the skin, thus enclosing the vein and cannula; the second suture is tied similarly, distal to the cannula. The skin incision may now be sutured as usual.

When the transfusion is discontinued the two venous sutures are readily removed. Any bleeding will cease if the limb is elevated and firmly bandaged: it is unnecessary to repair the wall of the vein.

In cases where the vein is visible through the skin, the subsequent patency of its lumen may sometimes be evident to the eye.

King Edward Memorial Hospital,
London, W.13. VIVIENNE WOLFSON.

FUTURE OF THE OCCUPATIONAL HEALTH SERVICES

SIR,—Many well-informed people believe that our occupational health services are inadequate. A few, in a rather nebulous and tentative way, have put forward plans for improvement. I confess I am surprised to find Dr. Lloyd Davies (Nov. 1) attacking, not a particular plan, but planning as such. *Wyld's Universal English Dictionary* defines planning as "methodical and considered arrangement of the various matters and steps necessary to carry out a project." It is difficult to see how Dr. Lloyd Davies could carry on either his own professional work or his personal life without planning. He obviously reserves the term, and his scorn, only for planning of which he disapproves. If there are planners of occupational health services who want "to hamper industry with unsatisfactory legislation" and who "assume that planning as such is a good thing"—i.e., that a bad plan is better than no plan—then they deserve criticism because their plans are bad, not because they are planners. Who are these people? I should like to read them in the original.

Before planning can begin, there must be agreement on the end in view. The collection of "accurate information, as opposed to theories and dogmatic summaries" which is what Dr. Lloyd Davies advocates, must be the next step. But by what reasoning does he equate planning with failure to do this?

West Midlands Gas Board,
Birmingham. F. H. TYRER.

SIR,—Whilst this subject is once more being debated in your columns, may I suggest a measure that could be taken at once without any increase in medical manpower or new legislation? My suggestion is that each local health authority should set up an occupational health service to cover its own staff. This would have three advantages in addition to the fact that the necessary machinery is already available. Firstly, a considerable number of employees not yet covered by any form of occupational health service would be given such a service: secondly, the local health department would gain experience of administering an occupational health service; and, thirdly, some facts and figures could be obtained in relation to small groups of office and outside workers.

I realise that a few authorities have such schemes, and that all authorities medically examine potential employees, but this latter measure is not an occupational health service. Is the lighting and heating in all our town halls adequate? Are the health and welfare regulations relating to building carried out on all local authorities' building sites? How much study has been devoted to dust suppression at refuse-disposal works? Do road workers suffer from tar-epithelioma, and what measures are advised and supervised to prevent it? Do librarians or park attendants get the most colds? Such questions indicate the scope of the problems that a local-authority occupational health service could tackle. Here, indeed, is a chance for the public-health department to do some spade work and by their results to gain the confidence of industrial medical officers.

London, W.5. M. D. WARREN.

BRITISH HOSPITALS CONTRIBUTORY SCHEMES ASSOCIATION

SIR,—In your notice last week (p. 943) of the annual conference of this association, held in Cardiff, you report me as saying:

"There was a lack of research and of health education. If people were properly informed about immunisation and other preventive measures they would be able to help themselves more and cost the National Health Service less."

I wish to point out that I did not say this or anything remotely resembling it. While painfully conscious of my limitations I at least believe myself to be incapable of uttering such platitudes.

Cambridge. FFRANGCON ROBERTS.

*** Our report was a correct abstract of an account sent to us by the association.—ED. L.

INTUSSUSCEPTION DUE TO ECTOPIC PANCREATIC TISSUE

SIR,—I should like to record an unusual case of intussusception.

A girl, aged 6½ years, the youngest of five children, was admitted to hospital at 8.30 P.M. on Sept. 4, 1952, with a history of intermittent abdominal pain and vomiting which had started suddenly about ten hours earlier. The pain was in the umbilical region and varied in intensity; when she arrived in hospital it was less severe but more frequent. The vomiting had stopped during the afternoon. Her bowels had been open normally before the onset of the pain, but not since. Micturition had been quite normal. She had had occasional attacks of abdominal pain with vomiting for the past three or four years and her mother thought these were getting more frequent; lately they had occurred at intervals of about a month. She was known to have had acetone in the urine during a number of these attacks. The latest attack had lasted longer and seemed to be more severe than any of the others. Except for pneumonia at the age of 4 she had had no serious illness.

The patient was lying quietly in bed and was not in any obvious pain. Temperature 98·8°F, pulse-rate 84 per min., respirations 22 per min. There was some fœtor oris, and the tongue was a little furred. Heart and lungs normal. The abdomen was not distended and moved well on respiration. There was some fullness in the right iliac fossa with guarding there on palpation. This revealed an elongated tumour about 2 in. (5 cm.) long with its axis parallel to the inguinal ligament; it was slightly mobile and not very tender. Nothing else abnormal was found in the abdomen or on rectal examination. The urine contained acetone and a trace of sugar.

The diagnosis appeared to be either an intussusception or an inflamed appendix surrounded by omentum.

The abdomen was opened through a lower right paramedian incision. There was some clear yellow fluid in the peritoneal cavity, and in the right iliac fossa there was an ileo-ileal intussusception about 5 in. (13 cm.) long, bent into nearly half a circle by the attachment of the mesentery. Reduction proved impossible, owing to the tightness of the proximal end: and a resection with end-to-end anastomosis was carried out, leaving about 1 ft. (30 cm.) of ileum between the anastomosis and the cæcum.

The patient's convalescence was uneventful, and she went home on the seventeenth day after operation.

Examination of the specimen showed a tumour about ½ in. (1·5 cm.) across in the wall of the intestine at the proximal end of the intussusceptum. It was about 30 in. (78 cm.) proximal to the ileocæcal valve in the position where a Meckel's diverticulum might be expected. The histological report was as follows: "The nodular lesion consists of ectopic pancreas. This is situated mainly in the submucosa, but extends into the muscularis. The overlying mucosa is hæmorrhagic and shows early ulceration. A mesenteric lymph-node shows a widely distended sinus and mild inflammation."

Pancreatic tissue is found occasionally in the duodenal region and the upper jejunum, but I can find no published record of its occurrence in the lower ileum.

I am indebted to Dr. C. C. S. Pike for the histological report.

Peace Memorial Hospital, Watford. **A. P. KITCHIN.**

A PREGNANCY TEST

SIR,—Although pregnancy tests, such as the Aschheim-Zondek and Friedmann tests, are well established, it is often difficult to obtain mice and rabbits in suitable condition in laboratories where these tests form only a small part of the routine work, such as those at military hospitals. For these laboratories a simple and reliable method, such as that described by Galli-Mainini,[1] by Frazer and Wohlzogen,[2] and by Haines,[3] would be an advantage.

In FARELF Command a test using the male frog, *Rana rugulosa*, has been in use in the physiology department of the University of Hong-Kong and at the public-health laboratories there, and by courtesy of the directors specimens have been examined for the Services. This frog, however, is not found in the wild state in Malaya. On the other hand, a toad, *Bufo melanostictus*, is found throughout South-East Asia; and though it hibernates in Hong-Kong, it is readily available all the year round in Malaya. An experiment by Dr. Audrey Driver and Dr. Hou Chien-Tsun, in the department of physiology at Hong-Kong showed that the frog was slightly more sensitive than the toad to the urine of pregnant women, but agreement was reasonable. It was decided therefore to adopt for routine use in the pathological laboratory at Singapore a test in which three toads were used and the urine concentrated by the method described by Scott.[4]

Technique

An early morning specimen is required. If it cannot be used at once it should be frozen to limit bacterial growth. It is advisable to concentrate the urine tenfold and this takes about an hour.

The following reagents are used:

(1) Bromphenol blue .. .. .. 0·4 g.
  0·05 *N*/NaOH .. .. .. 15 ml.
  Grind up to make 100 ml. with water.
(2) 20% aqueous suspension of kaolin (preferably kaolin B.D.H. washed with acid).
(3) 20% HCl.
(4) 0·1 *N*/NaOH.
(5) 10% HCl.

Take 100 ml. urine, 100 ml. water, and 1 ml. indicator in a measuring funnel. Adjust the pH to 4·0 with 20% HCl until the blue colour almost disappears. Add 10 ml. kaolin suspension. A coarse precipitate rapidly forms. Pour off supernatant liquid and transfer the deposit to a one-ounce bottle. Centrifuge, and extract the deposit with 10 ml. of 0·1 *N*/NaOH, shaking well. Centrifuge again, pour off the supernatant liquid, and adjust its reaction with 10% HCl until it is just acid to litmus.

Three male toads are then examined to make sure their urine contains no sperms. A glass pipette with rounded ends is inserted into the cloaca for ½–¾ in., and gently moved in and out until some urine is sucked up. This is then examined for sperms under the dry lens.

2 ml. of the concentrated urine is injected into the dorsal lymph-sac of the toads. Urine is collected from the animals after two and four hours, and a drop on a slide is examined for sperms.

Results

Of 93 tests made between August, 1951, and April, 1952, 76 are strictly comparable, for the technique did not vary and a follow-up was possible. The results in these cases were:

(1) 28 true positives (confirmed clinically);
(2) 34 true negatives;
(3) 14 false negatives;
(4) No false positives.

Some false negatives were not unexpected, for the tests were sometimes asked for after as little as four and a half weeks' amenorrhœa. False negatives also occurred when pregnancy was advanced and fœtal parts visible on X-ray examination. Other workers have found that the level of gonadotropins falls in these circumstances.

Toads

It was easy enough to catch toads at night either with a torch or near the street lamps where the insects gathered. They were kept in a brick enclosure, sheltered from the sun. There was 2 in. of water and some islands of bricks in the enclosure, and the toads usually hid under a collection of bricks or sat on an island. It was simpler to catch the toads as required, and to keep only a small stock of a dozen. It was then unnecessary to feed them. All toads that were positive in the tests were released far from the collecting area, but toads that were negative were used again.

All toads were examined for free sperms before being used, but no free sperms were ever found. Certain toads were found which did not react—hence the use of 3 toads for every test.

No animals died after injection of the concentrated urine, though in preliminary trials some unconcentrated urines were fatal to the toads. Scott[4] has pointed out that toxic substances are retained by the kaolin. Toads weighing 25 g. would be unaffected by 5 ml. of isotonic saline, but often killed by 5 ml. urine.

In our limited experience this test was sufficiently sensitive to be of clinical use. Moreover, it was inexpensive, it gave a result on the same day—in some positive cases within an hour and a half of receiving the sample of urine—and it never gave false positives.

Pathology Laboratory,
FARELF.

P. C. FARRANT
F. E. BUCKLAND.

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[1] Galli-Mainini, C. *J. Amer. med. Ass.* 1948, 138, 121.
[2] Frazer, J. F. D., Wohlzogen, F. X. *Brit. med. J.* 1950, ii, 330.
[3] Haines, M. *Nature, Lond.* 1948, 162, 446.
[4] Scott, L. D. *Brit. J. exp. Path.* 1940, 21, 320.

FATE OF THE FACE IN POLIOMYELITIS

SIR,—After seeing Dr. Moore's interesting report[5] on the outcome of facial paralysis in poliomyelitis, we thought that it would be of interest to follow up our cases seen in recent years.

Among 188 cases of poliomyelitis, including 72 non-paralytic, seen in the years 1947–50 there were 11 instances of facial weakness. (This excludes a further two or three cases of the severe bulbar form of the disease in which the patients died.) Of the 11 patients 10 were traced.

2 (male aged 18 years, female aged 17 years) had transient weakness which disappeared while they were in hospital.

3 (males aged 27 and 9 years, female aged 7 years) had mild weakness affecting the mouth only or the mouth and, very slightly, the eye. These recovered completely.

2 had moderately severe weakness of the mouth and the eye, though both mouth and eye still showed some movement. One patient (male aged 36 years) improved greatly for six months, then was left with slight but definite weakness of mouth and eye. The other patient (female aged 1 year 10 months) recovered completely.

2 had severe weakness of mouth and eye, with hardly any movement remaining. One of these (female aged 9 months) showed a slight flicker of the mouth, and after nine months her eyes were seen to close in sleep; but no further improvement ensued. The other (female aged 3½ years) showed little or no improvement.

1 patient (male aged 13½ years) recovered completely; but the degree of weakness was not recorded at the start.

South Middlesex Hospital,
Isleworth.

R. V. WALLEY
R. T. D. EMOND.

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[5] Moore, E. W. *Lancet*, 1952, i, 1092.

Public Health

Family Life in Great Britain

FAMILY life in the happy self-sufficient British tradition generally accepted in this country as an almost essential ngredient in the formation of good character: its bsence or disturbance is held responsible for juvenile elinquency, the problem child, and even the severer orms of mental disorder. From the narrower sociomedical standpoint, contentment and security of the amily circle plays an important part in recovery from lness; and, at the level of health-service administration, he medical care of the sick person without a family to ssist in that care is often a grave problem.

What now constitutes a typical British family? The econd instalment of the 1951 sample Census tabulations[1] the first was reviewed in our issue of July 19) provides n answer. A novel analysis, not attempted at any revious British Census, shows the internal composition f private households—the kind of people in them nd how they were related to one another. Of the otal of 14½ million households in Great Britain in 1951, 11½ million were of the simplest type—i.e., a married ouple, or a widowed person, with or without children, r persons living alone. Nearly another million households were of this simple type except for the inclusion of parents or non-married brothers or sisters of the head of a household. The remainder, numbering under 2 million, contained more distant relatives or non-relatives (often boarders) of the head. In three-quarters of the total households a married person was the head; in a sixth the head was widowed or divorced; while the remaining "heads" were single (five-sixths of them being over 40 years). Tables are given showing the frequency of different patterns of blood relationship. The medical social worker is interested not only in blood relationship but in psychological relationships and emotional attitudes. On these, of course, a Census must be silent. Social medicine must get out into the field.

Married couples living in other people's homes are often a social problem, and occasionally a medical problem. The sample enumerated some 820,000 couples in this situation. Most of them were married children of the head of the household or of his spouse. There were also about 400,000 widowed or divorced persons living in homes of their married children. Married couples living alone are also important, for a third of them were over 60 years old.

In one sense family life is unavoidably more self-sufficient than it was: the family retainer has almost disappeared. Resident domestic servants in private households have fallen in number from 706,800 in 1931 to 178,000 in 1951 (in this comparison the figures relate to England and Wales and not Great Britain).

What about people who are not in their own homes? There were 840,000 persons in hotels, boarding-houses, and the like; 120,000 in schools and children's homes; 380,000 in civilian hospitals and nursing-homes; 220,000 in mental institutions; 67,000 in homes for permanently disabled or aged; and 500,000 in Defence establishments—altogether about 2,400,000 living outside private households. The main change since 1931 lies in the large increase in the number in Defence establishments.

How big were the families? There is of course today a higher proportion of small families and a lower proportion of large families. The fertility question at the Census was addressed to married women under 50, many of whose families were incomplete. The proportion of these in the sample who had not so far borne a child was 21·5%; with one child 30·2%, with two children 25·9%, with three children 12·0%, and with four children 5·2%. There were barely 5% with families of five or more children and less than ⅓% with ten or more children. In 1911 more than a fifth of married women under 45 had five or more children. Families in social class 1 have not fallen in size so much as those in the lower social classes.

The Census tabulations give information of the birthplaces of people. Not all the families were British by birth, and not all of them have acquired British nationality. The large influx of aliens since 1931 colours the picture. The greatest increase has been in natives of Poland, from 45,000 in 1931 to 165,000 in 1951. The German-born rose from 29,000 in 1931 to 111,000 in 1951 and the Russian-born from 39,000 to 77,000. Large increases were also recorded for natives of Austria, Hungary, and Czechoslovakia.

Estimate of Future Births

The Registrar-General's final estimate for live births in England and Wales during the December quarter is 158,000, and his provisional estimate for the March quarter, 1953, is 170,000, giving an estimated total of 328,000 babies in the six months. There were 153,995 live births registered in the December quarter of last year and 173,503 in the March quarter of this year—a total of 327,498. This year's number of live births registered in the 160 Great Towns up to Oct. 25 was 328,915 compared with 338,618 in the same period last year.

Consumption of Milk in Schools

In his report for 1951, Dr. J. B. S. Morgan, medical officer of health for Derbyshire, wonders why there has been a decline in the proportion of school-children in the county who drink the free milk issued to schools. In 1946 89·3% of children in secondary schools took milk, but by 1951 the figure was down to 64·8%. During the same time the percentage in primary schools fell from 94·8 to 87·3. In a previous report Dr. Morgan recommended that the milk be made more attractive to children by adding some suitable flavouring, but the Ministry of Education was unable to sanction expenditure for this purpose. He says in this year's report that a survey of the county's schools is being made to find out why there has been this decline, and we are indebted to him for sending us the opinions given by the heads of schools. The following were among the reasons suggested:

(1) There is more milk at home, so less is needed at school;
(2) ice-cream is a growing counter-attraction;
(3) inducing children to drink milk puts them off it;
(4) taking milk off the ration has had a psychological effect;
(5) mid-morning milk spoils the appetite for lunch;
(6) time spent drinking milk is playtime lost;
(7) children think the milk is too cold in the winter or, quite wrongly, sour in the summer;
(8) some children are forbidden to drink milk by parents' or doctor's orders;
(9) the children just do not like milk;
(10) as the milk costs nothing, it is no longer appreciated.

Parliament

Accommodation for Mental Defectives

IN the House of Commons on Nov. 5, Mr. BERNARD BRAINE pointed out that institutions in England and Wales were accommodating 49,000 defectives, while there was a waiting-list of 8000, of whom half were children. Since the introduction of antibiotics and sulphonamides the death-rate in these institutions had fallen, and as a consequence many children remained on the waiting-list for years. High-grade mental defectives, once they were stabilised, could become useful citizens, but too often they were not admitted to institutions early enough to enable anything to be done for them. Sometimes they came into institutions through the courts because they had got into serious trouble. More accommodation and staff were required, and more voluntary workers to care for defectives outside the institutions. More should be done to attract the right kind of people for this work. Insufficient elasticity was allowed to hospital management committees in the appointment and pay of their staff.

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[1] Census, 1951, Great Britain, 1% Sample Tables. Part II. H.M. Stationery Office, 1952. £2.

Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, admitted that there was a serious shortage of accommodation, but could not agree that nothing had been done to meet the problem. On the contrary, 3066 new beds in the regional hospital board hospitals for mental defectives had been opened since the appointed day. In addition many under-staffed beds had been equipped. Despite this the waiting-list had risen from 3933 on the appointed day to 7929 at the beginning of this year. They had to face the fact that the demand was growing faster than it had been possible to open beds. They needed 15,000 new mental-deficiency beds. At the moment 2145 were out of use for lack of staff. The average percentage of hospital capital expenditure allocated to mental health had risen from 19·8 in 1950–51 to 26·1 in 1951–52, and it was expected to be 30·2 in 1952–53. For mental-deficiency treatment alone the proportion of capital expenditure allocated was 7·1 % in 1950–51 and 11·4 % in 1951–52, and it would be 10·9 % in 1952–53. There had also been an appreciable increase in nursing staff. The figures she quoted covered staff and beds in hospitals mainly used for mental defectives. In 1948 the number of full-time nurses was 5941, and this year it was 6542. The staffed beds were 48,793 in 1948, and they were now 54,025. This increase was not great enough, but it showed steady progress, and the Ministry were taking steps to see that greater accent was put on the problem by the regional boards.

One disquieting fact was the decline in the recruitment of student nurses. To meet this need the various advisory bodies who made recommendations to the Ministry of Health and the Ministry of Labour on the problem had been discussing pay and training in an endeavour to see if the training could be shortened for generally trained nurses who decided to take up mental nursing. Student mental nurses received £30 a year more at all stages than student nurses in general hospitals, and trained staff up to assistant matron and assistant chief male nurse got £20 more than the equivalent grade in the general hospitals. She believed that the recent increase agreed to by the Whitley Council for all nurses would do much to help recruitment.

Births, Marriages, and Deaths

BIRTHS

BRADFIELD.—On Nov. 4, at the Royal Hampshire County Hospital, Winchester, to Hazel (née Holloway), wife of Dr. Parker Bradfield—a daughter.

GILBEY.—On Oct. 29, at Parklands, Durban, to Joan Mary (née Hulse), wife of Dr. A. L. Gilbey—a daughter.

GIMSON.—On Nov. 4, at The Chantry, Aylesbury, to Elizabeth, wife of Dr. Peter Gimson—a son.

LEGGATT.—On Nov. 3, at St. Anne's Nursing Home, Oxford, to Elizabeth (née Newton), wife of Dr. H. D. Leggatt—a daughter.

MARTEN.—On Nov. 2, at Shearwood Road Nursing Home, Sheffield, to Margaret (née Pervical), wife of Dr. R. H. Marten, M.R.C.P.—a daughter.

MARTIN.—On Nov. 2, at Norgrove, The Bishops Avenue, N.2, to Mary (née Sowels), wife of Dr. A. J. Martin—a daughter.

PRIDAY.—On Nov. 5, at the Royal Bucks Hospital, Aylesbury, to Grace Josephine, wife of Dr. C. O. M. Priday, of Buckingham—a daughter.

ROBERTSON.—On Oct. 28, at Liverpool Maternity Hospital, to Elizabeth, wife of Dr. A. John Robertson—a daughter.

TEPPER.—On Nov. 8, at Bromley Maternity Hospital, Kent, to Rachel (née Claiman), wife of Dr. R. Tepper, M.R.C.P.—a daughter.

MARRIAGES

COOK—BALSTON.—On Oct. 28, Henry Pattullo Cook, F.R.C.S.E., lieut.-colonel I.M.S. retd, to Cecily Clare Balston, of Perth, Western Australia.

DEATHS

ANDREWS.—On Nov. 2, Maynard Campbell Andrews, M.D. Camb., aged 50.

MCKELVIE.—On Nov. 3, John Douglas McKelvie, M.D. Edin., of Blofield, Norwich.

MUNRO.—On Nov. 8, at Halton, Bucks, Sir David Munro, K.C.B., C.I.E., M.B. Edin., LL.D. St. And., F.R.C.S.E., air vice-marshal retd, of Crosshill, Wendover, aged 71.

PATERSON.—On Nov. 7, at Chatfield, Alton Road, Parkstone, Dorset, Archibald Richard Paterson, M.D. Camb., aged 81.

RIDEWOOD.—On Nov. 8, in London, Harold Edward Ridewood, M.D., M.S. Lond., F.R.C.S., of Victoria, British Columbia.

TURNER.—On Nov. 4, at Ravensnest, Hythe, Southampton, Arthur John Turner, M.B. Durh.

VERLING.—On Nov. 4, Algernon Verling, M.B. N.U.I., of Oxclose, Newmarket, co. Cork, Eire.

WOOD.—On Nov. 8, at the Queen Elizabeth Hospital, Birmingham, Helen Margaret Wood, M.B. Birm., D.A.

Notes and News

A FIRST FIVE YEARS

FIVE years can seem a long time or a short time according to what you are doing. If you are setting up a new university department the years soon pass, and in their first report the Nuffield Department of Industrial Health of the University of Durham have to record a packed and strenuous quinquennium. In many ways the new department had a good start. They were backed by a generous grant of £40,000 to be spread over ten years, from the Nuffield Foundation. Office and laboratory accommodation was provided for them in King's College, Newcastle upon Tyne, where other interested departments, such as chemistry, physics, and engineering, were close and helpful neighbours. Across the road a large teaching hospital offered clinical facilities, and a little further afield the varied industries of the district offered material for research.

The department's first task was to define industrial health, which they did as "the reciprocal relation between health, home, and job," and it is against the background of this definition that their programme of research and teaching has been planned. One of their difficulties was to strike a balance between the conflicting claims of research, teaching, and preventive medicine. They early realised that their programme "must be leavened by practical idealism and tempered by the realisation that work can only be done with the materials at hand." Accordingly they accepted the problems thrown up by the local industries and chose for their first research project studies of coalminers' nystagmus and pneumoconiosis, and a statistical survey of accidents and absence from work in shipyards. The growing demand that machines should be made to fit the man rather than that man should be expected to do the best he can with the machine has led the department to study human response to variations in design of machinery, and they have built a piece of apparatus to assess the speed and accuracy of response to different designs of visual indicators. The acid erosion of the teeth of workers in a local chemical factory has also been investigated.

As teachers the department have been responsible for the instruction of medical and engineering students, as well as of almoners. They have also held postgraduate lectures for candidates for the D.P.H. and for engineers studying for higher qualifications. Two outpatient clinics are held each week at the Royal Victoria Infirmary, and 6 beds have been allotted to the department for inpatient work. In all 1127 outpatients and 271 inpatients have been seen. An outpatient clinic has also lately been opened at Dryburn Hospital, Durham. The department also runs an advisory service which has answered industrial and medical inquirers living as far away as Dundee and Somerset.

The load of these busy five years has been carried by a team of twelve of which Prof. R. C. Browne, the director, and his two assistants are the medical members.

MANUFACTURE OF CORTISONE

CORTISONE acetate is now being produced in this country by Bayer Products Ltd., who delivered the first consignment to the Ministry of Health last month. Details of the process have not been disclosed, but the starting-point is a steroid derived from ox-bile. An ox-bile synthesis is also used in the manufacture of cortisone in the U.S.A. The Bayer process has been evolved at the Sterling-Winthrop Research Institute in New York and at the Bayer laboratories in this country. Production will depend largely on imported raw material, for there are not enough cattle in this country to provide all the bile needed. By July next year, however, home production should exceed the present rate of consumption, and some of the surplus may be exported. The drug will be issued in 25 mg. tablets for oral administration and as a crystalline preparation. The cost will be about £4 per g. All supplies will continue to be distributed by the Ministry.

Royal Society of Edinburgh

A David Anderson-Berry medal and prize (about £100) will be awarded during 1953 for work on the therapeutic effect of X rays on human diseases. Applications should reach the general secretary of the society, 22, George Street, Edinburgh 2, not later than March 31, 1953.

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1. Browne, R. C. *Lancet*, 1951, i, 721.

University of Oxford

On Nov. 1 the degree of D.M. was conferred on John Badenoch and A. I. Spriggs.

Royal College of Physicians of Edinburgh

At a meeting of this college held on Nov. 4 with Dr. W. A. Alexander, the president, in the chair, the following were elected to the fellowship:

T. F. Corkill, James Lawson, John Kinnear, J. M. Alston, A. W. E. Soysa, Freddy Himmelweit, Thomas Scott, J. J. J. Giraldi, D. R. MacCalman, R. W. D. Turner, W. I. Card.

The following were elected to the membership:

A. D. T. Govan, G. W. A. Dick, J. C. Bowe, K. B. Kapur, J. Harper, D. C. Campbell, J. S. Sodhy, T. F. McCarthy, M. A. Khan, Sheenah J. M. Russell, M. G. E. Hanno, H. Sadik, B. R. Billis, A. F. Fahmy, B. L. Agarwal, E. J. D. Nariman, R. M. Kapadia, O. T. Khoo, W. J. Mitus, L. Mirabel, Mariella Fischer-Williams, I. R. Yudaken, B. A. Akhtar, B. Seltzer, S. C. Shah, S. A. Singh, H. J. H. Hiddlestone, A. D. McInnes, J. H. Greig, H. Stein, A. W. M. Smith.

Scottish Conjoint Board

At recent examinations for licentiateship of the Royal Colleges of Physicians and Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow, the following were successful:

H. E. O. Adefope, Caroline D. Bell, I. K. Bond, Mary R. Cardwell, Stella M. Conway, R. M. Gabriel, Joan Gilbert, Chunilal Parbhoo Hargovan, E. A. Heywood, E. P. Jones, Anthony Yawovi Kpeglo, Heather J. Lopert, P. A. P. Mackenzie, R. W. Noblett, J. W. Parsons, James Peacock, E. S. O. Pratt, William Ritchie, Patricia J. A. Stewart, Ahmed El-Sayed Ahmed Touba, J. L. Tuton.

Royal Faculty of Physicians and Surgeons of Glasgow

The following have been elected office-bearers for the coming year:

President, Mr. Andrew Allison; visitor, Dr. Stanley G. Graham; hon. treasurer, Mr. Matthew White; hon. librarian, Dr. Archibald L. Goodall; representative on the General Medical Council, Mr. Andrew Allison; other members of council, Mr. Walter W. Galbraith (immediate past-president), Dr. D. F. Cappell, Dr. Alexander A. Charteris, Dr. Leslie J. Davis, Mr. W. Ian Gordon, Mr. A. D. Telford Govan, Mr. C. F. W. Illingworth, Mr. J. A. W. McCluskie, Mr. W. Arthur Mackey, Dr. Thomas Semple, and Mr. J. Forbes Webster.

Physiology of Respiration

Prof. H. Hartridge, F.R.S., will deliver a lecture on this subject on Nov. 17, 18, 19, and 20, at 5.30 P.M., at Gresham College, Basinghall Street, London, E.C.2.

Postgraduate Course in Radiology

The Faculty of Radiologists is holding postgraduate courses in diagnostic radiology and in radiotherapy at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, on Saturday afternoon and Sunday morning, Nov. 22 and 23.

London Hospital

Liddle Triennial Prize (£120).—The subject chosen for the next award of this prize is the Effect of Hormones on the Reaction of the Tissues to Injury. Essays must be delivered at the hospital not later than 4 P.M. on July 31, 1955.

Unestablished Practitioners Group

A general meeting of this group, which is an organisation for the newly qualified assistant and small-list practitioner will be held at the Hotel Russell, Russell Square, London, W.C.1, on Thursday, Dec. 4, at 8 P.M. All members of the profession are invited to attend.

Australasian Faculty of Anæsthetists

A Faculty of Anæsthetists has been set up within the Royal Australasian College of Surgeons. Till the new faculty has an opportunity of formally electing a board, Sir Victor Hurley, Mr. Henry Searby, Dr. H. J. Daly, Dr. J. Ellis Gillespie, Dr. S. V. Marshall, Dr. D. G. Renton, Dr. L. G. Travers, and Dr. G. R. Troup have been authorised to act on behalf of the faculty under the chairmanship of Dr. Renton, the acting dean. With the general approval of the Australian Society of Anæsthetists, 40 foundation fellows and 62 foundation members have been invited to join. In future applications for membership will be received from anæsthetists with appropriate qualifications, and recommendations will be made to the college council for admission to membership of those approved by the board of the faculty. The board may also submit a limited number of names annually to the college council for election to fellowship of the faculty. The secretary of the faculty is Mr. H. G. Wheeler, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1.

West Midlands Physicians Association

Dr. J. H. Sheldon has been elected president for the coming year in succession to Prof. T. L. Hardy.

Royal Society

The Buchanan medal has been awarded to Sir Rickard Christophers, F.R.S., for his research on malaria and on the anopheles mosquitoes which transmit the disease.

Metropolitan Branch of the B.M.A.

The centenary celebrations of this branch next year will include a ball in aid of medical charities which is to be held at B.M.A. House, Tavistock Square, London, W.C.1, on Thursday, Jan. 8 (tickets 2 guineas each).

Nutrition Society

This society is holding a conference at the Department of Biochemistry of the University of Sheffield, at 10.15 A.M. on Saturday, Dec. 20, on the Rôle of Vitamins in Metabolic Processes. Prof. H. A. Krebs, F.R.S., will be in the chair, and the speakers will include: Prof. C. P. H. Dam, Mr. L. J. Harris, D.SC., Mr. D. E. Hughes, Mr. T. Moore, D.SC., Mr. J. W. G. Porter, PH.D., and Dr. H. M. Sinclair. Further particulars may be had from Mr. R. J. L. Allen, Monkhouse & Glasscock Ltd., Snows Fields, London, S.E.1.

International Hospital Congress

The eighth International Hospital Congress is to be held in Church House, Westminster, from May 25 to 30, under the chairmanship of Dr. René Sand, emeritus professor of social medicine at the University of Brussels and president of the International Hospital Federation. The central theme of the congress will be Preventive Medicine as a Major Function of the Hospital, and its Implications. Further particulars may be had from Captain J. E. Stone, hon. secretary and treasurer of the federation, 10, Old Jewry, London, E.C.2.

Trials of Influenza Vaccine

The Medical Research Council, in conjunction with the Ministry of Health, is to organise trials of influenza vaccine this winter. About 15,000 volunteers—including a large number from industry, and others from among hospital nursing staffs, university students, and similar groups—will take part. The trials are due to start early next month. Two vaccines will be used: one selected on the experience of last winter's pilot trials, and the other similar to those which have been available for some years. Both are being produced in this country.

Rural Science Education

The Institute of Rural Life at Home and Overseas, in coöperation with the Association of Agriculture and the Institute of Education, University of London, have arranged two meetings on Food Science at Home and Overseas, to be held at the Institute of Education, Malet Street, W.C.1, on Saturdays, Nov. 22 and 29. Further particulars may be had from the secretary of the Institute of Rural Life, 84, Eccleston Square, S.W.1.

Princess Tsahai Memorial Hospital

Brigadier G. S. Parkinson, former dean of the London School of Hygiene and Tropical Medicine, will preside at a reception on behalf of this hospital to be held at the Belgian Institute, 6, Belgrave Square, London, S.W.1, from 3 to 6 P.M. on Wednesday, Dec. 3. The council of the hospital wishes to raise further funds to complete payment for equipment already installed in the hospital at Addis Ababa and to make other essential purchases. Donations should be sent to Lord Horder, the hon. treasurer, c/o Messrs. Gould & Prideaux, 88, Bishopsgate, E.C.2.

Register of National Medical Conferences

As a result of requests from medical societies, the British Medical Association has established a central register of national medical conferences. By means of this register, before finally fixing the date of a meeting a society can make certain that no other meeting on the same, or an allied, subject is being held in this country at the same time. The register will be complementary to the similar work in the international field by the Council of International Organisations of Medical Sciences, with which liaison will be maintained. Further details can be obtained from the public relations officer, B.M.A. House, Tavistock Square, London, W.C.1.

Society of Chemical Industry

At a meeting of the crop protection panel of the agriculture group of this society, to be held at the rooms of the Chemical Society, Burlington House, Piccadilly, London, W.1, on Monday, Dec. 15, at 5.30 P.M., Mr. H. E. Harbour of the Cooper Technical Bureau will deliver a lecture on the Chemical Control of Animal Parasites.

Race Problems in the Light of Modern Science

The British Social Biology Council are holding a conference on this subject on Saturday, Dec. 6, at University College, London, W.C.1. The speakers will include Dr. A. F. Mourant and Mr. Kenneth L. Little, PH.D. Tickets (*7s. 6d.*) can be had from the secretary of the council, Tavistock House South, Tavistock Square, W.C.1.

Ophthalmological Society of Egypt

This society will celebrate its 50th anniversary during its annual general meeting, which is to be held in Cairo in February. The speakers will include: Dr. D. C. Cogan (Boston), Prof. Karl Lindner (Vienna), Mr. Keith Lyle (London), Prof. Louis Paufique (Lyons), Prof. R. Thiel (Frankfort), and Prof. P. Thygeson (California). Further information may be had from Dr. Mohammad Khalil, the hon. secretary, 15A, Sherif Pasha Street, Cairo.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 947. The proportion admitted was 92·29%.

From the beginning of next year a new journal is to be published under the titl[illegible] [illegible]matica. *Ortho-pædagogica.* [illegible] [illegible]fice should be addressed to B[illegible] [illegible] Clinic, Leyden-Oegstgeest, H[illegible] [illegible] by S. Karger, of Basle, Switzerland.

Diary of the Week

NOV. 16 TO 22

Monday, 17th

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. *Mr. S. L. Hignett, B.SC.: Prenatal Mortality in Domestic Animals.*

HUNTERIAN SOCIETY
8.30 P.M. (Apothecaries' Hall, Black Friars Lane, E.C.4.) Dr. Ffrangcon Roberts, Mr. Ritchie Calder, Mr. James Griffiths, M.P., Prof. L. P. Garrod: That the Continued Advance in Medicine will Produce more Problems than it Solves.

Tuesday, 18th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. F. J. W. Roughton, F.R.S.: Kinetics of Rapid Chemical and Biological Reactions.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Section of Pathology.* Dr. W. N. Goldsmith, Dr. W. Feldberg, F.R.S., Prof. J. R. Marrack, Dr. J. F. Ackroyd, Dr. R. Lovell: Basis of Allergic Reactions.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. D. O'Neill: Psychiatric Aspect of Skin Disorders.

WEST END HOSPITAL FOR NERVOUS DISEASES, 73, Welbeck Street, W.1
5.30 P.M. Dr. T. Rowland Hill: Neurological demonstration.

EUGENICS SOCIETY
5.30 P.M. (Burlington House, Piccadilly, W.1.) Mr. Kenneth Hutton, D.PHIL.: Intelligence Quotients and Differential Fertility—Some Observations from Winchester College.

SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P.M. (Bolingbroke Hospital, S.W.11.) Dr. R. Ewing Rogers Coronary Disease.

[illegible] [illegible]L SOCIETY
[illegible] [illegible] of Manchester.) Prof. H. E. Sigerist (Yale): [illegible] [illegible]f Hippocrates.

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Section of General Practice.* Dr. M. Mautner: Peptic Ulceration.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5.30 P.M. Mr. L. H. Savin: Surgery of the Ocular Muscles.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. Wilfrid Sheldon: Children in War-time.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. I. W. Whimster: Reticuloses.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Mr. John Howkins: Surgical Treatment of Carcinoma of the Cervix.
3 P.M. Dr. L. Walter: Modern Trends in Radiotherapy of Pelvic Disorders.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. J. Sandrey: Urological Emergencies in General Practice.

Thursday, 20th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Prof. R. H. S. Thompson: Cholinesterases and Anti-cholinesterases.

ROYAL EYE HOSPITAL
5.30 P.M. Miss J. M. Dollar: Differential Diagnosis of Diplopia.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. Denis Williams: Neurological lecture-demonstration.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. D. A. G. Galton, Dr. E. M. Ledlie: Chronic Myeloid Leukæmia.

CHARTER[illegible] [illegible]NIC, 54, Weymouth Street, W.1
5 P.M. [illegible]: Simplicity and Profundity of [illegible] [illegible]cott lecture.)

RESEARCH DEFENCE SOCIETY
5.30 P.M. (University College, Gower Street, W.C.1.) Sir Howard Florey, F.R.S.: Advance of Chemotherapy by Animal Experiment. (Paget lecture.)

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
7.30 P.M. (Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, 3.) Laboratory meeting.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Dr. D. N. Nicholson: Congenital Infantile Hypertrophic Pyloric Stenosis.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. *Joint Meeting with Royal Medico-Chirurgical Society of Glasgow.* (242, St. Vincent Street, Glasgow, C.2.) Mr. John Gillingham, Dr. J. Romanes Davidson, Dr. R. A. Shanks: Epilepsies.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. W. N. Pickles: Epidemiology in Country Practice.

Friday, 21st

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
5.30 P.M. Prof. J. Gough: Pneumoconiosis the World Over.

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Epidemiology and Preventive Medicine.* Dr. Tom Anderson, Dr. Joyce Landsman, Dr. R. L. Mendez, Dr. M. Liker: Respiratory Infections.
8.15 P.M. *Section of Radiology.* Mr. G. W. Blomfield: Experience with Two Million Volt X-ray therapy, and a Preliminary Assessment of Clinical Results. Dr. J. S. Mitchell, F.R.S.: Experience with the 30 MeV Synchrotron as a Radiotherapeutic Instrument.

ROYAL EYE HOSPITAL
4.30 P.M. Mr. A. J. Cameron: Medical Ophthalmology.

FACULTY OF RADIOLOGISTS
4 P.M. *Therapy Section.* (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Dr. D. M. T. Cones: Use of Co^{60} in Treatment of Carcinoma of Bladder. Dr. John D. [illegible] in Diagnosis and Treatment of [illegible] during the Use of P^{32}. Dr. Simon [illegible] of Gliomata with 24 MeV X rays.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. F. R. Bettley: Atopy.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
4.30 P.M. Mr. I. Simson Hall: Conservative Treatment of Cancer of the Larynx.

EMPIRE RHEUMATISM COUNCIL
4.30 P.M. (Arthur Stanley Institute, Middlesex Hospital, Peto Place, Marylebone Road, N.W.1.) Prof. R. E. Tunbridge: Problems in the Diagnosis of the Rheumatic Disorders. (Opening of two-day course.)

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Brigadier J. S. K. Boyd, Dr. T. Parker: Epidemiology of *Salmonella typhi-murium* Infection.

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Royal National Throat, Nose, and Ear Hospital, London.
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LEAMING, H. L., M.R.C.S., D.A.: consultant anæsthetist, hospitals
in the Leicester area.
MACKIE, JOAN, M.B. Edin., M.R.C.O.G.: asst. obstetrician and
gynæcologist (consultant), Bruntsfield and Elsie Inglis hospitals.
MARTIN, K. W., M.S. Lond., F.R.C.S.: resident asst. surgeon,
St. Thomas's Hospital, London.

British Railways (London Midland Region):

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WADDELL, D. L., M.B. Glasg.: asst. M.O.
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LIPOMAS

Sir CECIL WAKELEY
Bt., K.B.E., C.B., LL.D., F.R.C.S.
SENIOR SURGEON, KING'S COLLEGE HOSPITAL AND BELGRAVE HOSPITAL FOR CHILDREN; SURGEON TO THE ROYAL MASONIC HOSPITAL; CONSULTING SURGEON TO THE ROYAL NAVY

PHILIP SOMERVILLE
M.A., M.B. Camb., F.R.C.S.
SURGICAL FIRST ASSISTANT, KING'S COLLEGE HOSPITAL, LONDON

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Although lipomas, especially if superficial, may seem a relatively simple problem, there are still fundamental points about them which remain uncertain—for instance, their origin, their position within the metabolic processes of the body, and their relation to other forms of local and general fat hypertrophy.

ORIGIN OF ADIPOSE TISSUE AND LIPOMA

Adipose tissue has not been studied to the same extent as other tissues. The most comprehensive review in recent times is that of Wells (1940). Briefly, the earliest view held was that adipose tissue was simply connective tissue loaded with fat. According to Wells this view remained unchallenged until Toldt, between 1870 and 1888, contended that adipose tissue was a specific tissue derived from specialised areas or organs and characterised by the formation of highly vascular lobular structures in which a special type of cell exists with the function of storing and giving up fat in accordance with supply and demand. Primitive fat-cells first take up fat in the form of fine droplets; as these enlarge, the cell takes on a mulberry or moruloid appearance, and only with an extreme degree of fat-deposit are large fat-spaces formed, the nucleus remaining central until pushed to one side.

In 1926 Wassermann and his associates placed the origin of adipose tissue on a firmer basis by showing its relation to undifferentiated mesenchymal cells. This relates the formation of adipose tissue and lymph-nodes to the same embryonic elements—i.e., the capillaries and reticulum cells of the adventitia. Supporting this is the observation of the relationship of fat and lymphoid tissue in lymph-glands and thymus, and the occasional occurrence of extramedullary hæmopoiesis in adipose tissues. In this way pre-adipose tissue is created which on maturity forms adult fat.

A great deal of investigation has been carried out on so-called glandular adipose tissue—i.e., fat composed of cells of moruloid appearance, similar to primitive fat-cells. It is not confined to embryonic life but is found in a variety of places—e.g., the adipose tissues of animals such as the hedgehog and dormouse in which it constitutes the hibernating gland. It is found also in parts of the human body, mainly in fœtal life, particularly the subcutaneous tissues of the cervicodorsal and interscapular regions as well as in the perirenal tissues of infants. These areas have been studied by Hatai (1902), Bonnot (1908), and Shattock (1909). Bonnot made a detailed study of adult and embryonic tissues and traced the origin of the glandular fat from the region of the primitive jugular vein. In man the interscapular gland is a light-brown, lobulated, and irregular vascular mass situated on the shoulder and side of the neck between the superior borders of the scapula and clavicle.

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The occurrence of fatty tumours in sites where fat does not normally exist—e.g., the brain, the kidney, and the periosteum—has been ascribed to misplacement of true or pre-adipose tissue. Ehni and Love (1945), on the other hand, in their review of intraspinal lipomas ascribed their origin to a failure of normal control over the formation of fat from normally present perivascular mesenchymal cells in the pia. These cells are capable of forming fat.

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The relation of the fat contained in a lipoma to that of the body metabolism has long been a matter of great interest, but the solution is still unknown. Wells (1912) concluded that there was no detectable chemical difference from normal fat. There appears to be no anatomical reason for the apparent isolation so well marked in the paradoxical condition of a growing fatty tumour, such as liposarcoma, and the adjacent wasting body. Wells puts forward the ingenious idea that the processes of laying down and giving up fat depend on cell differentiation and are not merely reversible physical or chemical processes.

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Society of Chemical Industry

At a meeting of the crop protection panel of the agriculture group of this society, to be held at the rooms of the Chemical Society, Burlington House, Piccadilly, London, W.1, on Monday, Dec. 15, at 5.30 P.M., Mr. H. E. Harbour of the Cooper Technical Bureau will deliver a lecture on the Chemical Control of Animal Parasites.

Race Problems in the Light of Modern Science

The British Social Biology Council are holding a conference on this subject on Saturday, Dec. 6, at University College, London, W.C.1. The speakers will include Dr. A. F. Mourant and Mr. Kenneth L. Little, PH.D. Tickets (*7s. 6d.*) can be had from the secretary of the council, Tavistock House South, Tavistock Square, W.C.1.

Ophthalmological Society of Egypt

This society will celebrate its 50th anniversary during its annual general meeting, which is to be held in Cairo in February. The speakers will include: Dr. D. C. Cogan (Boston), Prof. Karl Lindner (Vienna), Mr. Keith Lyle (London), Prof. Louis Paufique (Lyons), Prof. R. Thiel (Frankfort), and Prof. P. Thygeson (California). Further information may be had from Dr. Mohammad Khalil, the hon. secretary, 15A, Sherif Pasha Street, Cairo.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 947. The proportion admitted was 92·29%.

From the beginning of next year a new journal is to be published under the titl [illegible] *Ortho- pædagogica.* [illegible] be addressed to B [illegible] : Jen- Oegstgeest, H [illegible] ublished by S. Karger, of Basle, Switzerland.

Diary of the Week

NOV. 16 TO 22

Monday, 17th

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Mr. S. L. Hignett, B.SC.: Prenatal Mortality in Domestic Animals.

HUNTERIAN SOCIETY
8.30 P.M. (Apothecaries' Hall, Black Friars Lane, E.C.4.) Dr. Ffrangcon Roberts, Mr. Ritchie Calder, Mr. James Griffiths, M.P., Prof. L. P. Garrod: That the Continued Advance in Medicine will Produce more Problems than it Solves.

Tuesday, 18th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. F. J. W. Roughton, F.R.S.: Kinetics of Rapid Chemical and Biological Reactions.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Section of Pathology.* Dr. W. N. Goldsmith, Dr. W. Feldberg, F.R.S., Prof. J. R. Marrack, Dr. J. F. Ackroyd, Dr. R. Lovell: Basis of Allergic Reactions.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. D. O'Neill: Psychiatric Aspect of Skin Disorders.

WEST END HOSPITAL FOR NERVOUS DISEASES, 73, Welbeck Street, W.1
5.30 P.M. Dr. T. Rowland Hill: Neurological demonstration.

EUGENICS SOCIETY
5.30 P.M. (Burlington House, Piccadilly, W.1.) Mr. Kenneth Hutton, D.PHIL.: Intelligence Quotients and Differential Fertility—Some Observations from Winchester College.

SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P.M. (Bolingbroke Hospital, S.W.11.) Dr. R. Ewing Rogers Coronary Disease.

MANCHESTER MEDICAL SOCIETY
4 P.M. (University of Manchester.) Prof. H. E. Sigerist (Yale): The World of Hippocrates.

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Section of General Practice.* Dr. M. Mautner: Peptic Ulceration.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5.30 P.M. Mr. L. H. Savin: Surgery of the Ocular Muscles.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. Wilfrid Sheldon: Children in War-time.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. I. W. Whimster: Reticuloses.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Mr. John Howkins: Surgical Treatment of Carcinoma of the Cervix.
3 P.M. Dr. L. Walter: Modern Trends in Radiotherapy of Pelvic Disorders.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. J. Sandrey: Urological Emergencies in General Practice.

Thursday, 20th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Prof. R. H. S. Thompson: Cholinesterases a Anti-cholinesterases.

ROYAL EYE HOSPITAL
5.30 P.M. Miss J. M. Dollar: Differential Diagnosis of Dipl

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. Denis Williams: Neurological lecture-demonstratio

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. D. A. G. Galton, Dr. E. M. Leddie: Chronic Myel Leukæmia.

CHARTER[illegible] 54, Weymouth Street, W.1
5 P.M. [illegible] implicity and Profundity o [illegible] lecture.)

RESEARCH DEFENCE SOCIETY
5.30 P.M. (University College, Gower Street, W.C.1.) Sir Howa Florey, F.R.S.: Advance of Chemotherapy by Anim Experiment. (Paget lecture.)

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
7.30 P.M. (Liverpool School of Tropical Medicine, Pembro Place, Liverpool, 3.) Laboratory meeting.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh Dr. D. N. Nicholson: Congenital Infantile Hypertrop Pyloric Stenosis.

MEDICO-CHIRURGICAL SOCIETY O[illegible]
8.30 P.M. *Joint Meeting with* [illegible] *Society o Glasgow.* (242, St. Vi [illegible] C.2.) Mr. John Gillingham, Dr. J. Romanes Davidson, Dr. R. A. Shanks: Epilepsies.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. W. N. Pickles: Epidemiology in Country Practice.

Friday, 21st

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
5.30 P.M. Prof. J. Gough: Pneumoconiosis the World Over.

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Sect* [illegible] *Preventive Medicine.* Dr. Tom [illegible] ndsman, Dr. R. L. Mendez. [illegible] Infections.
8.15 P.M. *Secti* [illegible] Blomfield: Experience wit [illegible] therapy, and a Preliminary [illegible] s. Dr. J. S. Mitchell, F.R.S.: Experience with the 30 MeV Synchrotron as a Radiotherapeutic Instrument.

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LIPOMAS

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M.A., M.B. Camb., F.R.C.S.
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In addition to the embryonic theory described above, both trauma and heredity have been suggested as factors in ætiology. Trauma does not warrant further inquiry, since it is mentioned but infrequently in the clinical history of patients: but published examples of heredity are not difficult to find, running in a few instances through more than two generations. In the present series a female, aged 35, with multiple lipomas on the arms, gave a family history of lipoma in mother and grandfather.

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CLASSIFICATION

The number of cases collected for study in this series amounts to 170.

Both sexes are liable to develop lipomas, but with few exceptions the published records indicate a greater predisposition for females (in the present series 2 : 1). Geschickter (1934), in a series of 390 from the Johns Hopkins Hospital, gives the ratio as 3 : 2, whereas in the figures of Adair et al. (1932) 73% were females. The reason for this sex tendency has been variously stated to be either cosmetic or a greater tendency of females to develop abnormalities of adipose tissue possibly hormonal in origin.

Lipomas are seen at all ages but especially in middle life; only 10% occur in children according to Geschickter (1934). Some seem to be congenital, many examples having been reported. Some of these show progressive growth and may attain a large size indicating their neoplastic nature—e.g., a tumour of five years' duration on the back of the thigh and measuring 4 × 3 in. in a boy aged 13, in the present series. Others show heterotopic tissue or are mingled with normal structures of the affected part. Probably many of these are not true tumours but hamartomas—superfluous tumour-like masses of improperly blended tissue comparable to most angiomas (Willis 1948). From table I it can be seen that three-quarters of the present series occurred between the ages of 30 and 50, although allowance must be made for the time of tumour growth. This applies not only to the whole series but also to each sex after separation. There is no indication that they tend to appear at times of hormonal imbalance such as puberty and the menopause.

TABLE I—AGE-INCIDENCE OF LIPOMAS

Age (yr.)	Males	Females
0–9	1	3
10–19	2	2
20–29	0	14
30–39	9	25
40–49	14	28
50–59	20	31
60–69	8	11
70–79	0	1
80–89	1	0
Total	55	115

The duration of tumour growth is variable, but it is not uncommon to hear of a period of growth followed by arrest for many years. In the present series it varied from a few months to forty years.

TABLE II—SITES OF 182 LIPOMAS IN 170 PATIENTS (EXCLUDING MULTIPLE OF FOREARMS)

Site	No.	Site	No.
Shoulders	33	Forearm	8
Back	28	Abdominal wall	7
Thigh	23	Chest wall	6
Neck	16	Leg	6
Head	14	Visceral	4
Buttock	10	Other sites	9
Arm	9		
Axilla	9	Total	18

In their discussion on lipomas Adair et al. (1932) grouped their cases into four clinicopathological types: (1) single, (2) multiple, (3) congenital diffuse lipomatosis, and (4) degenerate lipomas. This was a classification of convenience, as they pointed out. The distinction of the first two groups remains unproved, and the fourth is a subgroup rather than a separate entity. Geschickter also used a clinicopathological classification for his series of lipoid tumours, dividing them into three groups—lipoma, recurrent lipoma, and liposarcoma. The merits and faults of these classifications will not be pursued, but for practical purposes ordinary lipomas may conveniently be classified on an anatomical basis according to the tissue plane or organ in which they lie. The following classification is suggested:

- (1) *Subcutaneous:* Subcutaneous
  - Breast
- (2) *Interstitial:* Subfascial
  - Intramuscular
  - Intermuscular
  - Subsynovial
  - Parosteal
  - Myelogenous
- (3) *Visceral:* Respiratory, Gastro-intestinal, Genito-urinary } Submucous, Subserous
- (4) *Thoracic:* Mediastinal
  - Subpleural
- (5) *Abdominal:* Retroperitoneal
  - Perirenal
  - Mesenteric
  - Broad ligament
- (6) *Nervous:* Cerebral
  - Spinal } Intradural (Intramedullary, Extramedullary, Radicular); Extradural (Congenital, Acquired)
  - (Peripheral Multiple Subcutaneous)

CLINICAL FEATURES

The commonest site is the subcutaneous tissue (figs. 1 and 2). In this situation the classical signs can easily be elicited of a soft, or elastic, lobulated swelling exhibiting translucency and in many cases a fine attachment to the skin. Because fat is a good insulator, the surface of many lipomas, particularly the larger variety, feels cooler than a symmetrical part on the other side of the body. For the most part symptoms are few and pain is inconspicuous except in a minority. The relation to nerves has been previously mentioned, but the reason for the pain is uncertain. Both congestion of the tumour and interstitial neuritis have been suggested but without proof. Alternatively both pain and lipoma may be secondary to some more distant nervous defect.

Comparison of the sites of subcutaneous lipomas in this series with those tabled (table II) by Geschickter (1934) shows a striking similarity. In both series the shoulder, the back, the back of the neck, and the thighs are the commonest sites. A possible reason for this has already been discussed.

Pedunculation is an interesting feature of a few lipomas of long standing. In the present series there were only 3 such cases,

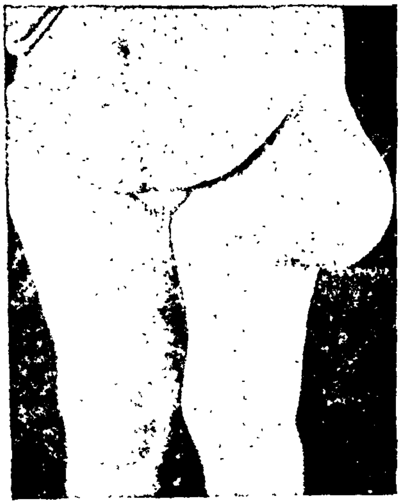

Fig. 1—Subcutaneous lipoma on upper and outer side of left thigh in a woman aged 69.

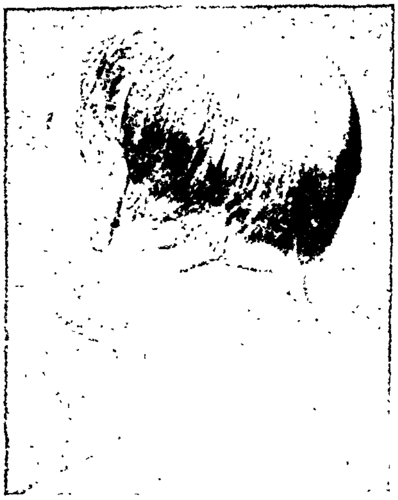

Fig. 2—Subcutaneous lipoma on neck of a man aged 61.

situated on the left arm, left buttock (fig. 3), and right scapula. These are fairly representative sites at which pedunculation occurs, possibly because of the looseness of the subcutaneous tissue and skin, and to the duration of the growth. In these 3 cases the duration was twenty, thirty, and sixteen years. It has been stated that a pedunculated lipoma never grows to a large size (Bland-Sutton 1906), because of its tenuous blood-supply. Though this may be generally true, there are exceptions. The third case of pedunculation in the present series weighed 4 lb. An unusually large lipoma, weighing 24 lb., was described by Duggan (1944); this had started in the neck twenty-six years previously and reached to the waist with a pedicle of skin and hypertrophied platysma as thick as the patient's arm. The patient reported for treatment owing to hæmorrhage from a congested vein at the fundus of the tumour. Secondary changes of this sort are characteristic. Owing to trauma to the surface associated with a stagnating blood-supply, ulceration is liable to occur (fig. 3). As the result of torsion of the pedicle a myxomatous appearance may develop in the tumour, and on rare occasions not only does growth cease but atrophy may occur.

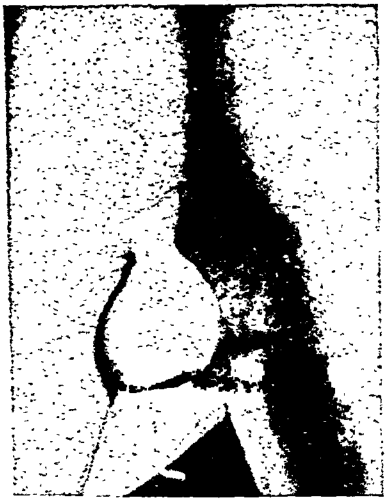
Fig. 3—Pedunculated lipoma of the buttock of a man aged 42. Ulceration has begun on under surface of lipoma.

Multiplicity of lipomas has been commented on already in connection with their possible relationship to subcutaneous nerves. Multiplicity is not uncommon, occurring in 6 cases in the present series, 4 females and 2 males with a total of 18 lipomas, 5 being the most found in one patient (fig. 4). There may be good grounds for placing multiple lipomas in a separate group, especially those cases in which many hundreds are present appearing even in places where fat is not normally found such as the lung and liver, suggesting a dyscrasia of fatty tissues (Virchow). But for those with only a few it seems equally plausible that the same factors are at work which cause a single lipoma to form. A symmetrical distribution was noted in 2 cases, both hips in one, and both deltoid regions in the other.

An important feature of lipomas is recurrence. Whereas for many types of tumour this may be of serious import, for most lipomas this does not apply. Undoubtedly some liposarcomas, as Stout (1944) points out, develop from a pre-existing lipoma—for example, the case he cites of a liposarcoma surrounded by a simple retroperitoneal lipoma. Probably, however, this change is rare. In the present series 4 cases gave a history of removal of a lipoma from a similar site at a previous date. It has not been possible to compare the histology, but on clinical grounds there seems little reason to suppose that a frankly malignant change had taken place. The dates of the previous operations were stated to be fifteen, seventeen, four, and two years previously. Recurrence is most probably due either to incomplete removal of all lobules of the original lipoma or to the persistence of local factors conducent to tumour formation from primitive cells with potential for fat formation. All recurrent tumours should, however, be searched carefully for areas of more primitive cells and more rapid growth.

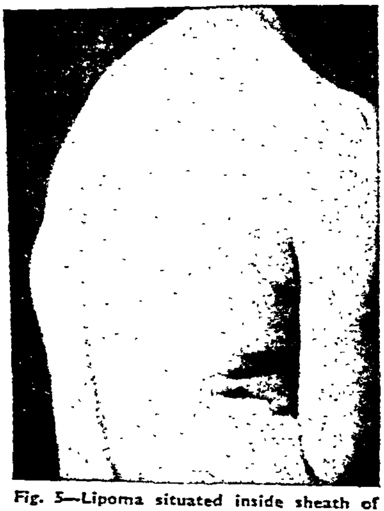
Fig. 5—Lipoma situated inside sheath of sacrospinalis muscle in a woman aged 40.

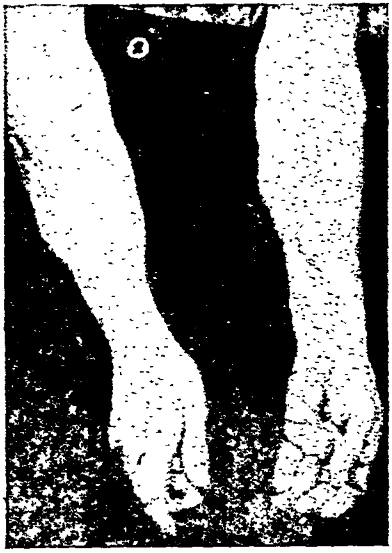
Fig. 4—Multiple lipomas on forearms of a woman aged 52.

In his classification of lipomas, Geschickter (1934) referred to recurrent lipomas as a group, calling them fibrolipomas and embryonic. Myxomatous and xanthomatous appearance may, he stated, be a sign of incomplete differentiation with embryonic cells capable of tumour formation. The term fibrolipoma seems inappropriate since it refers to a mixture of tissues often found in well-differentiated tumours showing no signs of recurrence.

Intermuscular and intramuscular lipomas occur not infrequently (8 in the present series) and do not differ in structure or appearance from their subcutaneous counterparts. They are, however, liable to cause difficulty in diagnosis, and for this reason may require investigation. Characteristically they are symptomless, causing no

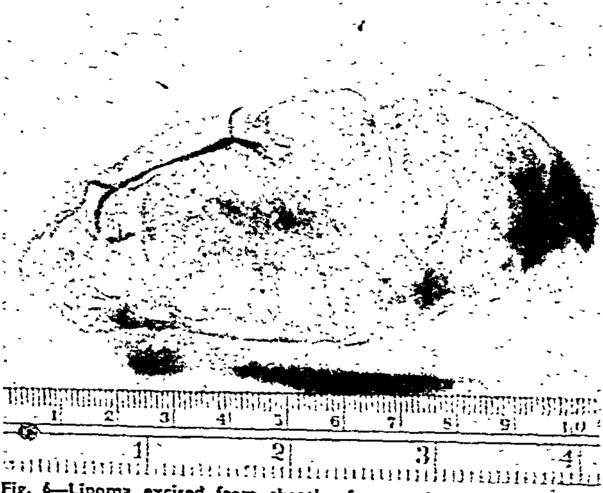

Fig. 6—Lipoma excised from sheath of sacrospinalis muscle (same lipoma as in fig. 5).

interference with function, and forming a soft lump which becomes harder with contraction of the muscle. Lobulation is impossible to define, but a characteristic shape may be produced by the muscle in which they lie—e.g., a spindle shape when the lipoma lies inside the erector spinæ or its sheath (figs. 5 and 6). A cortical depression may be formed by those tumours which are parosteal.

Subsynovial lipomas are less common, arising from the layer of fat which lies external to the joints. Lipoma arborescens, a term coined by Muller (quoted by Bland-Sutton 1906) and said to refer to a true lipoma, has in reality no connection and is associated with chronic and tuberculous arthritis.

It is in relation to the above types of tumour that radiology may prove of value in reaching a correct diagnosis. The basis of soft-tissue radiography depends on the photo-absorption coefficient of the soft tissue concerned. Air has a coefficient of 0, which in relation to that of soft tissue of the body is extremely low. Next to air comes fat. The radiological appearance of an intermuscular lipoma is that of a sharply demarcated semitranslucent lobulated tumour. The lobulated appearance is caused by the fibrous septa. Other tumours with a relatively large content of fat—e.g., dermoid cyst—may produce a similar picture.

Visceral lipomas, although rare, are sufficiently well known to require no introduction. They occur in the gastro-intestinal, respiratory, and genito-urinary tracts, but the first is by far the commonest site. Palazzo (1949) collected 36 cases of lipoma in the gastro-intestinal tract from the files of the Massachusetts General Hospital since 1900. These, as in other series, showed the general trend of increased frequency as the gut is descended: stomach 6, small intestine 16, colon 20. They may be classified as submucous and subserous, with a strong preponderance of the former, both occurring as either sessile or pedunculated tumours. Many intestinal lipomas are symptomless, especially subserous ones, but the 4 cases in the present series will serve well to illustrate the main ways in which they present.

Case 1.—A man, aged 64, who had always enjoyed good health, passed a little bright-red blood per rectum, and a week later some more blood with a mass of fatty tissue enclosed in a capsule.

The spontaneous passage of a submucous lipoma has not often been reported, but its cause is not difficult to understand. Dewis (quoted by Rankin 1926), in a series of 44 cases, included 9 of spontaneous expulsion. As ubserous lipoma may be freed into the peritoneal cavity.

Case 2.—A man, aged 53, was operated on because of a filling defect in the sigmoid colon discovered by radiography after a barium enema during investigation for abdominal pain. The bowel was resected, and the operation specimen contained a lipoma.

The problem of distinguishing a benign from a malignant tumour of the colon at laparotomy or on radiology has been commented on many times. Resection is often the wisest course; but, if accurate diagnosis is possible, simple excision of the lipoma is permissible.

Case 3.—A submucous lipoma was found during an operation for establishing a colostomy in a woman aged 60. It had caused no symptoms.

Case 4.—A woman, aged 49, complained of colicky abdominal pain in the right iliac fossa for two years. At operation the terminal ileum was found to be intussuscepting through the ileocæcal valve, but true intussusception was prevented by a submucous lipoma.

The interior of the thorax is an uncommon site for a lipoma, only about 50 cases having been reported. In this site lipomas give rise to few symptoms apart from those due to pressure on neighbouring structures. They arise from the extrapleural fat either in the mediastinum or subpleurally. Heuer and Andrus (1932), in a comprehensive report on this type, suggested classification into three groups on an anatomical basis: (1) hourglass tumours situated partly intrathoracically and partly subcutaneously; (2) intrathoracic but presenting in the neck; and (3) entirely intrathoracic. The peculiar distribution of the first group has led to the suggestion that they are congenital. Kittle et al. (1950) have described an intrathoracic lipoma of unusual type and histologically resembling glandular adipose tissue.

In the abdomen the retroperitoneal tissues are well known as a site for the formation of lipoma, interest lying in the size and extent to which they may grow as well as the difficulty in diagnosis and the possibility of sarcomatous change. Histologically they are tumours containing a variable mixture of fat and fibrous tissues, and myxomatous changes probably foreshadow not uncommon sarcomatous degeneration and recurrence after excision.

Ockuly and Douglass (1937), who also reviewed this type, record one in an infant only 15 days old. These authors consider that 35% of retroperitoneal lipomas are perirenal in origin, and bilateral examples are not unknown. Perirenal lipomas seem to be an anatomical variant of the retroperitoneal group arising from the renal capsule or the perirenal fat. They surround the kidney and occasionally compress its blood-supply to the point of atrophy. Retroperitoneal lipomas often have an intimate relation to important structures on the posterior abdominal wall and extend forwards into the mesentery of the small intestine. They may rarely occur primarily in this latter situation, as described by S lman and Bender (1948); who discussed the preoperative diagnosis by radiography.

The symptoms are usually those of pressure and mild gastro-intestinal disturbance, but removal by operation is warranted since without it the growth of these tumours leads slowly to death.

The origin of lipomas in the broad ligament, normally free from adipose tissue, has been ascribed to metaplasia of connective tissue or to extension from the retroperitoneal tissues. From the previous discussion on the origin of adipose tissue the former may be discarded. An alternative view, similar to that for some neural lipomas, is the presence of undifferentiated perivascular cells with fat-forming potentialities. This is an uncommon site; 19 cases were collected from the literature and 1 added by Lang and Bland (1940). They were bilateral in a fifth of the reported cases and likely to cause difficulty in diagnosis.

Intracranial or intraspinal masses of adipose tissue are relatively rare and may be separated into several different groups. Undoubtedly they do not all represent tumour formations in the same way as a lipoma of the subcutaneous tissues. An example of this is the collection of adipose tissue found in the lumbosacral region, continuous with the subcutaneous tissues of the gluteal region and penetrating the dura through a bony defect. They may or may not be associated with a meningocele and represent a congenital error in development and closure of the neural tube with overabundant growth of adipose tissue and its inclusion.

Extradural lipomas occurring later in life are not congenital. They have no characteristic segmental distribution and may be associated with obesity or with multiple lipomas. They arise from the extradural fat, a constant layer with a greater vascularity than the subcutaneous tissues. This increase in vessels has its counterpart in many lipomas in this situation which histologically appear as hæmangiolipomas. Other histological variants may also be found.

Intradural lipomas have always been of great interest because of their occurrence in a situation normally regarded as being free from fat. Ehni and Love (1945) collected 2 cases in a comprehensive review of spinal lipomas, and List et al. (1946) collected 30 cases affecting the corpus callosum from about 100 published cases of lipoma of the brain. This latter site is one of the commonest for intracranial lipomas, often being associated with local agenesis of the corpus callosum. A good account of the theories of origin is to be found in the above two papers. The site of origin of intradural lipomas requires consideration. Most if not all are extramedullary. According to Ehni and Love all, with one possible exception, lay in this position. The superficial resemblance to an intramedullary tumour may, however, be striking. A further subdivision, suggested by Cornil and Mosinger (1934) and discussed by Ehni and Love, is the rare tumour associated with nerve-roots and the cauda equina.

In conclusion no discussion on lipomas or their classification would be complete without reference to the wider concept of natural phenomena and pathological disturbances of adipose tissue—conditions which are not widely separated from lipomas or each other.

The naturally occurring phenomena are steatopygy and the sucking-pad of infants. Steatopygy, which has been discussed at length by Shattock (1909), is seen most notably as the prominent buttocks of the Bushmen and the Hottentots—prominent masses of unencapsulated fat. The sucking-pad, or corpus adiposum buccæ, lying isolated in the cheek has been regarded by some as a congenital lipoma. Its function is stated to be that of preventing the cheeks from falling inwards. Like lipomas it remains isolated from the body processes during wasting and becomes prominent in the marasmic infant. Lipomas of the sucking-pad have been reported, and Cameron (1921) collected 15 cases from the literature and added 1 of his own.

Much more has been written about the many types of acquired disturbance of less definite neoplastic nature. Dercum (1892) described adiposis dolorosa, with which his name is associated: painful masses of fat associated with a tendency to obesity, closely related to generalised obesity and to symmetrical diffuse lipomatosis. This latter condition is best known in the form of Madelung's (1888) neck, and although unencapsulated as a whole, it may contain masses of fat closely resembling lipomas in its midst.

Fig. 7 shows a man, aged 46, who four years previously had had removed from his abdominal wall a lipoma which had been growing for some time. Shortly afterwards he noticed a swelling on the right side of his neck; this was followed by another swelling on the left side. These swellings slowly increased until the condition illustrated in fig. 7 was reached. The tumours were removed in four stages.

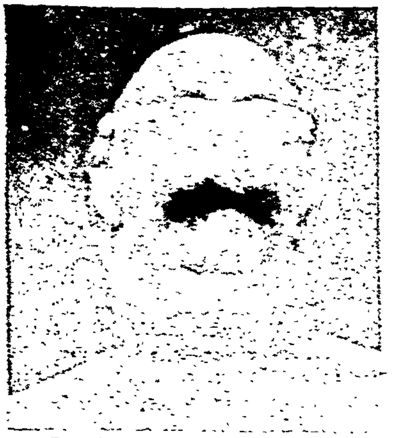

Fig. 7—Diffuse lipoma of neck in a man aged 46.

Recurrence is not usual in this condition except sometimes round the periphery. This condition is not confined to the neck but may also involve the axillæ and upper extremities. Unilateral or asymmetrical lipomatosis of a limb may also occur, as depicted by Adair et al. (1932), associated with hypertrophy of neighbouring tissues such as bone, a feature advanced in support of their view of the relationship of lipoma and nerves on an analogy with neurofibromatosis.

Lyon (1910) studied these conditions comprehensively, and not unnaturally suggested a basic common feature for the whole group. Ewing (1940) thought that the relation of lipoma to other forms of fat hypertrophy may be similar to that of fibroma to fibromatosis. Glandular disturbances, particularly those of the pituitary, thyroid, and genital glands, have often been blamed, and it is well known that the injection of insulin for diabetes may have a profound but diverse effect on the local subcutaneous tissues, producing either atrophy or hypertrophy, a situation reminiscent of that as yet unsolved disease progressive lipodystrophy.

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GENERAL ANÆSTHESIA FOR TONSILLECTOMY BY DISSECTION IN CHILDREN*

A TECHNIQUE BASED ON INTRAVENOUS THIOPENTONE

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UNNECESSARY suffering is still being meted out unthinkingly to thousands of children who have their tonsils and adenoids removed. It seems to be assumed that under the age of about 10 a child has no feelings, or none that are important compared with those of adults. Actually, of course, the reverse is true, children being more sensitive and having long memories for emotional experiences.

I believe that today, apart from the casualty department, the crudest and most distasteful forms of induction of anæsthesia are used at the tonsillectomy session. Administration of the anæsthetic is usually delegated to a junior because the seniors consider their own skill to be better used in conjunction with major surgery. My purpose here is to plead for a higher standard in the administration of anæsthetics for tonsillectomy, and more care and respect for these patients.

REQUIREMENTS

The requirements are a quick smooth induction, as pleasant as possible for all concerned: relaxation of the jaw muscles at the beginning of the operation for insertion of a gag; suppression of the pharyngeal and laryngeal reflexes during the operation; and a rapid return of these reflexes at the end of the operation. Recovery again should be as pleasant as possible for all concerned.

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* Based on a paper read to the Liverpool Society of Anæsthetists on May 23, 1952.

Now let us consider the agents and techniques in present use, and see how they meet these requirements.

PREMEDICATION

The use of atropine is advisable in all cases, but there are two opposing schools of thought on the use of hypnotic or narcotic drugs. Some hold that a child should be sound asleep before the induction of anæsthesia and have no recollection of the event. Others think this unnecessary in most cases; that, if the child is properly looked after by the nurses, it does not matter if he is awake; and that all hypnotics have disadvantages which outweigh their advantages.

Hypnotics.—The hypnotics in general use for these children are pentobarbitone ('Nembutal') and quinalbarbitone ('Seconal'). Both are usually given by mouth because rectal administration has further disadvantages. There may be difficulty in persuading the child to take the drug, in whatever form it is offered. Moreover, absorption of the drug from the stomach is notoriously unreliable in children. Although induction of anæsthesia may be facilitated, the production of the required depth of anæsthesia may be delayed by respiratory depression, and the return of reflexes at the end of the operation may be delayed. There is occasionally extreme restlessness in the immediate postoperative period, during which the child is difficult to control, makes a great deal of noise, and upsets all the other children, some of whom may be waiting to go to the theatre. This can be remedied by the injection of an analgesic such as 'Nepenthe,' but involves further nursing care.

Narcotics.—Some children may be frightened of coming into hospital for an operation. As the time approaches for his turn to go to the theatre, the child may become terrified. He is then very difficult to anæsthetise by any inhalational method, and induction becomes a very crude procedure because it has to be forced on the unwilling child. It is not always possible to tell in advance which child will react in this way. The psychological effect on such a child cannot be other than harmful, and the child's future relationship with doctors will hardly be improved.

Thiopentone has been used since 1941 as a basal anæsthetic (narcotic) given rectally in a dosage of 15–20 mg. per lb. body-weight. In this dosage its action starts rapidly, the child falling into a deep sleep in about ten minutes and remaining thus for an hour or so. During this time the jaw muscles are well relaxed, the jaw may need supporting, and the child requires close supervision. Dosage and timing must be accurately assessed. This technique is not suitable for routine tonsillectomy sessions, although it is very valuable on occasion.

INDUCTION OF ANÆSTHESIA

Ethyl chloride on an open mask has a potent smell, even if disguised by eau-de-cologne, and many children dislike both it and the mask. If a child is asleep after having been given a hypnotic drug he is likely to be wakened by the vapour of ethyl chloride, when he may be more difficult to control than a child who has received no hypnotic. Ethyl chloride has toxic properties, but fatalities appear to be rare; the jaw muscles are not always relaxed; vomiting is common on recovery.

Vinyl ether ('Vinesthene'), although not possessing the toxic properties of ethyl chloride, has an unpleasant smell, and the difficulty of persuading the child to inhale the vapour arises again. If it is given on an open mask, the cost is high. If it is given in a closed inhaler, the child suffers the experience of having a mask firmly applied to his face while conscious. Both ethyl chloride and vinyl ether are better avoided in coöperative children of this age, or children who are already asleep, though they can be very useful for suppressing noisy uncoöperative children.

Nitrous oxide has the advantage that, to all intents and purposes, it is odourless and lacks pungency. If a child is asleep, the gas may be blown over his face until he is unconscious, with very little likelihood of waking him. It is probably the most useful drug for induction in children who are already asleep. Its action, however, is very weak, and the oxygen intake must necessarily be somewhat restricted during induction. In an uncoöperative child induction may be prolonged and will often be followed by a short period of anoxia.

MAINTENANCE OF ANÆSTHESIA

Anæsthesia during tonsillectomy is usually maintained with diethyl ether, often supplemented by trichlorethylene ('Trilene'). The use of trilene during the first half of the anæsthesia seems to produce moderate post-operative analgesia and to decrease the incidence of post-operative restlessness after tonsillectomy. This matter is being investigated. Trilene is turned off half-way through the operation because it delays the return of the laryngeal reflex for a few minutes.

POSSIBLE OBJECTIONS TO INTRAVENOUS THIOPENTONE

Veins.—The difficulty of finding a suitable vein may be fairly common in children under the age of 5; but even at this age a surprisingly large number of children have accessible veins—probably more than half of them.

Needles.—Children are said to dislike needles. This difficulty can largely be overcome by starting each session with two brand-new needles size 16–18. Only about 10% of children have any appreciable objection to the use of these needles, if properly handled; and if the alternative is a face-mask many of them will prefer the needle.

Sensitivity to Thiopentone.—A child's respiratory centre has been said to be very sensitive to thiopentone. I have found that, provided thiopentone is given at a proportionately slower rate and in proportionately smaller dosage, the effect is very little different from that in the adult. The smaller blood volume in a child should be borne in mind, with consequently less dilution of thiopentone on its passage to the brain. I am not alone in believing that thiopentone can safely be given to children; for instance, Stephen (1952), in the U.S.A., writes:

> "There is no anatomic, physiologic, or biochemical contra-indication to the employment of barbiturates or curare in children, provided that the anaesthetist is sufficiently trained to take the same precautions as he would in an adult."

Recovery of Reflexes.—It might be thought that there is a danger of delay in recovery of reflexes at the end of the operation, but this is not so (see below).

TECHNIQUE WITH NITROUS OXIDE, TRILENE, AND ETHER

Before describing the technique when thiopentone is used, I will describe the technique when induction is by nitrous oxide, followed by trilene and ether. The method of administration of the inhalation anæsthetic following a thiopentone induction differs only slightly from the one now to be described.

Premedication in every case is an injection of atropine gr. $^1/_{100}$.

Induction takes place on the operating-table, because there is no anæsthetic room. The child is carefully laid on the table with as little disturbance as possible. A high flow of nitrous oxide is blown over the child's face from a Boyle's apparatus, using the by-pass. After about fifteen breaths, or one minute, the child loses consciousness; the face-mask is then gently placed over the face, and the inhaled mixture is 9 litres (90%) of nitrous oxide and 1 litre (10%) of oxygen. Trilene is immediately added in a concentration of about $^1/_4$% (lever at top of second division of Boyle's bottle). Ether is next cautiously added, with an attempt to prevent any coughing or straining, because this increases operative bleeding. When the child is coming under the influence of the ether, the oxygen is increased to 25% (nitrous oxide 6 litres, oxygen 2 litres). After an average of four minutes from the start of induction the child is settled in upper plane 2, the gases now passing over the surface of the ether (lever full on)—a concentration of about 25%. The child's head is raised to allow towels to be placed, no respiratory obstruction being allowed. The surgeon inserts a Boyle-Davies gag, and the same gases are insufflated through the gag. Only three or four breaths of air are allowed during insertion of the gag.

Discontinuance.—When the first tonsil has been removed, the trilene is turned off. When the second tonsil has been removed, the ether is turned off. When the adenoids have been curetted, the nitrous oxide is turned off. Oxygen alone is now being given, while the pharynx is cleared by suction. After a minute or two the bleeding has stopped and the pharyngeal reflex is active.

Postoperatively the child is placed in the semi-prone position on a trolley, with an airway in place if tolerated, and returns to bed. After half an hour or so he sits up in bed to minimise postoperative oozing from the tonsillar bed.

Carbon Dioxide.—A flow of 100 ml. per minute of carbon dioxide may very usefully be added to the inhaled mixture throughout—concentration 1–2%. This hastens induction, prevents hypocapnia during insufflation, and hastens recovery. Bleeding during the operation, however, may be increased.

TECHNIQUE WITH THIOPENTONE

I first thought of using intravenous thiopentone as a combined agent for basal anæsthesia and induction of anæsthesia in these children about two years ago. I had long been using small doses of thiopentone as a prelude to nasal gas-oxygen in adults for dental extraction, after the manner described by Macintosh and Bannister (1950), and it occurred to me that this technique could be applied to children for tonsillectomy, nitrous oxide being supplemented by trilene and ether. I have found no published account of similar techniques, but they have doubtless been used.

Induction.—The dosage of thiopentone is 25 mg.—i.e., 0·5 ml. of the usual 5% solution—per year of age. This is injected at the rate of 1 ml. every five seconds until the child is unconscious, or until the whole dose has been given, usually the latter. If it is injected more quickly, apnœa is likely to follow for fifteen to forty-five seconds; if more slowly, the child may not lose consciousness. No apology is made for basing the dose on age, or for using a 5% solution, because the results are satisfactory. A $2^1/_2$% solution has to be injected at twice the rate, and its effects are almost identical with those of a 5% solution.

When the child is unconscious, a face-mask is immediately placed over his face, and nitrous oxide (85–90% with oxygen), followed by trilene and later by ether, is administered very much the same as already described. Here is the time-table in a typical case, a boy aged 6 years:

Min.	*Sec.*	
0	0	Venepuncture.
0	15	Thiopentone injected.
0	30	Nitrous oxide 6 litres per min., oxygen 1 litre per min., trilene $^1/_4$ on.
1	0	Ether added, concentration slowly increased.
2	0	Ether full on, over surface. Oxygen increased to 2 litres per min.
4	0	Towels applied; gag inserted; gases insufflated through gag.
6	0	First tonsil removed; trilene turned off.
8	0	Second tonsil removed; ether turned off.
9	0	Adenoids curetted; nitrous oxide turned off.
10	0	Pharyngeal toilet.
11	0	Pharyngeal reflex returns; child placed on trolley in semi-prone position.

This dosage of thiopentone produces one or two minutes' anæsthesia, followed by about ten minutes' basal narcosis and rapid recovery. There is no delay in the return of reflexes. In fact, in this series, the average time from induction of anæsthesia to the return of the pharyngeal reflex was slightly shorter than when no thiopentone was given. The average time for those receiving thiopentone was 11·1 minutes; for those receiving nitrous oxide induction it was 11·4 minutes. This is presumably because the children receiving thiopentone required less volatile anæsthetic. These figures are given only to show that recovery time was not prolonged.

The explanation of the rapid recovery emerges if we compare the dosage of barbiturate given in this technique with that given by other methods. A child aged 6 years and weighing 3 stone would receive an oral dose of gr. 2 of nembutal, gr. $2^1/_4$ of seconal, or 0·8 g. of rectal thiopentone as premedication. By the present technique he receives only 0·15 g. of thiopentone, which dosage is equal to that of the longer-acting barbiturates, or a fifth of the dose of rectal thiopentone. The action of the dose might thus be expected to be about a fifth as long, and this appears to be so in practice, because the action of thiopentone has largely worn off by the end of the operation.

RESULTS

Of 172 children operated on by one surgeon, Mr. E. Lewis Reid, at one hospital in twelve months, thiopentone was used in 98; thialbarbitone ('Kemithal') was used in 3 for comparison; and 71 received nitrous oxide induction as controls. Some of the latter had no accessible veins; 3 of them had declined injection; in 7 the injection had failed because the needle became dislodged, usually through the child moving his arm (a point to be guarded against). If the needle became dislodged, a second venepuncture was not attempted, lest the child's confidence be lost. The children were otherwise unselected. No appreciable difference was found between thialbarbitone and thiopentone, the dosage being doubled. The average quantity of ether used for each case was 1 oz. The average age of the children was 7·9 years; the commonest age was 6 years, 31 children being of this age. There were 102 boys and 70 girls. 6 children were crying softly when they came to the theatre; 2 of these were coöperative enough to receive thiopentone. One child was very upset and was induced with nitrous oxide in the ward. There was no case of failed venepuncture in a child over the age of 5, when visible or palpable veins were present. The average turnover was 1 patient every twelve minutes. There was 1 case of prolonged postoperative oozing in the series, unrelated to anæsthesia; this patient did not require ligation of the bleeding vessel.

CONCLUSIONS

The advantages of the technique are as follows:

(1) It is pleasant for the patient. The child's only recollection of his visit to the theatre is the prick of a needle. In the vast majority of cases children, like adults, appreciate this, and there seems to be no reason for withholding the technique. The children have been heard talking enthusiastically at outpatient clinics about "the needle." Many of the children learn from other children, or from the nurses, what is in store for them, and, perhaps for this reason, very few of them are particularly nervous about coming to the theatre awake.

(2) It is pleasant for the anæsthetist.

(3) It is pleasant for the surgeon; induction is quickly achieved, with little straining or coughing, and operative bleeding is slight.

(4) It is pleasant for the nurses. There has been no comparable restlessness in the postoperative period, such as not uncommonly occurs after the use of the other barbiturates. The explanation of this is not known.

reflexes during the operation; and a rapid return of these reflexes at the end of the operation. Recovery again should be as pleasant as possible for all concerned.

Now let us consider the agents and techniques in present use, and see how they meet these requirements.

PREMEDICATION

The use of atropine is advisable in all cases, but there are two opposing schools of thought on the use of hypnotic or narcotic drugs. Some hold that a child should be sound asleep before the induction of anæsthesia and have no recollection of the event. Others think this unnecessary in most cases; that, if the child is properly looked after by the nurses, it does not matter if he is awake; and that all hypnotics have disadvantages which outweigh their advantages.

Hypnotics.—The hypnotics in general use for these children are pentobarbitone ('Nembutal') and quinalbarbitone ('Seconal'). Both are usually given by mouth because rectal administration has further disadvantages. There may be difficulty in persuading the child to take the drug, in whatever form it is offered. Moreover, absorption of the drug from the stomach is notoriously unreliable in children. Although induction of anæsthesia may be facilitated, the production of the required depth of anæsthesia may be delayed by respiratory depression, and the return of reflexes at the end of the operation may be delayed. There is occasionally extreme restlessness in the immediate postoperative period, during which the child is difficult to control, makes a great deal of noise, and upsets all the other children, some of whom may be waiting to go to the theatre. This can be remedied by the injection of an analgesic such as 'Nepenthe,' but involves further nursing care.

Narcotics.—Some children may be frightened of coming into hospital for an operation. As the time approaches for his turn to go to the theatre, the child may become terrified. He is then very difficult to anæsthetise by any inhalational method, and induction becomes a very crude procedure because it has to be forced on the unwilling child. It is not always possible to tell in advance which child will react in this way. The psychological effect on such a child cannot be other than harmful, and the child's future relationship with doctors will hardly be improved.

Thiopentone has been used since 1941 as a basal anæsthetic (narcotic) given rectally in a dosage of 15–20 mg. per lb. body-weight. In this dosage its action starts rapidly, the child falling into a deep sleep in about ten minutes and remaining thus for an hour or so. During this time the jaw muscles are well relaxed, the jaw may need supporting, and the child requires close supervision. Dosage and timing must be accurately assessed. This technique is not suitable for routine tonsillectomy sessions, although it is very valuable on occasion.

INDUCTION OF ANÆSTHESIA

Ethyl chloride on an open mask has a potent smell, even if disguised by eau-de-cologne, and many children dislike both it and the mask. If a child is asleep after having been given a hypnotic drug he is likely to be wakened by the vapour of ethyl chloride, when he may be more difficult to control than a child who has received no hypnotic. Ethyl chloride has toxic properties, but fatalities appear to be rare; the jaw muscles are not aways relaxed; vomiting is common on recovery.

Vinyl ether ('Vinesthene'), although not possessing the toxic properties of ethyl chloride, has an unpleasant smell, and the difficulty of persuading the child to inhale the vapour arises again. If it is given on an open mask, the cost is high. If it is given in a closed inhaler, the child suffers the experience of having a mask firmly applied to his face while conscious. Both ethyl chloride and vinyl ether are better avoided in coöperative children of this age, or children who are already asleep, though they can be very useful for suppressing noisy uncoöperative children.

Nitrous oxide has the advantage that, to all intents and purposes, it is odourless and lacks pungency. If a child is asleep, the gas may be blown over his face until he is unconscious, with very little likelihood of waking him. It is probably the most useful drug for induction in children who are already asleep. Its action, however, is very weak, and the oxygen intake must necessarily be somewhat restricted during induction. In an uncoöperative child induction may be prolonged and will often be followed by a short period of anoxia.

MAINTENANCE OF ANÆSTHESIA

Anæsthesia during tonsillectomy is usually maintained with diethyl ether, often supplemented by trichlorethylene ('Trilene'). The use of trilene during the first half of the anæsthesia seems to produce moderate postoperative analgesia and to decrease the incidence of postoperative restlessness after tonsillectomy. This matter is being investigated. Trilene is turned off half-way through the operation because it delays the return of the laryngeal reflex for a few minutes.

POSSIBLE OBJECTIONS TO INTRAVENOUS THIOPENTONE

Veins.—The difficulty of finding a suitable vein may be fairly common in children under the age of 5; but even at this age a surprisingly large number of children have accessible veins—probably more than half of them.

Needles.—Children are said to dislike needles. This difficulty can largely be overcome by starting each session with two brand-new needles size 16–18. Only about 10% of children have any appreciable objection to the use of these needles, if properly handled; and if the alternative is a face-mask many of them will prefer the needle.

Sensitivity to Thiopentone.—A child's respiratory centre has been said to be very sensitive to thiopentone. I have found that, provided thiopentone is given at a proportionately slower rate and in proportionately smaller dosage, the effect is very little different from that in the adult. The smaller blood volume in a child should be borne in mind, with consequently less dilution of thiopentone on its passage to the brain. I am not alone in believing that thiopentone can safely be given to children; for instance, Stephen (1952), in the U.S.A., writes:

> "There is no anatomic, physiologic, or biochemical contra-indication to the employment of barbiturates or curare in children, provided that the anaesthetist is sufficiently trained to take the same precautions as he would in an adult."

Recovery of Reflexes.—It might be thought that there is a danger of delay in recovery of reflexes at the end of the operation, but this is not so (see below).

TECHNIQUE WITH NITROUS OXIDE, TRILENE, AND ETHER

Before describing the technique when thiopentone is used, I will describe the technique when induction is by nitrous oxide, followed by trilene and ether. The method of administration of the inhalation anæsthetic following a thiopentone induction differs only slightly from the one now to be described.

Premedication in every case is an injection of atropine gr. $^1/_{100}$.

Induction takes place on the operating-table, because there is no anæsthetic room. The child is carefully laid on the table with as little disturbance as possible. A high flow of nitrous oxide is blown over the child's face from a Boyle's apparatus, using the by-pass. After about fifteen breaths, or one minute, the child loses consciousness; the face-mask is then gently placed over the face, and the inhaled mixture is 9 litres (90%) of nitrous oxide and 1 litre (10%) of oxygen. Trilene is immediately added in a concentration of about $^1/_4$% (lever at top of second division of Boyle's bottle). *Ether is next cau-*

tiously added, with an attempt to prevent any coughing or straining, because this increases operative bleeding. When the child is coming under the influence of the ether, the oxygen is increased to 25% (nitrous oxide 6 litres, oxygen 2 litres). After an average of four minutes from the start of induction the child is settled in upper plane 2, the gases now passing over the surface of the ether (lever full on)—a concentration of about 25%. The child's head is raised to allow towels to be placed, no respiratory obstruction being allowed. The surgeon inserts a Boyle-Davies gag, and the same gases are insufflated through the gag. Only three or four breaths of air are allowed during insertion of the gag.

Discontinuance.—When the first tonsil has been removed, the trilene is turned off. When the second tonsil has been removed, the ether is turned off. When the adenoids have been curetted, the nitrous oxide is turned off. Oxygen alone is now being given, while the pharynx is cleared by suction. After a minute or two the bleeding has stopped and the pharyngeal reflex is active.

Postoperatively the child is placed in the semi-prone position on a trolley, with an airway in place if tolerated, and returns to bed. After half an hour or so he sits up in bed to minimise postoperative oozing from the tonsillar bed.

Carbon Dioxide.—A flow of 100 ml. per minute of carbon dioxide may very usefully be added to the inhaled mixture throughout—concentration 1–2%. This hastens induction, prevents hypocapnia during insufflation, and hastens recovery. Bleeding during the operation, however, may be increased.

TECHNIQUE WITH THIOPENTONE

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Dr. Robert [illegible]

The disadvantages of the technique are few. There is a possibility of laryngospasm immediately after induction, or when ether vapour is given; this should be guarded against by keeping the airway absolutely clear throughout, and by adding ether cautiously. Trilene paves the way for ether very conveniently. Some skill is required for venepuncture. An apparatus capable of delivering oxygen under pressure must, of course, be to hand. The children are usually less active in the postoperative period than children who have received no hypnotic drug whatever, and require reasonable supervision. No analgesics were used in this series, but, if they were to be used, more supervision would be required.

This technique is offered to those anæsthetists with the skill and experience to carry it out, who do not for some reason wish to give a preoperative hypnotic but wish to prevent children from becoming frightened, and who desire a rapid recovery of reflexes and avoidance of postoperative restlessness and the necessity to administer a postoperative analgesic.

The surgeon with whom I developed this technique, a man of over twenty years' experience, and who has probably seen every available type of anæsthetic given for this operation, is of the opinion that it is the best, both from his and the children's point of view, that he has ever seen. We await the reaction of other surgeons and anæsthetists who care to give it a trial.

SUMMARY

A brief survey is made of the requirements for anæsthesia for tonsillectomy in children aged 4–12 years.

Premedication is briefly discussed, and the commoner techniques of induction of anæsthesia are criticised. Possible objections to the use of intravenous thiopentone for these children are considered.

A method of anæsthesia by nitrous oxide, trilene, and ether is described. The technique with thiopentone differs from this only at induction. A time-table of a typical case is given. The rapid recovery is explained.

Some figures from a series of 172 cases are given. The advantages and disadvantages are enumerated.

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Macintosh, R. R., Bannister, F. B. (1950) Essentials of General Anæsthesia. Oxford.
Stephen, C. R. (1952) *Curr. Res. Anesth.* 31, 36.

HYPOTENSIVE ACTIONS OF HEXAMETHONIUM BROMIDE AND SOME OF ITS HOMOLOGUES

THEIR USE IN HIGH BLOOD-PRESSURE

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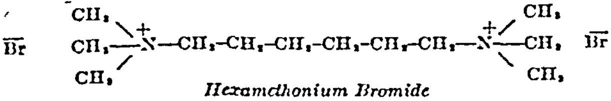
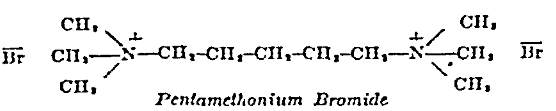
IN this paper the action of hexamethonium bromide (H.M.B.) is compared with those of two new ganglion-blocking agents, 'Ciba 9295' (N,N,N′, N′, 3-pentamethyl-N, N′-diethyl-3-aza-pentylene-(1,5)-diammonium-dibromide) and 'M. & B. 1863' (hexamethylene bisethyldimethylammonium bromide). The close chemical relation between these compounds is apparent from the structural formulæ:



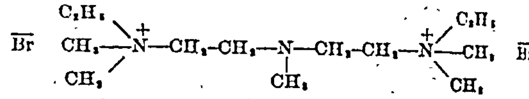
$\overline{\mathrm{Br}}\ (CH_3)_3\overset{+}{N}-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\overset{+}{N}(CH_3)_3\ \overline{\mathrm{Br}}$

Hexamethonium Bromide



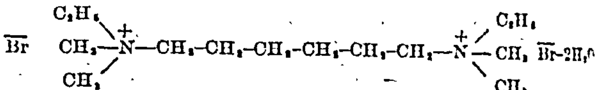
$\overline{\mathrm{Br}}\ (CH_3)_3\overset{+}{N}-CH_2-CH_2-CH_2-CH_2-CH_2-\overset{+}{N}(CH_3)_3\ \overline{\mathrm{Br}}$

Pentamethonium Bromide



$\overline{\mathrm{Br}}\ (C_2H_5)(CH_3)_2\overset{+}{N}-CH_2-CH_2-N(CH_3)-CH_2-CH_2-\overset{+}{N}(C_2H_5)(CH_3)_2\ \overline{\mathrm{Br}}$

Ciba 9295 (Pendiomide)



$\overline{\mathrm{Br}}\ (C_2H_5)(CH_3)_2\overset{+}{N}-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\overset{+}{N}(C_2H_5)(CH_3)_2\ \overline{\mathrm{Br}}\cdot 2H_2O$

M. & B. 1863 (Gaplegin)

The ganglion-blocking action of pentamethonium and hexamethonium salts, leading among other effects to fall of blood-pressure, is mentioned by Paton and Zaimis (1948, 1949), Organe et al. (1949), Arnold and Rosenheim (1949), Arnold et al. (1949), Burt and Graham (1950), Kay and Smith (1950), Enderby (1950), Paton (1951), and Restall and Smirk (1952). The use of methonium compounds in the treatment of high blood-pressure has been described by Restall and Smirk (1950), Saville (1950), Turner (1950), Campbell and Robertson (1950), Smirk (1950), Locket et al. (1951), Freis (1951a and b), Smirk and Alstad (1951), Smirk (1951a and b), Mackey and Shaw (1951), Kilpatrick and Smirk (1952), Campbell et al. (1952), and Locket et al. (1952).

Observations on Ciba 9295 ('Pendiomide') by Bein and Meier (1950, 1951) and Bernsmeier et al. (1951) show that this substance behaves essentially like H.M.B. The pharmacology of M. & B. 1863 ('Gaplegin') has been described by Wien and Mason (1951), and clinical studies have been reported by Campbell et al. (1952) and Locket et al. (1952). Campbell et al. (1952) indicate that M. & B. 1863 is about twice as active as H.M.B. in lowering the blood-pressure.

The effects of H.M.B. injections have now been observed here in more than 300 hypertensive patients, and only 2 or 3 of these did not exhibit an appreciable fall of blood-pressure with adequate dosage, provided the observations were made with the patient *sitting* or standing, in which postures blood-pressure falls more. More than 170 patients have now been treated for from two to thirty-two months, with similar results to those reported earlier (Restall and Smirk 1950, Smirk and Alstad 1951). Effective and well-controlled treatment by subcutaneous (not intramuscular) injections produces good results in a much larger proportion of patients than receive benefit either from oral H.M.B. (Kilpatrick and Smirk 1952) or from oral administration of veratrum alkaloids (Smirk and Chapman 1952). The results reported here indicate that M. & B. 1863 is useful in some patients in whom the side-effects from H.M.B. are sufficient to keep the dose of H.M.B. below *the optimal* level for control of blood-pressure.

ADMINISTRATION

Subcutaneous Injection

Ciba 9295, M & B. 1863, and H.M.B. may be administered either orally or subcutaneously. Simple 5–10% aqueous solutions are non-irritant when injected; 0·5% chlorbutol is a suitable preservative.

Patients vary in the dosage of H.M.B. which they require to lower the blood-pressure (Smirk and Alstad 1951), and there is wide variation also in the hypotensive responses of different patients to a first dose of 15 mg. of Ciba 9295 or 7·5 mg. of M. & B. 1863. Thus, after initial subcutaneous injections of 15 mg. of Ciba 9295, the blood-pressure in the sitting posture fell by 60/36 mm. Hg in one patient and 14/20 mm. Hg in another. After 7·5 mg. of M. & B. 1863, given before the development of toleration, the blood-pressure in the sitting posture fell by 78/35 mm. Hg in a third patient and 28/12 mm Hg in a fourth.

Though sensitivity to the hypotensive action of these ganglion-blocking agents differs from patient to patient, in any given patient a high (or low) degree of sensitivity to one of the drugs is usually accompanied by a high (or low) sensitivity to the others. Suitable initial doses which (in the absence of developed tolerance) produce approximately equal falls of blood-pressure are 15 mg. of H.M.B., 17 mg. of Ciba 9295, and 7·5 mg. of M. & B. 1863. The relation between the effective doses of H.M.B. and M. & B. 1863 seems rather stable, and the ratio is preserved throughout the development of drug toleration (see below). With Ciba 9295 the relation seems less precise, and sometimes, with the development of full toleration, the effective dose of Ciba 9295 becomes considerably larger than the effective dose of H.M.B.

Oral Administration

Trials with various doses show that with Ciba 9295 and M. & B. 1863, as with H.M.B., the effective oral dose is 10 or more times as great as an equally hypotensive dose given subcutaneoulsy (see table). It is important to compare only tests made at about the same stage in the development of drug toleration.

The effective subcutaneous dose of Ciba 9295 before toleration is about 17/15 of the dose of H.M.B., and the effective oral dose is also rather greater than the oral dose of H.M.B. The effective subcutaneous dose of M. & B. 1863 is about half that of H.M.B., and the effective oral dose of M. & B. 1863 is about half that of H.M.B. (see table). Apparently there is no great difference between the three substances in the proportion of oral doses that is absorbed.

COMPARISON OF EFFECTS OF SUBCUTANEOUS AND ORAL ADMINISTRATION OF CIBA 9295 AND M. & B. 1863

Drug	Case no.	Subcutaneous			Oral		
		Dose (mg.)	Greatest fall in blood-pressure (mm. Hg)	Duration of effect (hr.)	Dose (mg.)	Greatest fall in blood-pressure (mm. Hg)	Duration of effect (hr.)
Ciba 9295	268	25	36/2	2½	750	14/15	Short and indefinite
	262	80	30/10	4	500	42/22	1
	Average	52·5	33/6	3¼	625	28/19	1
M. & B. 1863	262	25	70/32	3	375	40/6	5
	23	10	56/24	2	375	46/36	6
	229	38	84/50	5	250	30/4	4½
	137	50	104/36	5½	525	44/18	3
	110	7·5	112/52	5	325	30/4	1
	Average	26·1	85/39	4	370	38/14	4

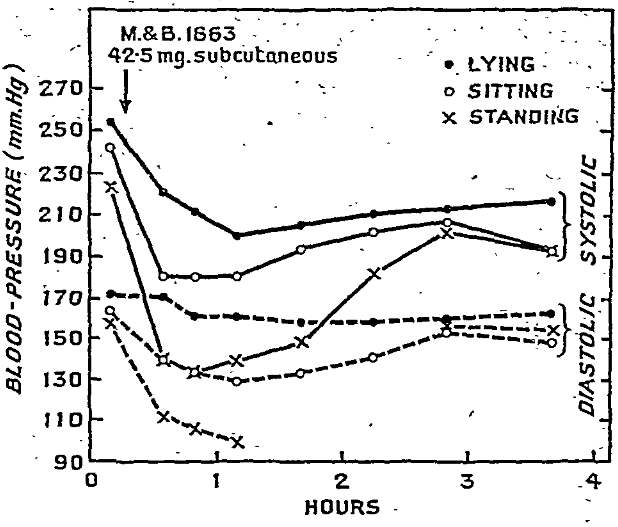


Fig. 1—Systolic and diastolic blood-pressures in lying, sitting, and standing postures after subcutaneous injection of 42·5 mg. of M. & B. 1863.

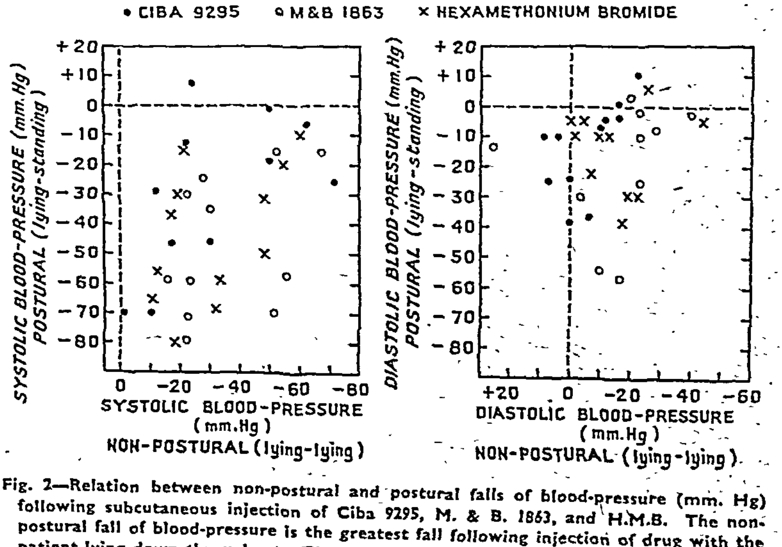


Fig. 2—Relation between non-postural and postural falls of blood-pressure (mm. Hg) following subcutaneous injection of Ciba 9295, M. & B. 1863, and H.M.B. The non-postural fall of blood-pressure is the greatest fall following injection of drug with the patient lying down throughout. The postural fall of blood-pressure is the difference between the blood-pressures in standing and lying postures, measured when the blood-pressure fall is greatest. It will be noted that in some tests the non-postural fall was associated with a small postural rise, or vice versa.

COURSE OF HYPOTENSIVE ACTION OF CIBA 9295, M. & B. 1863, AND H.M.B. AFTER SUBCUTANEOUS INJECTION

Fig. 1 shows the fall of blood-pressure after an injection of M. & B. 1863; and the fall is similar in the two other substances. After an effective subcutaneous dose the blood-pressure falls in ten to twenty minutes. The time taken after the injection to reach the lowest level of blood-pressure varies from twenty minutes to two hours. The duration of the hypotensive action is greater with larger doses but ordinarily is two to five hours (average about three hours). In these respects there is no consistent or important difference between the three substances, provided the doses given are adjusted to produce about equal decreases of blood-pressure at the trough of the fall.

The decrease in the systolic pressure is often about, or slightly more than, twice the fall in diastolic pressure. This relationship holds for the averages of the results with the three substances. Some of the results are set out in fig. 2. The blood-pressure fall produced by Ciba 9295 is less than that produced by an equivalent dose of H.M.B. A marked postural hypotension is present in the standing posture with both drugs, and there is no notable difference in the amount of postural hypotension relative to the extent of non-postural fall in blood-pressure. Non-postural falls in blood-pressure are measured by noting the difference between the blood-pressures, both taken in the lying posture, before and after giving the drug. The postural hypotension is studied by noting the difference between the blood-pressure in the standing and lying postures when, as the result of the drug action, the blood-pressure has reached its lowest level for the lying posture. It can be seen from fig. 2 that the postural element in the fall of blood-pressure differs from patient to patient, but in most instances the postural fall is greater than the non-postural fall. There is no difference between the three drugs in the importance of the postural effect relative to the non-postural effect on the blood-pressure.

The effects of M. & B. 1863 and Ciba 9295 on the pulse-rate are variable and similar to those already described for H.M.B. (Smirk and Alstad 1951, McMichael 1952). The additional fall in blood-pressure after meals, which is caused by H.M.B., is caused also by M. & B. 1863 or Ciba 9295 and is probably due to reduced ability, after the administration of methonium, to compensate for splanchnic dilatation. Although patients treated with methonium salts or with veratrum alkaloids vary in the extent to which they show blood-pressure falls after meals, the response of a given patient may be consistently of sufficient magnitude to determine postponement of a second injection until an hour after the meal. Ordinarily such postponement is unnecessary.

ACQUIRED TOLERANCE TO CIBA 9295, M. & B. 1863, AND HEXAMETHONIUM SALTS

It has been shown already that repeated administration of pentamethonium or hexamethonium bromide leads to toleration, noticeable sometimes even on the first day of administration, and with regular dosage toleration continues to increase for weeks or months, until ultimately the dose required becomes stable. The degree of toleration acquired varies from patient to patient, and the eventual dose needed to reproduce the initial response may be only 2 or 3 times the first dose, but ordinarily it is 6 or 12 times. Among patients whose reaction to the drug appears to have become stable some manage on subcutaneous H.M.B. 30–40 mg. thrice daily, and at the other extreme is a patient who receives 450 mg. thrice daily. Side-effects are no more pronounced in this last patient than in many of those on small doses. Side-effects on a good régime are comparatively slight in most patients. Fortunately the acquisition of toleration seems to become more complete to parasympathetic side-effects than to sympathetic effects. Dryness of the mouth and blurring of vision, though they seldom disappear, may become less prominent in time, even though equally effective falls of blood-pressure are maintained. Delay in emptying the bladder may be observed with early doses but tends to pass off as toleration develops.

The present observations show that toleration is also acquired rapidly on repeated administration of Ciba 9295 and M. & B. 1863. Where patients have been given doses (sometimes of Ciba 9295, sometimes of M. & B. 1863, and sometimes of H.M.B.) and have been observed for weeks or months, it is clear that toleration to all three substances has developed concurrently. 6 patients who had never received M. & B. 1863 before, but who had already acquired a tolerance to H.M.B., were given an equivalent dose of M. & B. 1863. Thus in case 206 the optimal subcutaneous dose of H.M.B. was 150 mg. When 75 mg. of M. & B. 1863 was substituted it had about the same effect on the blood-pressure. This would happen only if, concurrently with the acquisition of toleration to H.M.B., there had developed a corresponding degree of toleration to M. & B. 1863. 75 mg. of M. & B. 1863 given without the previous acquisition of tolerance would be an excessive dose causing fainting in the sitting posture.

Similar investigations made with Ciba 9295 gave similar results.

To see if toleration for homologues can be acquired in the reverse direction, we first gave a patient M. & B. 1863 and continued with this substance until a good measure of toleration to it had developed. We then administered H.M.B. in twice the dose and found that its effect was about the same as that of M. & B. 1863, indicating that, when toleration was acquired to M. & B. 1863, a corresponding degree of toleration was also acquired to H.M.B.

Two other tests were made by giving Ciba 9295 until a toleration was acquired. Then, although no H.M.B. had been given beforehand to these patients, the responses indicated that a considerable measure of toleration to it was acquired as the result of giving Ciba 9295. Evidently when, as the result of repeated administration, toleration has been acquired to one of the methonium compounds studied, simultaneously toleration is acquired to certain other methonium compounds, even though these have not been administered previously.

M. & B. 1863 AND CIBA 9295 AS ALTERNATIVES TO H.M.B. IN TREATMNET OF ARTERIAL HYPERTENSION

Ordinarily there is little difference in the side-effects produced by Ciba 9295, M. & B. 1863, and H.M.B. There has been slightly less dryness of the mouth and blurred vision from M. & B. 1863 for equal hypotensive action. The difference is quantitative, and no qualitative difference has been observed with either of these substances. A minority of patients have appreciable trouble with side-effects from H.M.B. Some of these patients have compared the effects of H.M.B. and M. & B. 1863 and noted that, for equal hypotensive effects, there have been fewer side-effects from M. & B. 1863.

In 14 patients treated for periods of from one to four months with M. & B. 1863 it has been possible in all instances to obtain as good control over the arterial level as with H.M.B., using approximately half of the dose. Of 8 patients given both drugs, 2 could distinguish no symptomatic difference between their actions, 1 could distinguish a difference but had no preference, and 5 claimed that they were more comfortable on M. & B. 1863 because side-effects were less pronounced.

ILLUSTRATIVE CASE-RECORDS

CASE 207.—A man, aged 57, had malignant hypertension with severe headache and breathlessness on exertion. The average arterial blood-pressure was reduced by subcutaneous H.M.B.; papillœdema cleared entirely, headaches and breathlessness disappeared, and he returned to his occupation as an engineer without restriction of activity. Adequate control of arterial blood-pressure by H.M.B. injections caused occasional diarrhœa at night. On control with M. & B. 1863 the patient felt generally better, and diarrhœa, dryness of the mouth, and blurring of vision were less than with H.M.B. His treatment with H.M.B. lasted four months and with M. & B. 1863 one month. The first effective dosage of subcutaneous H.M.B. was 75 mg. thrice daily; but, as toleration developed, the effective dosage increased to 210 mg. thrice daily. The treatment was next changed to 102 mg. of M. & B. 1863 thrice daily, which had a similar effect on the blood-pressure. The blood-pressure was initially about 220/146 mm. Hg and seldom fell below 170/120 mm. Hg in the early weeks of treatment, but latterly with H.M.B. the blood-pressure usually was 122/80–190/130 mm. Hg. On M. & B. 1863 the blood-pressures were in the same range.

CASE 228.—A woman, aged 43, with essential hypertension, had had hemiplegia before treatment but when first seen by us was otherwise symptomless, and treatment with H.M.B. was prophylactic. As a side-effect of H.M.B. she had considerable colicky pain 1½–2 hours after the injection and was relieved to some extent by atropine gr. 1/100. She had not experienced such discomfort before treatment with H.M.B. M. & B. 1863 in doses which produced about the same amount of hypotension did not cause colicky pain. Dryness of the mouth and blurring of vision were also less. After two weeks H.M.B. injections were resumed without recurrence of the pain, but dryness of the mouth and blurring of vision were accentuated, and the patient could distinguish between equal hypotensive doses of H.M.B. and M. & B. 1863. The dosage of H.M.B. increased from 15 to 60 mg. thrice daily. The treatment was then changed to 35 mg. of M. & B. 1863 thrice daily for three weeks. The blood-pressure recorded before treatment was 240/150 mm. Hg, which fell under basal conditions to 188/138. With H.M.B. the blood-pressure in the sitting posture fell to 132/110. Between injections the pressure did not ordinarily rise much above 182/130. On M. & B. 1863 the blood-pressure was usually 132/98–180/130.

CONCLUSION

H.M.B. has now been tried here for two years and eight months and has given very little indication of toxicity other than that which arises as a temporary phenomenon from overdosage. So far it has not caused any adverse permanent tissue change, but no doubt in the course of time occasional instances will be reported. Ciba 9295 and M. & B. 1863 have not been tried as long, but they behave like H.M.B.

SUMMARY

Hexamethonium salts and the ganglion-blocking homologues Ciba 9295 and M. & B. 1863 are qualitatively similar in reducing blood-pressure, causing postural hypotension, and inducing toleration after repeated administration.

The administration of any one of these substances induces toleration to its homologues.

All these substances when given orally require ten or more times the subcutaneous dose.

By subcutaneous injection, before toleration has developed, approximately equal falls of blood-pressure are induced by 7 mg. of M. & B. 1863, 15 mg. of H.M.B., and 17 mg. of Ciba 9295. After toleration has developed, Ciba 9295 is usually much less effective than either H.M.B. or M. & B. 1863.

In a few hypertensive patients M. & B. 1863 is rather better tolerated than H.M.B. in the sense that, for equal falls of blood-pressure, side-effects are less prominent.

Thanks are due to Miss M. Poppelwell for secretarial work, and to Miss J. Rivers, Miss N. Hoggan, and Miss B. Stanton for technical assistance. Messrs. May & Baker Ltd. supplied the hexamethonium bromide and M. & B. 1863, and Ciba Laboratories Ltd. the Ciba 9295. The expenses of the work were defrayed in part by the Medical Research Council of New Zealand.

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"... It is a convenient working rule to assume our fellow men, if not our equals, are at least in general not very much more stupid or wicked than we are ourselves. If that be admitted, then the more reprehensible their conduct appears the greater should our curiosity become. The quality that the academic mind can bring to the conduct of affairs is that of reasonableness. There are no short cuts and no cure-alls, but there is a great deal of inaccurate thinking. The call is for hard work, full and precise knowledge, clear exposition, and refusal to accept a comfortable evasion of unpalatable conclusions."—Prof. H. H. BELLOT, addressing the students of Hull University College, reported in the *Manchester Guardian*, Nov. 3, 1952, p. 9.

A "HARLEQUIN" COLOUR CHANGE IN THE NEWBORN

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ON a day in March, 1951, each of us on separate occasions saw a particular baby in the nursery of this hospital undergo a most bizarre and striking colour change with which we were previously unfamiliar. At the age of 3 days she was lying naked on her right side in an oxygen box, when the left half of her body became much paler than usual, although the right half remained the usual pink. The dividing line between the two halves was as sharp and straight as if it had been drawn with a pencil and ruler, and it ran exactly in the midline—down the centre of the forehead, nose, chin, and trunk, through the centre of the umbilicus and genitalia, and up the back over the tips of the vertebral spines. This surprising appearance passed off spontaneously after a few minutes on both occasions, the whole body reverting to its usual colour.

The sister in charge of the nursery remembered having seen a similar colour change in two babies in the nursery during the previous year, and the case-notes confirmed this. Accordingly, the nursing and medical staffs of the nursery began to watch for such attacks in case these might have some pathological significance, and during the next twelve months a further 21 babies were observed to be affected (each on one or more occasions). These observations were made by the sister-in-charge, four staff midwives, and ourselves. In addition, we observed 2 instances elsewhere, and had 3 further instances reported to us by interested colleagues from other hospitals.

THE ATTACKS

There is always a clear-cut line of demarcation running exactly in the midline of the body, and gravity determines the distribution of colour between the two halves of the body, the side which is uppermost always being the paler. The intensity of the attack varies considerably from one baby to another, the pallor being much more striking in some than in others, and in some of the mildest attacks there has been no line of demarcation visible on the skin of the face and genitalia. Even in severe attacks, no difference is apparent in the colour of the two halves of the lips and tongue. Respiration, responsiveness to stimuli, and muscle tone appear to be normal during the attack; and a single observation of the state of the pupils showed them to be of equal size. If the baby is left undisturbed, the attack passes off spontaneously after anything from thirty seconds to twenty minutes, and the baby then looks quite normal again.

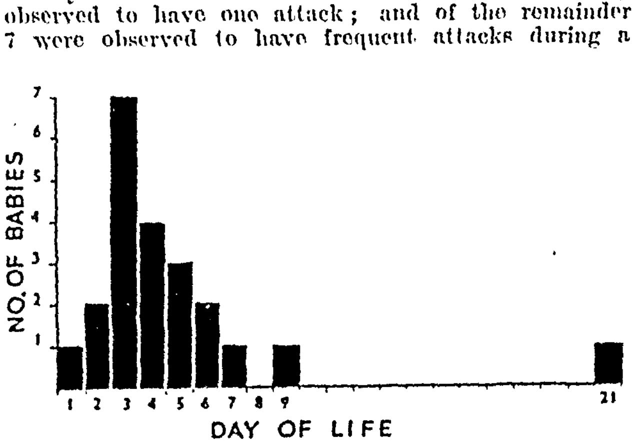
The attacks may occur with the baby in almost any posture, so long as he is more or less turned on one side: he may be lying horizontally, his feet may be above or below the level of his head, or he may even be almost sitting in the nurse's arms. In several cases we have confirmed the effect of gravity; for the whole picture has been reversed by turning the baby on to the opposite side during an attack, without disturbing his sleep. The previously pale half gradually becomes suffused with blood till the whole baby is a uniform colour for a few seconds; then the previously darker half, now uppermost, gradually goes pale. The time taken for this reversal to be completed is between a half and one minute. If, instead, the baby is simply turned on to his back, the attack is brought to an end in about a quarter of a minute. We have tried to find out if it is the position of the baby's trunk, or head, or both, that determines the distribution of colour, but have so far failed to make convincing observations on this point.

One of the reasons for this difficulty is that attempts to rotate the baby's head and trunk independently usually disturb him; and, if he becomes too active, the pale half begins to flush irrespective of posture. If he actually cries, of course, the intense flush which results rapidly obliterates the whole picture. These effects of posture and activity also, in part, explain the difficulty of getting satisfactory photographs of the colour change in these attacks. We have so far failed to obtain one good enough for reproduction in black and white.

INCIDENCE OF ATTACKS

The minimum incidence of the condition has been estimated by recording every attack observed in the selected group of 250 babies admitted to the nursery, rather than to the lying-in wards with their mothers, from mid-March, 1951, to mid-March, 1952. This group included all babies with a birth weight of 5 lb. or less, and babies above this weight who showed clinical evidence of cerebral damage, or whose obstetric history suggested that they were particularly liable to develop it, together with a few severe cases of hæmolytic disease and hæmorrhagic disease. Of the 250 babies admitted only 126 spent more than the first forty-eight hours of life in the nursery, since the rest had either died or been discharged to the lying-in wards by that age. These babies in the nursery were under closer observation than the normal babies in the lying-in wards: for they were examined relatively frequently by the doctors, they were hand-fed by nurses who were familiar with the harlequin colour change, and many of them spent days or weeks naked in oxygen boxes.

Of the 250 babies admitted, 22 were observed to have one or more of these attacks (see figure). In only 3 babies was the first attack observed in the first forty-eight hours of life; the remaining 19 instances were observed in the 126 babies who stayed in the nursery longer than forty-eight hours, giving an incidence among them of 15%. The true incidence is presumably higher, since other babies must have had attacks without their being observed. This infrequency of recorded attacks during the first forty-eight hours of life surprised us, but we have no reason to believe that attacks at that stage were less likely to be observed (rather the reverse, if anything). Most of the first attacks were observed on the third or fourth day of life, but one was observed on the twenty-first. 12 of the affected babies were only observed to have one attack; and of the remainder 7 were observed to have frequent attacks during a single period of twenty-four hours (the greatest number recorded for any one baby being twelve).



Age at time of first recorded harlequin attack in 22 nursery babies.

An analysis to discover whether any particular group of babies has a special tendency to these attacks suggested that this might be true of the smaller prematures, but the difference in incidence between those weighing less than 4 lb. and the larger premature babies (6 out of compared with 13 out of 98) is not regarded as statistically significant.

Since the year covered by these observations, an attack has been observed in a mature baby about a minute after delivery; and in a premature baby fifty-four attacks were observed in the first two weeks of life.

SIGNIFICANCE OF ATTACKS

These attacks seem to have no pathological significance. During the year in question, they were observed in babies with very varied and apparently unrelated pathological states in the nursery, and in 6 apparently normal premature babies. We have also observed attacks elsewhere in 2 mature babies: one on the sixth day of life in a baby with scaphocephaly, and the other on the sixteenth day in a baby convalescent from pneumonia. Finally, we have received reports from colleagues of attacks in a perfectly normal mature baby on the day and in 2 normal premature babies in other hospitals.

DISCUSSION

We have not found any previous description of the phenomenon. Our own limited speculations about the mechanism involved are based on the observations described. We have deduced that the essential asymmetry, or incoördination, must occur at a level of the central nervous system where there are centres controlling the tone of the skin blood-vessels in each half of the body separately. This is the only way in which we can explain the precise distribution and demarcation of the colour changes (the fact that the lips and tongue do not show these changes, even in severe attacks, and that the face and genitalia are unaffected in the mildest attacks might perhaps be due to the greater vascularity of the skin over these parts). Richards (1946) suggests that there are such centres in the hypothalamus, and that the vasomotor centres in the medulla are concerned only with the "more vital activities of the heart and great vessels." The existence of cortical centres seems to be open to doubt. Instability of these hypothalamic centres in the neonatal period would accord well with the accepted view that the unstable heat-regulating mechanism of the newborn is controlled from centres at the same level of the nervous system. The apparently greater susceptibility of smaller premature babies to attacks, if confirmed, would also correspond well to their less stable heat-regulating mechanism. What is less easy to explain is the relative infrequency of attacks in the first forty-eight hours of life, when any such instability would be expected to be at its height.

Our view that the attacks have no pathological significance is without conclusive support as yet; our own observations have all been made in babies who were abnormal in some way (if only because of prematurity or a recent infection), and only one of the observations reported by our colleagues concerned a completely normal baby. We feel that this is merely an index of the sort of babies we tend to look at most closely and frequently during our normal day's work; and we have certainly failed to trace any logical connection between the various abnormalities of the affected babies. Conclusive proof, however, awaits the observation of attacks in a sufficient number of perfectly normal mature babies.

A better interpretation of these attacks may come from future observations in the clinical field. Part of our object in presenting this report is the that it may interest others working in more experimental fields.

SUMMARY

In the premature and sick nursery of a maternity hospital it has been noted that the babies are liable to attacks, of short duration, in which one exact half of the body becomes much paler than the other half. The clinical features of these attacks are described.

In a single year, of 250 babies admitted to the nursery, 22 had one or more of these attacks. The attacks seem to be more liable to occur after the first forty-eight hours of life; and of the 126 babies who spent more than their first forty-eight hours in the nursery 19 (15%) had one or more attacks at that stage. The true incidence is presumed to be higher than this.

No connection has been found between these attacks and any particular pathological state. The attacks are believed to be of no pathological significance.

The mechanism involved in the attacks remains purely conjectural; but the precise distribution of the colour changes suggests a temporary imbalance in the central nervous system (possibly in the hypothalamus).

We wish to thank Sir James Spence and Dr. Donald Court for their interest and for their advice about the preparation of this report; and Dr. E. G. Knox, Dr. T. C. Noble, and Dr. J. M. Stansfeld for letting us know about cases in other hospitals.

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PRIMARY CARCINOMA OF THE LIVER FOLLOWING VIRAL HEPATITIS

REPORT OF TWO CASES

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ALTHOUGH primary carcinoma of the liver is one of the commonest forms of malignant disease in certain African and Asiatic races it is generally agreed to be a rare tumour in Western Europe. In the Bantu (Berman 1951) and in China (Tull 1932) it appears to be secondary to dietary cirrhosis and parasitic infestations of the liver. In European races, however, dietary cirrhosis of the liver is rare. Primary carcinoma of the liver, when it does occur, is usually found in association with cirrhosis, either diffuse hepatic fibrosis (Schupbach and Chappell 1952) or nodular hyperplasia (Muir 1908, Himsworth 1950). Although the ætiology of hepatic cirrhosis, in this country, is often obscure, many cases are probably due to viral hepatitis; certainly hepatic fibrosis is now a well-recognised sequel to this disease (Stokes and Miller 1947, Watson and Hoffbauer 1946, Havens 1948, Post et al. 1950). It is therefore surprising that the sequence of events—infective hepatitis, cirrhosis of the liver, carcinoma of the liver—has not been described more frequently. Sherlock (1952) was able to cite only one published report, by Sheldon and James (1948), in which 5 cases of hepatic cirrhosis are described; 2 of these developed primary carcinoma of the liver. The cause of the cirrhosis in all 5 was stated to be viral hepatitis, although both patients in whom a carcinoma was found were chronic alcoholics.

We believe that the 2 cases described here began with a viral hepatitis, and proceeded to postnecrotic scarring, nodular hyperplasia, and finally tumour formation. In the first case the hepatitis was either of the epidemic infective or of the serum variety and the carcinoma was diagnosed during life. In the second case the hepatitis was probably of the epidemic variety and the carcinoma was an incidental finding at necropsy.

THE FIRST CASE

A man, aged 35, was admitted to St. Helier Hospital on Aug. 10, 1951.

History

He had joined the Army in 1940 and had been sent to India in 1942. In 1943 he was treated for benign and malignant tertian malaria. In May, 1944, he contracted syphilis, for which he was treated with neoarsphenamine and bismuth injections. In December, 1944, after having two courses of antiluetic treatment, he developed anorexia, nausea, and upper abdominal discomfort, followed by jaundice. His stools became pale and his urine dark. He was on active service in Burma at that time, and there was an epidemic of infective hepatitis among the troops serving in the area.

From December, 1944, to January, 1946, he was treated in various military hospitals, at first in India and later in England. Throughout this period he had persistent jaundice, with enlargement of the liver and spleen. His Wassermann reaction which had been positive in May, 1944, had become negative by December of the same year. He was discharged from the Army with the diagnosis of subacute hepatitis. He returned to work as a clerk; but, except for a short period in 1948, his jaundice never subsided completely.

In August, 1949, he developed increasing lassitude and his jaundice became more intense. He was admitted to Dulwich Hospital and was found to have an enlarged liver and spleen and several pulsating arterial telangiectases on his arms and trunk. Investigation at that time gave the following results: hæmoglobin 94%, serum-bilirubin 6·8 mg. per 100 ml., thymol turbidity 15 units, alkaline phosphatase 21 King units, serum-albumin 2·92 g. per 100 ml., and serum-globulin 4·39 g. per 100 ml. He was discharged, after three weeks, still slightly jaundiced. Subsequently he developed œdema of his legs. By May, 1950, the thymol turbidity had risen to 30 units with flocculation, but the serum-bilirubin level had fallen to 2·0 mg. per 100 ml. In August, 1951, he suddenly developed severe pain in the right side of his chest, worse on breathing, and six days later he was again admitted to hospital. There was no history of alcoholism either before or after the beginning of his illness in 1944.

Condition on Admission

He looked ill, was moderately icteric, and complained of severe right-sided pleuritic pain. His temperature was 99·2°F. There was a large pulsating arterial telangiectasis on his left shoulder, and there were several smaller ones on the arms and on the chest wall. Both thenar and hypothenar eminences showed the erythema of "liver palms." A firm and slightly tender liver edge was palpable 1 in. below the right costal margin. The spleen was considerably enlarged and firm, extending 2 in. below the left costal margin. There was pitting œdema of both legs and thighs, but there was no demonstrable ascites. A pleural friction rub was audible in the right axilla, and there were râles at both bases. The cardiovascular and central nervous systems were normal.

Investigations

His hæmoglobin was 98%, and the white-cell count 3100 per c.mm. (polymorphs 86%, lymphocytes 14%). The serum-bilirubin was 4·5 mg. per 100 ml., the thymol turbidity 5 units with flocculation, and the serum-alkaline-phosphatase 18·5 units. The total serum-proteins were 7 g. per 100 ml. (albumin 2·8 g., globulin 4·2 g.), and the Wassermann reaction negative.

Radiography of the chest revealed scattered areas of consolidation at both bases, and several rounded opacities, in both lung fields, suggestive of secondary malignant deposits. The primary growth was thought to be in the liver.

Course

The patient continued to have low-grade pyrexia up to 100°F. He became more deeply jaundiced, the œdema of his legs increased, and he developed ascites. His condition gradually deteriorated until he died a month after admission.

Post-mortem Findings

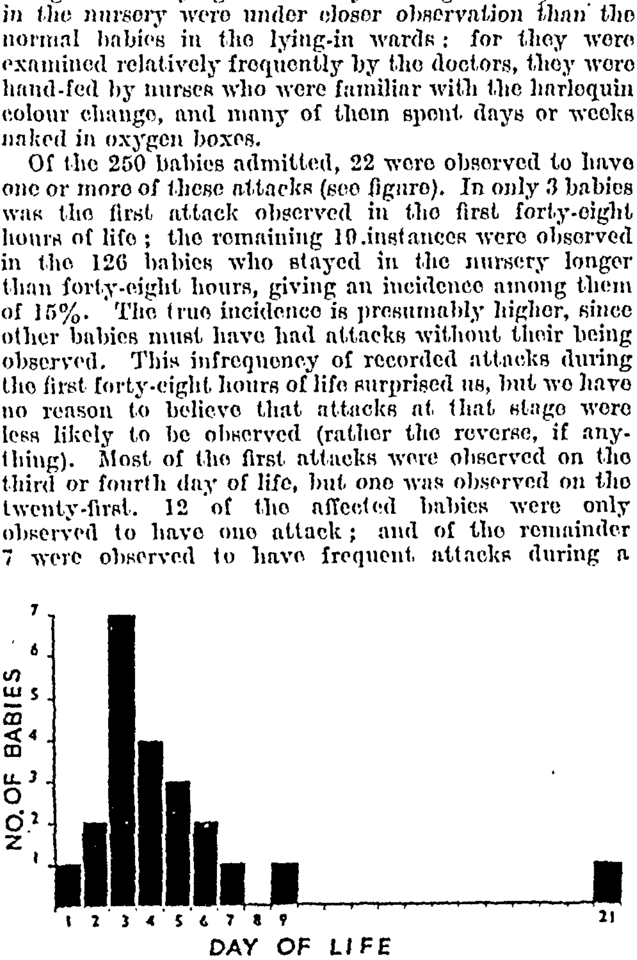
Necropsy (Dr. T. E. W. Goodier).—The liver, of normal size, contained a yellow mass of tumour tissue 5·0 cm. in diameter in the right lobe, and several smaller yellow nodules reversal to be completed is between a half and one minute. If, instead, the baby is simply turned on to his back, the attack is brought to an end in about a quarter of a minute. We have tried to find out if it is the position of the baby's trunk, or head, or both, that determines the distribution of colour, but have so far failed to make convincing observations on this point.

One of the reasons for this difficulty is that attempts to rotate the baby's head and trunk independently usually disturb him; and, if he becomes too active, the pale half begins to flush irrespective of posture. If he actually cries, of course, the intense flush which results rapidly obliterates the whole picture. These effects of posture and activity also, in part, explain the difficulty of getting satisfactory photographs of the colour change in these attacks. We have so far failed to obtain one good enough for reproduction in black and white.

INCIDENCE OF ATTACKS

The minimum incidence of the condition has been estimated by recording every attack observed in the selected group of 250 babies admitted to the nursery, rather than to the lying-in wards with their mothers, from mid-March, 1951, to mid-March, 1952. This group included all babies with a birth weight of 5 lb. or less, and babies above this weight who showed clinical evidence of cerebral damage, or whose obstetric history suggested that they were particularly liable to develop it, together with a few severe cases of hæmolytic disease and hæmorrhagic disease. Of the 250 babies admitted only 126 spent more than the first forty-eight hours of life in the nursery, since the rest had either died or been discharged to the lying-in wards by that age. These babies *in the nursery were under closer observation than the* normal babies in the lying-in wards: for they were examined relatively frequently by the doctors, they were hand-fed by nurses who were familiar with the harlequin colour change, and many of them spent days or weeks naked in oxygen boxes.

Of the 250 babies admitted, 22 were observed to have one or more of these attacks (see figure). In only 3 babies was the first attack observed in the first forty-eight hours of life; the remaining 19 instances were observed in the 126 babies who stayed in the nursery longer than forty-eight hours, giving an incidence among them of 15%. The true incidence is presumably higher, since other babies must have had attacks without their being observed. This infrequency of recorded attacks during the first forty-eight hours of life surprised us, but we have no reason to believe that attacks at that stage were less likely to be observed (rather the reverse, if anything). Most of the first attacks were observed on the third or fourth day of life, but one was observed on the twenty-first. 12 of the affected babies were only observed to have one attack; and of the remainder 7 were observed to have frequent attacks during a single period of twenty-four hours (the greatest num recorded for any one baby being twelve).



Age at time of first recorded harlequin attack in 22 nursery babies.

An analysis to discover whether any particular g of babies has a special tendency to these attacks sugg that this might be true of the smaller premature, the difference in incidence between those weighing than 4 lb. and the larger premature babies (6 out of compared with 13 out of 98) is not regarded statistically significant.

Since the year covered by these observations, attack has been observed in a mature baby about minute after delivery; and in a premature baby fi four attacks were observed in the first two weeks life.

SIGNIFICANCE OF ATTACKS

These attacks seem to have no pathological significa During the year in question, they were observed in babies with very varied and apparently unrelated pat logical states in the nursery, *and in 6 apparently* norm premature babies. We have *also observed* atta elsewhere in 2 mature babies: one on the sixth day of in a baby with scaphocephaly, and the other on t sixteenth day in a baby convalescent from pneumo Finally, we have received reports from colleagues attacks in a perfectly normal mature baby on the fi day and in 2 normal premature babies in other hospit

DISCUSSION

We have not found any previous description of t phenomenon. Our own limited *speculations* about t mechanism involved are based on the observati described. We have deduced that the essential asy metry, or incoördination, must occur at a level of t central nervous system where there are centres contr ling the tone of the skin blood-vessels in each half of *body separately. This is the only way in which* we explain the precise distribution and demarcation of t colour changes (the fact that the lips and tongue do show these changes, even in severe attacks, and that face and genitalia are unaffected in the mildest attack might perhaps be due to the greater vascularity of t skin over these parts). Richards (1946) suggests th there are *such centres* in the hypothalamus, and th the vasomotor centres in the medulla are conc only with the "*more vital* activities of the heart a great vessels." The existence of cortical centres se to be open to doubt. Instability of these hypothalamic centres in the neonatal period would *accord* well with th accepted view that the unstable heat-regulating mech ism of the newborn is controlled from centres at the level of the nervous system. The apparently gr susceptibility of smaller premature babies to atta if confirmed, would also correspond well to their stable heat-regulating mechanism. What is less *to explain is the relative* infrequency of attacks in first forty-eight hours of life, when any such instab would be expected to be at its height.

Our view that the *attacks* have no patholo significance is without conclusive support as yet; own observations have *all* been made in babies who abnormal in some way (if only because of prematu or a recent infection), and only *one* of the observat reported by our colleagues concerned a compl normal baby. We feel that this is merely an ind the sort of *babies we tend to* look at most closely frequently during our normal day's work; and we certainly failed to trace any logical connection bet the various abnormalities of the affected babies. clusive *proof*, however, awaits the observation of att in a sufficient number of *perfectly normal* mature ba

A better *interpretation* of these attacks may *from future* observations in the clinical field. part of our object in presenting this report is the

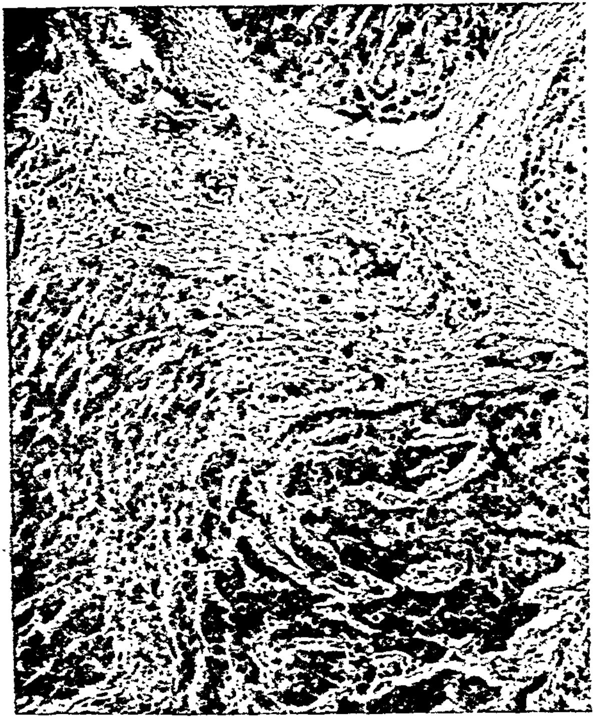


Fig. 3—Section of liver (case 2) showing transition zone between normal and neoplastic cells. (Hæmatoxylin and eosin. × 60.)

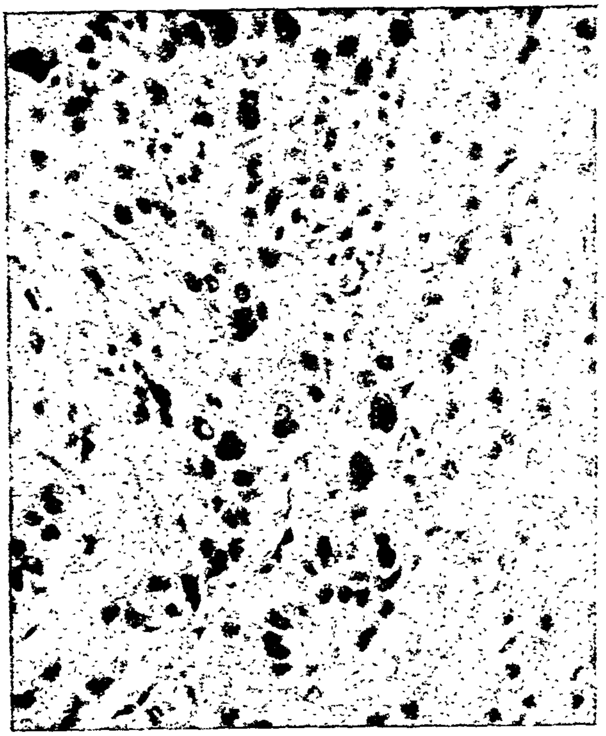


Fig. 4—Transition zone between normal and neoplastic cells (case 2) showing great variation of nuclear size in neoplastic cells, and multinucleate cells. (Hæmatoxylin and eosin. × 235.)

plasma infusions did not relieve his ascites, and repeated tappings were necessary. He got steadily worse and died in coma six weeks after admission.

Post-mortem Findings

Necropsy (Dr. R. H. D. Short).—The liver was small and coarsely scarred. It weighed 1180 g., and contained multiple regeneration nodules up to 2 cm. in diameter. In the right lobe one nodule was yellowish and appeared to be infiltrating the surrounding liver. The spleen was enlarged and weighed 520 g. Apart from ascites and dilated œsophageal veins there were no significant abnormalities in any other organ.

Histologically the liver showed coarse bands of fibrous tissue intersecting regeneration nodules of different sizes. In some of the nodules the relation of the central vein to the portal triads appeared to be undisturbed, and the nodules seemed to be composed of groups of apparently normal liver lobules. In other areas the normal liver architecture was completely distorted and there were small groups of cells cut off by fibrous tissue. The yellowish nodule from the right lobe showed irregular columns of cells of different sizes, in some areas almost syncytial, with many multinucleate cells, irregular-sized nuclei, and many mitoses. There was a well-marked transition from the normal to the abnormal cells. The appearance was typical of a primary liver-cell carcinoma arising in a cirrhotic liver, probably in postnecrotic scarring (toxic cirrhosis of Mallory) (figs. 3 and 4).

DISCUSSION

It is clear that the initial illness in both these cases was a viral hepatitis. In case 1 the hepatitis started during an epidemic of infective hepatitis in Burma, and the patient was receiving antiluetic treatment with arsenic and bismuth at the time. The illness could therefore have been either epidemic infective hepatitis or homologous serum jaundice. In case 2 there was an initial episode of liver injury, probably serum hepatitis contracted during the course of arsenotherapy. This was followed fourteen years later by a severe attack of hepatitis which was almost certainly of the epidemic variety because the patient's wife had a similar though milder illness at the same time.

After the attack of viral hepatitis both patients developed cirrhosis of the liver. In case 1 the acute illness passed directly into the stage of subacute hepatitis, and some jaundice persisted almost without interruption until his death seven years later. In case 2 there was a latent period of five years between the attack of infective hepatitis and the first appearance of symptoms of portal hypertension. This long latent period has also been described by Kunkel and Labby (1950), who recorded the development of cirrhosis in 5 patients from two to six years after an attack of infective hepatitis. In both our cases the histological appearances were more in keeping with those of postnecrotic scarring than those of Laennec's diffuse fibrosis, although it is admitted that the histological differentiation between these two types of cirrhosis is often difficult if not impossible (Hoffbauer 1947).

Though there is a history of syphilis in both our cases, there is no evidence that this played any direct part in the ætiology of the cirrhosis. Prolonged oral administration of arsenic may predispose to fibrosis of the liver (Himsworth 1950), but the short courses of parenteral arsenic which these two patients had received are unlikely to have played any part in the development of the cirrhosis.

It seems probable that the neoplastic change was a consequence of the process of continuous regeneration of liver cells that is known to take place in cirrhosis due to other causes (Muir 1908). It is possible, however, that the virus had remained active and had in some way caused the regenerating liver cells to undergo malignant change. On the other hand, it is known that dietary factors can influence the formation of hepatic tumours. Miller et al. (1941) and Cramer (1942) showed that casein and riboflavine partially protected rats against hepatoma induced by butter yellow. Opie (1944) showed that rice, in some unexplained way, favoured the formation of hepatic tumours. Copeland and Salmon (1946) produced hepatoma-like tumours in rats maintained for a long time on choline-deficient diet. Though such abnormal diets are common among the native populations in those parts of the world where hepatic cancers are

0·5–2·0 cm. in diameter in the remainder of the right and in the left lobe. The intervening portions of the liver had the appearance of a coarse nodular cirrhosis. The spleen was firm and enlarged to three times its normal size. The lungs contained numerous bile-stained secondary deposits. There was no significant abnormality in any other organ.

Histological examination of the liver showed complete disorganisation of its architecture. Dense tracts of fibrous tissue divided groups of parenchymal cells into lobules of different sizes. Bile-duct regeneration was conspicuous. Many of the liver cells showed fatty infiltration. Scattered throughout the section were irregular areas consisting of neoplastic cells. In many places these were arranged to form alveolar spaces of different sizes, whereas in other places the cells formed solid columns and irregular syncytial masses. Multinucleate cells, irregularity of nuclear size, and mitotic figures were all common. Most of the cells surrounding the alveolar spaces were cuboidal; some were flattened, and the alveolar spaces were filled with a homogeneous pink-staining material. Broad bands of fibrous tissue separated the irregular collections of neoplastic cells. The appearances were those of a mixed bile-duct and liver-cell carcinoma arising in a liver which was the site of a multilobular cirrhosis (figs. 1 and 2).

THE SECOND CASE

A man, aged 40, was admitted to University College Hospital on Feb. 7, 1949.

History

The first six years of his life were spent in India, and during that time he had both typhoid fever and malaria. In 1928 he contracted syphilis, which was treated with intravenous arsenic. Eighteen months later, while still under treatment, he had a transient attack of jaundice lasting only a few days. He was then well until 1942, when he had an illness starting with malaise and anorexia and followed by jaundice. He was treated at home with a low-protein low-fat high-carbohydrate diet. The jaundice lasted three months; during this time his wife also had an attack of jaundice, which lasted two weeks.

For two months after the jaundice had cleared he had frequent attacks of sore throat and fever, which caused him to leave his work as a type moulder and seek lighter employment. From the end of 1942 he was well until January, 1948, when, after passing black stools for two days, he had a large hæmatemesis. He was admitted to the West Middlesex Hospital, where his hæmoglobin was found to be 45%. He was treated by blood-transfusion and improved, but after a few days he developed ascites and intermittent pyrexia. Investigations showed an erythrocyte-sedimentation rate of 25 mm. in 1 hour, a negative Wassermann reaction, and strongly positive serum-flocculation reactions. Chest radiography was normal, and a barium swallow did not show any œsophageal varices. Gastroscopy also failed to reveal any source of hæmorrhage. The ascitic fluid was reabsorbed spontaneously, and it then became possible to feel a firm liver and an enlarged spleen. He was discharged after two months in hospital.

He returned to work and was well until December, 1948, when his abdomen began to swell and he developed bilateral inguinal herniæ. During January, 1949, he was troubled by occasional nose-bleeds, swelling of the ankles, and breathlessness on effort. There was no history of alcoholism at any time.

Condition on Admission

He was wasted and anicteric, with temperature 99°F and pulse-rate 100. He had no complaints apart from the discomfort of his greatly distended abdomen. There were several pulsating arterial telangiectases on his neck, and he also showed well-developed "liver palms." There was no clubbing of the fingers, and no abnormal veins were visible on the abdomen or flanks. There was pitting œdema of the ankles. The abdomen was grossly distended with fluid, and it was impossible to palpate the liver or the spleen. The lungs and cardiovascular system were normal.

Investigations

The hæmoglobin was 88% and the white-cell count normal. The prothrombin concentration was 50% of normal. The serum-flocculation tests were all strongly positive, and the thymol turbidity was 20 units with flocculation. The Wassermann reaction and Kahn test were negative. The serum-albumin level was 3·7 g. per 100 ml. and serum-globulin 4 g. per 100 ml. Later the serum-albumin fell to 1·9 g., while the serum-globulin remained constant. A barium swallow showed œsophageal varices.

Course

After the ascites had been drained, a firm irregular liver edge could be felt in the epigastrium and the tip of the spleen was palpable. The patient had continued irregular pyrexia up to 102°F while in hospital, and this was not influenced by sulphonamides or by penicillin. Intravenous

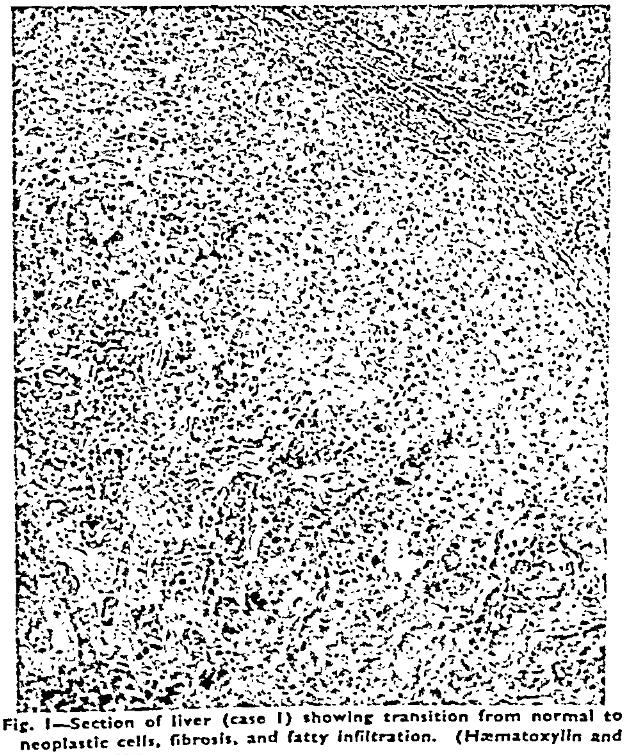


Fig. 1—Section of liver (case 1) showing transition from normal to neoplastic cells, fibrosis, and fatty infiltration. (Hæmatoxylin and eosin. × 60.)

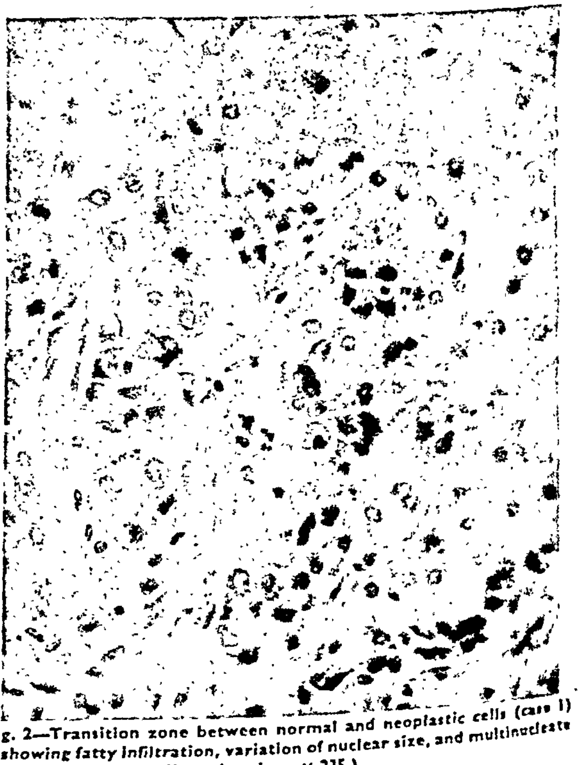


Fig. 2—Transition zone between normal and neoplastic cells (case 1) showing fatty infiltration, variation of nuclear size, and multinucleate cells. (Hæmatoxylin and eosin. × 235.)

only in Yemenite Jews but also in Oriental Jews and in Jews from Central Europe. The significant facts were that it could not be obtained regularly by the moist-stasis technique and never by using any of the conventional reducing agents (Dreyfuss et al. 1951). Yet in the single case of sickling discovered in a survey of Arabs (Dreyfuss and Benyesch 1952) the drepanocytes could be produced regularly by using ascorbic acid as recommended by Daland and Castle (1948).

On the occasion of the visit of one of us (H. L.) to Israel blood from some 30 unrelated Oriental Jews other than Yemenites was examined chemically for sickle cells, and none were found. Blood from 3 Central European Jews who had previously produced sickle cells in moist-stasis tests were re-examined chemically and found negative; they were also negative when tested by the moist-stasis technique on this occasion.

We next examined 59 unrelated Yemenites, all being recent immigrants living at Zorah. None of the samples showed sickle cells. The method used was incubation with 2% sodium metabisulphite. The reducing agent was dissolved in boiled distilled water on the day of use. Solutions similarly prepared from the same batch of the salt had been efficacious in producing sickle cells in numerous Veddians only a few days before in India.

Several weeks later one of us (F. D.) collected a further 27 blood samples in Zorah, 6 of them being from people whose blood had been examined on the first occasion. The blood was flown to London and examined within five days for the sickle-cell trait. The following reducing agents were used: sodium metabisulphite 2%, sodium dithionate 2·4%, and sodium hydrosulphite 2·1%. On this occasion African sickle cells from Uganda, which had been collected seven days before and were sent to us by courtesy of Dr. P. W. Hutton, were used as a control. In none of the Yemenite samples was sickling found, although it was demonstrated readily with each of the reagents in the African blood. A third consignment of 24 specimens, all from hospital patients, was sent two months later; 19 specimens were examined within three days, and the rest within four days of collection. Again no sickle cells could be produced by chemical means. Altogether 104 blood samples of unrelated Yemenites were examined with negative results.

TABLE I—BLOOD-GROUPS OF YEMENITE JEWS (ABO)

Blood-group	No. observed	Frequency observed	Frequency expected	No. expected
O	46	0·4423	0·4469	46·48
A_1	33	0·3173	0·3220	33·48
A_2	12	0·1154	0·1058	11·01
B	10	0·0962	0·0907	9·43
A_1B	3	0·0288	0·0248	2·58
A_2B	0	0·0000	0·0097	1·01
Total	104	1·0000	0·9999	103·99

Gene frequencies

O	0·6685
A_1	0·1918
A_2	0·0750
B	0·0647
Total	1·0000

Sickle cells are formed when the relatively insoluble reduced sickle-cell hæmoglobin crystallises intracellularly (Perutz et al. 1951), but they can also be produced by extracellular stress on normal cells (Isaacs 1950). A possible explanation of the earlier findings of Dreyfuss and Benyesch (1951) is that, on prolonged moist-stasis incubation, compounds were formed in the plasma which caused the red cells to sickle. The sera of the 3 Central Europeans whose blood had on previous occasions shown sickling were examined in London for numerous possible abnormalities, but the only remotely significant finding was a raised β-globulin content shown on filter-paper electrophoresis (by courtesy of Dr. W. G. Dangerfield). Experiments aiming at converting normal red cells into sickle cells by incubating them in β-globulin solutions of different strengths, however, gave negative results. One of us (F. D.) is continuing to investigate the possible causes—both extracellular and intracellular—of the observed phenomenen.

TABLE II—PHENOTYPES OF YEMENITE JEWS (MNS)

Phenotype	No. observed	Frequency observed	Frequency expected	No. expected
MMS	38	0·3654	0·3780	39·31
M_sM_s	19	0·1827	0·1917	19·94
MNS	21	0·2019	0·1840	19·14
M_sN_s	22	0·2115	0·1862	19·36
NNS	1	0·0096	0·0149	1·55
N_sN_s	3	0·0288	0·0452	4·70
Total	104	0·9999	1·0000	104·00

Chromosome frequencies

MS	0·3169
M_s	0·4379
NS	0·0326
N_s	0·2125
Total	0·9999

BLOOD-GROUPS

From all the people whom sickling tests were done in Israel samples were taken for blood-grouping and flown to London for testing at the Blood Group Reference Laboratory. Subsequent consignments sent by air to London for sickling tests were also examined for blood-groups. All the samples were tested with anti-A, anti-A_1 where relevant, anti-B, anti-C, anti-C^w, anti-D, anti-E, anti-c, anti-M, anti-N, anti-S, and anti-Henshaw. Positives with anti-E were tested with anti-e. Specimens negative with a saline anti-D were examined by means of the indirect anti-human-globulin test with a strong incomplete anti-D serum to detect the D^u antigen. In view of the exceptionally high frequency of D^u found in the first batch, second samples from several people were sent from Israel, and, apart from one which arrived in poor condition on the second occasion, all the results agreed with those found the first time. As an additional precaution D^u bloods of the second and third batches, and the repeat samples, were submitted to a direct anti-globulin test; they gave negative results. Hence the high D^u frequency found may be accepted with confidence.

The results of the blood-group tests are shown in tables I–III. Gene frequencies were calculated by the methods which have been briefly described by Chalmers et al. (1949) and Prasad et al. (1949) and are to be more fully described by A. E. Mourant (in the press).

TABLE III—PHENOTYPES OF YEMENITE JEWS (RHESUS)

Phenotype	No. observed	Frequency observed	Frequency expected	No. expected
CCDee	26	0·2500	0·2441	25·38
CcDee	45	0·4327	0·4044	42·06
CcDEe	3	0·0288	0·0667	6·93
ccDEe	11	0·1058	0·0589	6·12
ccDee	1	0·0096	0·0120	1·24
CcD^uee	3	0·0288	0·0288	3·00
ccD^uee	11	0·1058	0·1316	13·69
ccddee	4	0·0385	0·0479	4·98
ccDEE	0	0·0000	0·0045	0·47
CCD^uee	0	0·0000	0·0012	0·12
Total	104	1·0000	1·0001	103·99

Chromosome frequencies

cDe	0·0139
cD^ue	0·2049
CDe	0·4611
CD^ue	0·0340
cDE	0·0673
cde	0·2188
Total	1·0000

frequently found, there is no evidence that they played any significant part in our two cases.

SUMMARY

Two cases are described in which viral hepatitis was followed by cirrhosis and finally by primary carcinoma of the liver. Reference to the literature suggests that carcinoma of the liver is a rare complication of viral hepatitis.

Our thanks are due to Dr. J. B. Harman for permission to publish case 1; to Sir Harold Himsworth for permission to publish case 2; to Prof. G. R. Cameron for confirming the histological diagnosis; and to Mr. A. Bligh for the photomicrographs.

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AN INVESTIGATION OF BLOOD-GROUPS AND A SEARCH FOR SICKLE-CELL TRAIT IN YEMENITE JEWS

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THE modern Jew is not necessarily a close racial relation of the people of the Bible some 3000 years ago. Furthest removed from them are probably the Ashkenazim (Central and Eastern European), less so the Sephardim (Spanish and Mediterranean), and least the Oriental Jews of Asia Minor and Arabia.

There was undoubtedly a period in Roman times when the Jews made proselytes, an activity which waned when Christianity became fully established. It was also the custom for a slave on becoming a free man to accept the religion of his former master. Thus there must have been an influx of non-Semitic blood into the Jewish community in those times. Moreover in Eastern Europe whole communities, such as the Chazars near the Black Sea, embraced the Jewish faith.

There exist still, however, the Jews of Yemen, who have lived in isolation for nearly 2000 years. They are a deeply religious community among whom miscegenation with the surrounding Arabs must have been very rare. These Yemenite Jews have recently migrated to the new state of Israel and thus become much more readily accessible for anthropological investigation.

BLOOD-GROUPS OF JEWS

Broadly, the Jews resemble their neighbours in their ABO-group frequencies but tend to have a higher B frequency than peoples in the West of Europe, and a higher A frequency than the indigenous populations in Eastern Europe, including Russia.

In their Rh groups the Jews tend to a somewhat low frequency of the Rh-negative group and of the cde (r) chromosome, and a relatively high frequency of CDe (R_1), in both respects resembling the peoples of southern rather than Central and Northern Europe. The Jews also have rather more of the cDe (R_0) chromosome than have most Europeans. This chromosome is typical of Africa, but frequencies above the normal European level of 2% are found in various peoples near the Mediterranean Sea, especially the Egyptians and Iraq Arabs. There can be little doubt that the Jews have derived this chromosome ultimately from an African source. There was contact with that continent during the sojourn in Egypt; Moses's wife was an Ethiopian and was therefore resented by Miriam and Aaron (*Numbers*, XII). It is also probable that the Jews, like other Mediterranean groups, received some African blood in Roman times.

The Yemenite Jews present a rather special local problem. Their ABO blood-group frequencies differ from those of most other Jewish peoples. With a high frequency of O, a moderate frequency of A, and a low frequency of B they closely resemble, rather surprisingly, those of the Yemenite Arabs, of the white Berbers and Touaregs of North Africa, and of the "Celtic" peoples of the British Isles. On the other hand, their high frequency of M is typically Asiatic rather than European or African. A preliminary Rh survey of Yemenite Jews showed the very low frequency of 2·3% of Rh-negatives (D-negatives) (Gurevitch et al. 1947). A more recent and detailed study of 500 Yemenite Jews showed 10% of Rh-negatives, together with 5% of the ccDee (R_0) phenotype or more than 6% of the cDe chromosome, suggesting a small but appreciable African component in the population (Brzezinski et al. 1952). Dreyfuss and Benyesch (1951) made sickling tests in Israel on newly arrived immigrants from Yemen and reported positive results in 17 children. This trait has hitherto been found almost exclusively in African Negroids and, sporadically, in Mediterranean peoples among whom it was not unreasonable to expect contributions from an occasional African ancestor. The trait has also been found in Veddians in South India (Lehmann and Cutbush 1952a and b); hence it becomes possible for the trait to be derived from non-Negroids. However it still holds for practical purposes that sickle cells, in the first place at any rate, suggest connections with Africa.

The history and traditions of the Yemenite Jews and the major features of their blood-group picture thus gave no indications of any African ancestry; but the reported presence of sickling and of a somewhat raised cDe frequency showed that the presence of an African component had to be considered. To investigate a possible African connection, two of us (F. D. and H. L.) met in Israel to look for the sickle-cell trait and to collect blood for grouping.

SICKLE-CELL TRAIT

Dreyfuss and Benyesch (1951) had seen the sickle-cell trait when they incubated blood samples by the moist-stasis method of Scriver and Waugh (1930). It could not be shown regularly in the same persons, and often consisted only in the conversion into the sickle shape of a very few cells after prolonged incubation, though in some instances there was a very full development of the abnormal cell configuration over the whole field of the sample. This phenomenon was eventually noted not only in Yemenite Jews but also in Oriental Jews and in Jews from Central Europe. The significant facts were that it could not be obtained regularly by the moist-stasis technique and never by using any of the conventional reducing agents (Dreyfuss et al. 1951). Yet in the single case of sickling discovered in a survey of Arabs (Dreyfuss and Benyesch 1952) the drepanocytes could be produced regularly by using ascorbic acid as recommended by Daland and Castle (1948).

On the occasion of the visit of one of us (H. L.) to Israel blood from some 30 unrelated Oriental Jews other than Yemenites was examined chemically for sickle cells, and none were found. Blood from 3 Central European Jews who had previously produced sickle cells in moist-stasis tests were re-examined chemically and found negative; they were also negative when tested by the moist-stasis technique on this occasion.

We next examined 59 unrelated Yemenites, all being recent immigrants living at Zorah. None of the samples showed sickle cells. The method used was incubation with 2% sodium metabisulphite. The reducing agent was dissolved in boiled distilled water on the day of use. Solutions similarly prepared from the same batch of the salt had been efficacious in producing sickle cells in numerous Veddians only a few days before in India.

Several weeks later one of us (F. D.) collected a further 27 blood samples in Zorah, 6 of them being from people whose blood had been examined on the first occasion. The blood was flown to London and examined within five days for the sickle-cell trait. The following reducing agents were used: sodium metabisulphite 2%, sodium dithionate 2·4%, and sodium hydrosulphite 2·1%. On this occasion African sickle cells from Uganda, which had been collected seven days before and were sent to us by courtesy of Dr. P. W. Hutton, were used as a control. In none of the Yemenite samples was sickling found, although it was demonstrated readily with each of the reagents in the African blood. A third consignment of 24 specimens, all from hospital patients, was sent two months later; 19 specimens were examined within three days, and the rest within four days of collection. Again no sickle cells could be produced by chemical means. Altogether 104 blood samples of unrelated Yemenites were examined with negative results.

TABLE I—BLOOD-GROUPS OF YEMENITE JEWS (ABO)

Blood-group	No. observed	Frequency observed	Frequency expected	No. expected
O	46	0·4423	0·4469	46·48
A_1	33	0·3173	0·3220	33·48
A_2	12	0·1154	0·1058	11·01
B	10	0·0962	0·0907	9·43
A_1B	3	0·0288	0·0248	2·58
A_2B	0	0·0000	0·0097	1·01
Total	104	1·0000	0·9999	103·99

Gene frequencies

O	0·6685
A_1	0·1918
A_2	0·0750
B	0·0647
Total	1·0000

Sickle cells are formed when the relatively insoluble reduced sickle-cell hæmoglobin crystallises intracellularly (Perutz et al. 1951), but they can also be produced by extracellular stress on normal cells (Isaacs 1950). A possible explanation of the earlier findings of Dreyfuss and Benyesch (1951) is that, on prolonged moist-stasis incubation, compounds were formed in the plasma which caused the red cells to sickle. The sera of the 3 Central Europeans whose blood had on previous occasions shown sickling were examined in London for numerous possible abnormalities, but the only remotely significant finding was a raised β-globulin content shown on filter-paper electrophoresis (by courtesy of Dr. W. G. Dangerfield). Experiments aiming at converting normal red cells into sickle cells by incubating them in β-globulin solutions of different strengths, however, gave negative results. One of us (F. D.) is continuing to investigate the possible causes—both extracellular and intracellular—of the observed phenomenen.

TABLE II—PHENOTYPES OF YEMENITE JEWS (MNS)

Phenotype	No. observed	Frequency observed	Frequency expected	No. expected
MMS	38	0·3654	0·3780	39·31
M_sM_s	19	0·1827	0·1917	19·94
MNS	21	0·2019	0·1840	19·14
M_sN_s	22	0·2115	0·1862	19·36
NNS	1	0·0096	0·0149	1·55
N_sN_s	3	0·0288	0·0452	4·70
Total	104	0·9999	1·0000	104·00

Chromosome frequencies

MS	0·3169
M_s	0·4379
NS	0·0326
N_s	0·2125
Total	0·9999

BLOOD-GROUPS

From all the people whom sickling tests were done in Israel samples were taken for blood-grouping and flown to London for testing at the Blood Group Reference Laboratory. Subsequent consignments sent by air to London for sickling tests were also examined for blood-groups. All the samples were tested with anti-A, anti-A_1 where relevant, anti-B, anti-C, anti-C^w, anti-D, anti-E, anti-c, anti-M, anti-N, anti-S, and anti-Henshaw. Positives with anti-E were tested with anti-e. Specimens negative with a saline anti-D were examined by means of the indirect anti-human-globulin test with a strong incomplete anti-D serum to detect the D^u antigen. In view of the exceptionally high frequency of D^u found in the first batch, second samples from several people were sent from Israel, and, apart from one which arrived in poor condition on the second occasion, all the results agreed with those found the first time. As an additional precaution D^u bloods of the second and third batches, and the repeat samples, were submitted to a direct anti-globulin test; they gave negative results. Hence the high D^u frequency found may be accepted with confidence.

The results of the blood-group tests are shown in tables I–III. Gene frequencies were calculated by the methods which have been briefly described by Chalmers et al. (1949) and Prasad et al. (1949) and are to be more fully described by A. E. Mourant (in the press).

TABLE III—PHENOTYPES OF YEMENITE JEWS (RHESUS)

Phenotype	No. observed	Frequency observed	Frequency expected	No. expected
CCDee	26	0·2500	0·2441	25·38
CcDee	45	0·4327	0·4044	42·06
CcDEe	3	0·0288	0·0667	6·93
ccDEe	11	0·1058	0·0589	6·12
ccDee	1	0·0096	0·0120	1·24
CcD^uee	3	0·0288	0·0288	3·00
ccD^uee	11	0·1058	0·1316	13·69
ccddee	4	0·0385	0·0479	4·98
ccDEE	0	0·0000	0·0045	0·47
CCD^uee	0	0·0000	0·0012	0·12
Total	104	1·0000	1·0001	103·99

Chromosome frequencies

cDe	0·0139
cD^ue	0·2049
CDe	0·4611
CD^ue	0·0340
cDE	0·0673
cde	0·2188
Total	1·0000

Our blood-group results are in fair agreement with those of previous workers cited above, but in certain respects the disagreement is sufficient to suggest that our specimens and theirs are not drawn from a single homogeneous population. As regards ABO, whereas we found rather lower frequencies of O and higher frequencies of A than did either Younovitch (1933) or Brzezinski et al. (1952), there is still a considerable resemblance to the Yemenite Arabs, the white North Africans, and the inhabitants of the British Isles (rather to the English than to the Scots, Irish, and Welsh). The frequency found by us for the A_2 gene is higher than any other reported for Asia, and compares closely with those found in the extreme West of Europe.

Our frequencies for the MN groups are extremely close to those of Brzezinski et al. (1952), the frequency of M being very high. We also found a relatively high frequency of S, mainly associated with M. The whole of this MNS picture is similar to that found in Northern India, Anglo-Egyptian Sudan, and Abyssinia (but not in Egypt or in Negro Africa). High frequencies of M are found throughout Eastern Europe and Western Asia, but only in the above-mentioned cases has S been tested for. S frequencies are high among Europeans and western Asiatics but low in most other races.

Tests were made for the Henshaw antigen (Ikin and Mourant 1951) so far known almost solely in Negroes. Had it been found it would have been important evidence of African connections; but, since it is only present in 3% of Africans so far tested, its absence from the Yemenite Jews means little.

The most interesting feature of the blood-groups of the Yemenite Jews is their Rh picture. Like most other series of Jews hitherto examined, they show relatively high CDe (R_1) and low cDE (R_2) and cde (rr). They do not, however, show the usual cDe (R_0) frequency of 5–10%. They have only 1·3% of this chromosome, but they show the quite exceptional frequency of 20% of cD^ue. When the first batch of specimens gave this surprising result, arrangements were made, as stated above, to repeat the tests on the blood of some of the people concerned, and in the subsequent batches special control tests were made, including direct anti-human-globulin tests. There is thus no doubt that the phenomenon is genuine. Possibly the discrepancy in the frequency of Rh-negatives in the two previous series of tests on Yemenite Jews is due to this high frequency of D^u, since cells with the D^u antigen (and without D) might give positive results with one anti-D serum and negative results with another.

Everywhere outside Africa the chromosome cD^ue is extremely rare or unknown. In most Negro populations its frequency is about 1%, and it had hitherto been supposed that this represented mutations from the commonest Negro chromosome cDe (and that in Europe mutation from CDe had similarly produced CD^ue). One other group of people has, however, recently been found which appears to have a frequency of cD^ue comparable to that of the Yemenite Jews. These are the Touaregs of Agades, one of the most southerly Touareg peoples. In this case only 71 persons have yet been tested, and the specimens were several days old—rather older than is desirable for such critical examinations. Hence the results need confirmation. The Northern Nigerians all have about 7% of cD^ue; this may well be due to mixing with white peoples of the Sahara, and possibly a high frequency of cD^ue will prove to be an important characteristic of a series of white peoples in North Africa and the near East.

The genetical picture revealed by an examination of the blood of Yemenite Jews thus shows resemblances to Europe, Asia, and white North Africa. Negro characters, such as sickling of cells on deoxygenation and a raised cDe frequency, are absent.

SUMMARY

Among 104 unrelated Yemenite Jews no sickle-cell trait was found when their blood was reduced by chemical means.

Their blood-group picture resembles that of the peoples of Europe and Western Asia and the white peoples of North Africa.

Their Rh chromosome cDe has a frequency of 1·4%, compared with about 2% in Europe and more than 50% in Negroes.

Their chromosome cD^ue has the exceptionally high frequency of 20%. The only other known community with a comparable frequency is that of the Touaregs (North-African whites).

We are grateful to Dr. R. N. Salaman, F.R.S., for pointing out that, although most of the experts assume that the Yemenite Jews arrived in South Arabia at the time of the destruction of the second temple, others hold the view (unpublished) that there were but few of them, and that the present-day Yemenite Jews are descended from Arab converts. Even then they would represent a "Semitic" group which did not experience the miscegenation of the Jews of Europe. One of us (F. D.) was helped by the Research Council of the Government of Israel and one (H. L.) by the Nuffield Foundation. We are indebted to these two organisations and would also like to acknowledge gratefully the help of Mrs. A. C. Kopeć, D.SC., of the Nuffield Blood Group Centre of the Royal Anthropological Institute, London, in calculating the frequencies reported here.

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ISONIAZID IN LEPROSY

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THE link between tuberculosis and leprosy is perhaps most obvious in the similarity of the causative organisms, and in the fact that some chemotherapeutic agents seem to act on both organisms. Indeed the two groups of drugs most effective in leprosy (sulphones and thiosemicarbazones) were originally designed for use in tuberculosis; and the promising early reports on the action of isoniazid in tuberculosis have naturally led to its trial in leprosy.

A trial began here in April, 1952, and lasted 5½ months. The reports of the action of isoniazid in tuberculosis suggested that it might be of value in leprosy in two ways; it might be effective as a basic treatment of the disease itself; or it might be of value in the treatment of the acute and subacute complications of leprosy. The trial was therefore planned to study both these aspects of the chemotherapy of leprosy.

ISONIAZID IN UNCOMPLICATED LEPROSY

Newly diagnosed and completely untreated cases of leprosy were selected. Moreover, patients were chosen who showed easily visible lesions in which clinical improvement could be readily detected. There were 20 patients in this trial: 10 had "lepromatous" disease, in which the prognosis without treatment is poor and improvement with treatment is slow; 10 had "tuberculoid" leprosy, in which prognosis is relatively good, in which slow spontaneous improvement is often seen, and in which improvement under treatment is often rapid.

Dosage

At the start of the trial the *initial* dose of isoniazid was 50 mg. a day, rising to 100 mg. and 150 mg. in the second and third weeks respectively. As the trial progressed it became clear that isoniazid was very well tolerated but the response to treatment was poor, so an attempt was made to improve the response by starting with doses of 200 or even 300 mg. a day. The highest dosage given was 300 mg. a day.

Results in Tuberculoid Leprosy

The 10 patients were treated for periods varying between eight and nineteen weeks. In all cases the disease was active, with thickened raised red lesions in the skin, and often with thickening and inflammation of nerves, including the cutaneous nerves supplying the lesions and the nerve-trunks of the affected parts, particularly the ulnar and peroneal nerves. Ordinary bacteriological examination of the lesions for leprosy bacilli was usually negative, and the assessment of results had to be made on clinical grounds alone.

As I have previously pointed out (Lowe 1936), these lesions often subside slowly without treatment, and they usually respond to sulphones or thiosemicarbazones in a few weeks (Lowe 1950, 1952, Lowe and Davey 1951).

Under treatment with isoniazid, only 1 patient out of the 10 showed any definite improvement; 3 showed possibly a slight improvement; 5 showed no change whatever; and 1 became definitely worse.

These results are very disappointing, for they could easily have been just the same with no treatment at all. They were in no way comparable to those regularly obtained with sulphones and thiosemicarbazones in similar cases. The therapeutic action of isoniazid in such cases seems negligible.

Results in Lepromatous Leprosy

The 10 lepromatous patients had had no previous treatment; the disease was not too severe, and there were easily visible lesions in which clinical improvement could be quickly detected. These patients were treated for periods up to twenty-three weeks, and only 1 had less than fourteen weeks' treatment. They were all very suitable cases for chemotherapy. The general condition of the patients and the appearance of the lesions were watched for signs of improvement, and repeated bacteriological examinations of the lesions were made to detect any decrease in the number of bacilli or any change in their morphology.

At the end of the trial, not a single patient showed definite improvement; there were 4 who might have improved very slightly; 4 showed no change; and 2 were clearly worse. In no case were bacilli definitely less, and no distinct morphological change in bacilli was observed.

In this form of leprosy, the disease usually gets worse without treatment, but very slowly, and improvement under treatment is also very slow. It may, therefore, seem difficult or impossible to assess the value of isoniazid in such cases after only twenty-three weeks or less. Nevertheless, I have no hesitation in saying that in this group of very favourable cases, sulphone or thiosemicarbazone would have produced definite clinical and some bacteriological improvement in a considerable number within this time. These findings, while not proving that isoniazid is inactive in lepromatous leprosy, strongly suggest that it has little or no action.

ISONIAZID IN THE COMPLICATIONS OF LEPROSY

Some reports of the use of isoniazid in tuberculosis have emphasised its value in the control of acute and subacute manifestations, suggesting that it might have a similar action in leprosy.

To investigate this point, 7 patients were chosen in whom treatment with sulphone or thiosemicarbazone had become difficult because of acute and subacute complications. They were all lepromatous cases. The complications, which had probably been precipitated by the previous treatment, took the form of repeated "reactions," with fever, erythema nodosum, neuritis, and other acute or subacute manifestations. Such attacks are well known during chemotherapy; they usually subside slowly when treatment is stopped, but they often recur if treatment is resumed, or even if it is withheld indefinitely. Isoniazid was tried in the hope that it might diminish the frequency and severity of these attacks.

All 7 patients were given isoniazid for the first time during an attack, and the acute symptoms subsided in 6 of them. Thus the early results were good, but the late results were very variable. After treatment for from fifteen to twenty-three weeks, 3 of the 7 patients were relatively free from acute symptoms; 2 were perhaps slightly better; 1 was no better; and 1 (with ulnar neuritis) had responded only to surgical treatment. These results are very similar to those obtained simply by stopping chemotherapy, and they again suggest that isoniazid is inactive in leprosy. None of the patients showed any evidence of definite improvement in the underlying infection.

CONCLUSIONS AND SUMMARY

Isoniazid has produced no significant improvement in 27 patients with leprosy who were treated for periods of from fourteen to twenty-three weeks. The patients were chosen as particularly suitable for showing the results of chemotherapy.

Isoniazid is possibly of slight benefit in leprosy, but its action is much less than that of sulphone or thiosemicarbazone in comparable cases. It may have some value in the treatment of acute and subacute manifestations of the disease, but the findings in this trial were not at all conclusive.

My thanks are due to Miss F. McNulty, laboratory superintendent, for her help with this work; to Dr. K. S. Seal, of the Nigeria Leprosy Service, for supervising the work during my absence; to Dr. T. F. Davey, Leprosy Adviser to the Nigeria Government, and Dr. S. L. A. Manuwa, Inspector-General of Medical Services, Nigeria, for permission to publish these results; and to Dr. R. Forgan of Messrs. May & Baker for supplies of izoniazid.

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DIETARY LIVER NECROSIS

INFLUENCE OF ENVIRONMENTAL TEMPERATURE AND MODE OF FEEDING ON ITS PRODUCTION IN THE RAT

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In a previous paper (Naftalin 1951) I showed that, when young male albino rats were offered a low-protein diet deficient in vitamin E, the incidence of acute liver necrosis depended on the environmental temperature and on the mode of feeding—i.e., whether the rats were allowed to eat to appetite or not. On comparing the results of three separate experiments it was *postulated* that the same degree of food restriction would give different results at different environmental temperatures. Experiment 4 described below was designed to test this postulate in one experiment. Littermates were used so that the ratios of food eaten by the different groups would be directly comparable. Two degrees of restriction and two environmental temperatures were studied. This experiment and experiment 5 define the lower and upper limits of favourable environmental temperatures for the production of acute dietary liver necrosis in the rat.

METHODS

Male albino rats were studied in both experiments. The procedures of rearing, management, and acclimatisation were as previously described (Naftalin 1951).

Environments

In both experiments the dry-bulb air-temperature was recorded on seven-day thermographs placed in the centre of one wall in the room:

Experiment 4 (November, 1950–February, 1951).—Two environments were studied: (1) heated animal-house, usual range of temperature 70°–78°F, extreme range 64°–80°F (groups A, B, and C, of 12 rats each); (2) heated animal-house, usual range 60°–64°F, extreme range 58°–70°, each extreme on one occasion for short period of half a day (groups D, E, and F, each of 12 rats).

Experiment 5 (March–June, 1951).—Two environments were studied: (1) heated animal-house, extreme range 72°–76°F (group H of 9 rats); and (2) heated animal-house, extreme range 88°–92°F (groups I of 10 rats, J of 6 rats, and K of 9 rats). The temperatures remained within these ranges throughout the experiment.

Food

The *diets* used in experiment 4 were those previously described—i.e., diet no. 51 containing 16% casein (Glaxo 'Vitamin-Free') and 3% yeast from the 18th day of age till the 37th day, and diet no. 47 containing 8% casein and 3% yeast from the 38th day. In experiment 5 choline chloride (200 mg. per 100 g. of diet) was added to both diets to prevent an acute hæmorrhagic lesion of the kidneys. This lesion was found in experiment 4 when 8 rats died aged 25–28 days—i.e., in the pre-experimental period—but was not encountered in the three previous experiments with diet no. 51.

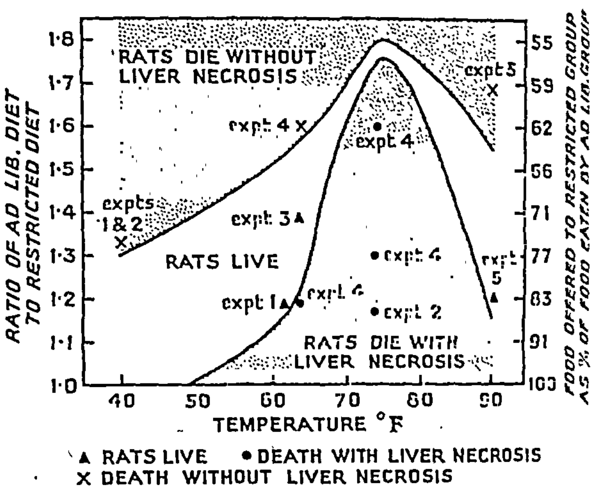
Feeding.—Groups A and D of experiment 4 and groups H and I of experiment 5 were allowed to eat according to appetite. The food consumption of each rat in both experiments was measured at about 10 A.M. daily.

"*Restricted*" *feeding.*—Groups B, C, E, and F of experiment 4 and groups J and K of experiment 5 were not fed to appetite. The degree of food restriction aimed at was such that in experiment 4 the ratio of food eaten by group A to group B was 1·2; A/C 1·5; D/E 1·2; and D/F 1·5; and in experiment 5 I/J 1·2; and I/K 1·6. The ratio was determined daily by taking the average food intake of the rats in the corresponding groups fed to appetite and then feeding to the "restricted" groups the calculated amount. At the conclusion of the experiment a calculation for the *group* average degree of food restriction for groups B, C, E, or F was made by taking the average of the food eaten daily by the rats in the groups fed to appetite (group A or D) and dividing by the average amount of food offered daily to these "restricted" groups. These ratios differed slightly from the ratios aimed at, because after a rat died its average food intake was not taken into account in the feeding of the "res[illegible]" [illegible]. These final ratios are indicated in the [illegible].

RESULTS AND DISCUSSION *

Optimum Environmental Temperature for Production of Liver Necrosis

In experiment 4, in the rats fed to appetite in the environmental temperature of 60°–64°F the incidence of acute liver necrosis was 4 among 12 rats (group D); in the environmental temperature of 70°–78°F (group A) the incidence of acute liver necrosis was 12 among 12 rats. The probability of such a difference in incidence between groups A and D arising by chance is less than 1 in 100.



The values "food restriction/environmental temperature" obtained in experiments 1–5 have been plotted and two curves drawn round them. These curves are appoximate, and the exact values may not hold for other diets of different percentage composition. It has been assumed that optimal temperature for the production of dietary liver necrosis is about 75°F.

In experiment 5, in group H, environmental temperature of 72°–76°F, the incidence of acute liver necrosis was 9 among 9 rats, with a median survival-time of 15 days, whereas at 88°–92°F, group I, 9 of 10 rats died of acute liver necrosis, the median survival-time being 29 days, a difference which did not quite reach the 5% level of significance.

It is thus evident that 60°–64°F is too low, and 88°–92°F too high for the optimum environmental temperature for the production of liver necrosis. As the range of 80°–88°F has not yet been studied, the optimum temperature has not been defined within narrower limits. Meanwhile it can be said that an environmental temperature of about 75°F is suitable for the production of a high incidence of dietary liver necrosis in rats.

Degree of Food Restriction

The results obtained with different degrees of food restriction depend on the environmental temperature.

At 70°–78°F the greater degree of restriction, 1·6, was insufficient to prevent liver necrosis in every rat in group C, 3 of 12 rats dying from liver necrosis, whereas a similar degree of restriction led to deaths without liver necrosis at 60°–64°F and 88°–92°F (group F, 3 deaths; group K, 7 deaths). This supports the postulate put forward previously. When the temperature fell below about 45°F, even a moderate degree of restriction, 1·3–1·4, led to death without liver necrosis (experiment 1). With a lower degree of restriction, 1·2–1·3, the incidence of liver necrosis at 70°–78°F was the same as in the groups fed "ad lib." (experiments 2 and 4). This high incidence of liver necrosis in group B, experiment 4, took place despite a fall in temperature to about 68°F (lowest 64°F for half a day) from Dec. 26, 1950, to Jan. 11, 1951. During this period there were no deaths in group B, the median survival-time thus being exaggerated (group B, 50 days; group A, 15 days).

In contrast with these results, at an environmental temperature of about 63°F in experiment 1 liver necrosis was prevented by a low degree of food restriction (1·15). The rats survived the experiment. However, in the corresponding group fed to appetite the food intake of only 2 rats was studied for a week. In experiment 3 the degree of food restriction of 1·6 was used at the beginning, but, though this was dropped to 1·25–1·4, liver necrosis did not result, the rats again surviving the experiment. However, in experiment 4, group B environmental temperature 60°–64°F, 6 of 12 rats died from acute liver necrosis when the group average degree of food restriction was 1·2, the median survival time being 64 days. It thus seems that a group average degree of food restriction of 1·2 is too low at 60°–64°F to prevent liver necrosis in every rat. In group D of this experiment the wide range of food eaten, 7·2 g. to 12·1 g. per rat per day made it difficult to assess the degree of food restriction in individual rats. Again, at 88°–92°F a small degree of restriction of 1·2 sufficed for protection against liver necrosis.

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* Multigraphed tables showing the results in detail may be had on application to the office of THE LANCET, 7, Adam Street, Adelphi, London, W.C.2.

The evidence from studying the degree of food restriction thus confirmed that the optimum temperature for production of the disease was above 64°F and below 88°F. Further, from the study of the amount of food eaten it was shown that it was the manner of feeding and the degree of food restriction in relation to the environmental temperature and not the amount of food eaten per se that determined whether a rat survived or died of liver necrosis or of inanition.

For experiments 1–5 the degree of food restriction was plotted against environmental temperature, and two curves were drawn by hand, separating the groups which died from necrosis from the survivals and from those which died from inanition. This is shown in the accompanying figure which brings out clearly the relation between food restriction and environmental temperature. The base-line represents the rats which ate to appetite. It has been assumed that their sensitivity to liver necrosis is greatest in the region of 75°F. The values are not to be taken as absolute, because sufficient points have not been obtained experimentally. Furthermore, these ratios are based on observations on young male albino rats weaned on their 24th day of life, given the experimental low-protein diet about their 38th day when they weighed 60–80 g., and fed on the diet described in this paper and the previous one. Although the trend is clear, the exact values may not hold for diets of other percentage composition or with ingredients of different make.

The biochemical significance of these changes in ratios is not yet clear. The prevention of necrosis by low environmental temperature or the increased survival-time at a high temperature may not be an expression of the same changes in metabolism as those due to a "restricted" method of feeding. These results support the view that different pathways of metabolism are followed under different conditions, and the manner in which the liver functions depends on the total body metabolism.

SUMMARY

A high incidence of acute liver necrosis was produced in young male albino rats when they were housed in a suitable environment and allowed to eat to appetite of a diet containing 8% casein (Glaxo 'Vitamin-Free'), 3% yeast (Pharmaco-Chemical Products), 7% lard, 2% cod-liver oil (B.P.), 76% sucrose, and 4% McCollum's salt and B vitamins, but without added vitamin E.

Of the three ranges of environmental temperature studied—60°–64°F, 70°–78°F, and 88°–92°F—the best temperature for the production of acute liver necrosis was 70°–78°F.

A sufficient degree of food restriction prevented liver necrosis at all environmental temperatures studied, but a too severe degree of food restriction led to death without liver necrosis. Whether a rat survived or died of necrosis or of inanition depended on the degree of food restriction in relation to the environmental temperature and not on the amount of food eaten.

I am indebted to Mr. A. W. Boyne, of the Rowett Institute, for the statistical design of the experiments and for much helpful discussion.

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RICKETS AND AMINO-ACIDURIA

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SMALL amounts of amino-acids, peptides, and conjugates are found in the urine of healthy children. The quantities of these depend to some extent on the composition of the food (Dunn et al. 1947, Harvey and Horwitt 1949), but the concentration of the free amino-nitrogen in the 24-hour urine of a normal child seldom exceeds 20 mg. per 100 ml. This is approximately equivalent to a concentration of free amino-acids of 200 mg. per 100 ml. When the amino-acid composition of the diet is incomplete or when certain drugs are taken—e.g., salicylates—which are partly excreted as glycine-conjugates, the urinary output of amino-acids is considerably greater. Of the individual amino-acids it is normal for the urine of adults and infants to contain some glycine and histidine, smaller amounts of serine, threonine, alanine, and lysine, and only a trace of many others. Acid hydrolysis may free considerable amounts of glutamic acid and aspartic acid, and generally also additional glycine.

When investigating the differences in the amino-acid excretion of infants fed on breast-milk or cow's milk Jonxis (1951) noticed that some children with incipient rickets excreted considerably more amino-acids than the others, and this observation led to a more detailed study of the amino-aciduria in rachitic children. Little is known about this. Abnormal amino-aciduria is part of the Toni-Fanconi-Debré syndrome (McCune et al. 1943), but this form of osteomalacia is not thought to be due primarily to a vitamin-D deficiency.

MATERIAL AND METHODS

Nine children with uncomplicated rickets have been examined. Their ages ranged from 6 to 15 months, and none of them had been given any vitamin D. The X-ray pictures of their bones showed the usual abnormalities. After admission to the hospital the children were given a diet suitable to their age and weight and containing about 2·5 g. of protein per kg. of body-weight. The main source of this protein was cow's milk, of which 500 ml. daily was given to each child. Since a deficiency of vitamin C may cause an increased output of amino-acids (Jonxis and Wadman 1951) 100 mg. of ascorbic acid was given daily to each child during the first few days after admission. A sample of blood was withdrawn for the determination of calcium, phosphate, and phosphatase, and the urine was collected for 72 hours. Vitamin D 300,000 I.U. dissolved in 3 ml. of arachis oil, was then given by mouth, and 8–35 days later the levels of calcium, phosphate, and alkaline phosphatase in the serum were again determined, and the urine was again collected over 72 hours. Further radiographs were also taken. The amino-acid excretion of 10 healthy children of ages similar to those with rickets was also studied over 72 hours. In addition to this, siblings and other relatives of some of the rachitic children were examined clinically and biochemically.

The urine was stored at −20°C till it could be examined for amino-acids. The simple copper method of Albanese and Irby (1944) was used to get a general impression of the extent of the amino-aciduria, but the more accurate ninhydrin and carbon dioxide method of van Slyke et al. (1941) was also usually applied before and after acid hydrolysis. The increase of the percentage of amino-nitrogen after hydrolysis gave a measure of the quantity of amino-acids which had been present as peptides and conjugates. In addition to this, two-

TABLE I—EXCRETION OF α AMINO- NITROGEN BY RACHITIC CHILDREN BEFORE AND AFTER TREATMENT

Case no.	Age (mos.)	Serum: mg. per 100 ml.: P	Serum: mg. per 100 ml.: Ca	Serum: Phosphatase (Bodansky units)	Urine: 24 hr. volume (ml.)	Urine: α amino- nitrogen (mg. per 100 ml.): Copper method	Urine: α amino- nitrogen (mg. per 100 ml.): van Slyke	Urine: α amino- nitrogen (mg. per 100 ml.): van Slyke after hydrolysis
Before treatment:								
1	6	4·3	6·2	..	210	85	33	105
2	8	2·8	9·1	..	185	31	22	46
3	9	2·8	9·6	74	225	103	30	57
4	9	3·0	6·8	98	160	138	17	167
5	7	2·4	10·2	43	200	125	78	128
6	12	3·1	10·0	19	225	70	16	36
7	14	3·1	10·1	64	230	90	27	57
8	15	2·7	9·2	69	210	63	17	62
9	9	2·5	9·0	80	230	129	44	72
	No. of days after treatment							
After treatment:								
1	8	7·4	11·1	..	220	57	23	64
2	14	6·1	10·4	..	210	13	8	20
3	21	6·0	10·3	36	240	23	7	14
4	28	6·2	10·7	17	185	53	20	45
5	21	5·4	10·7	18	195	54	13	36
6	28	6·4	10·9	13	220	23	12	27
7	21	5·7	9·4	51	240	40	19	40
8	35	4·5	10·1	56	200	23	12	27
9	28	5·9	10·5	19	215	36	16	34

dimensional paper chromatograms were made by the technique described by Dent (1949).

RESULTS

Table I shows the findings in the serum and in the urine of the rachitic children before and after treatment, and table II the quantities of amino-acids and peptides excreted by normal children. It will be seen that the excretion of free amino-acids and of peptides and conjugates by children with florid rickets was much greater than normal. During recovery the excretion both of free and bound amino-acids decreased, and in some of the children—e.g., case 4—the fall in the excretion of bound amino-acids was the greater. Six other children were examined less completely, and the findings in them were essentially similar. If the changes in the serum are compared with those in the urine, it will be noted that the decrease of the amino-acid excretion, like that of the phosphatase activity in the serum, was relatively slow, requiring about a month to be complete. Before this time the serum-calcium and serum-phosphorus levels had reached their normal values, and an improvement could be demonstrated radiologically in the bones. Serial findings in case 4 are shown in table III.

TABLE II—EXCRETION OF α AMINO- NITROGEN BY HEALTHY CHILDREN

Food	Case no.	α amino- nitrogen excreted in urine (mg. per 100 ml.): Copper method	van Slyke	van Slyke after hydrolysis
Breast-milk ..	10	6	3	6
,, ,, ..	11	13	6	12
,, ,, ..	12	11	5	9
Cow's milk ..	13	15	5	13
,, ,, ..	14	17	4	22
,, ,, ..	15	14	7	18
,, ,, ..	16	21	14	18
Mixed food ..	17	18	..	..
,, ,, ..	18	21	..	..
,, ,, ..	19	28	..	..

TABLE III—FINDINGS IN CASE 4

Time after administration of vitamin D, 300,000 I.U. (weeks)	Serum-phosphorus (mg. per 100 ml.)	Alkaline phosphatase (Bodansky units)	α amino-nitrogen excreted in urine (mg. per 100 ml.)
0	3·0	98	70
1	4·9	75	68
2	5·8	50	49
3	5·0	30	35
4	6·2	17	23

From tables I and II it seems that, even after recovery, the urinary output of amino-acids of some of the patients remained greater than that of normal healthy children. An older brother of patient no. 5 had already been under treatment for severe rickets, and this led us to investigate the excretion of amino-acids by all the members of this family. Table IV shows that two of the brothers (aged 5 and 13) and the mother of patient no. 5 excreted an increased amount of amino-acids in the urine and had signs of former rickets. The mothers of three other patients (nos. 4, 7, and 9) also showed signs of having had severe rickets and excreted abnormally high concentrations of amino-acids in their urine.

DISCUSSION

There is still much to be learnt about the increased excretion of amino-acids, which has been found to be part of the rachitic syndrome and to persist throughout life in persons who have had rickets. The indications at present are that the fault lies in the kidneys, because the level of amino- nitrogen in the plasma of these patients is within the normal range and does not exceed 7 mg. per 100 ml. Results of two-dimensional paper chromatography of the urine indicate that the amino-acids excreted are those which are normally present in urine in appreciable quantities (glycine, histidine, alanine, lysine, serine, and threonine), and not those which would be expected if the levels in the plasma were to rise abnormally after a meal (arginine, lysine, and

TABLE IV—α AMINO- NITROGEN EXCRETION IN URINE OF CASE 5 AND IMMEDIATE RELATIONS

—	mg. per 100 ml.	—	mg. per 100 ml.
Father	20	Brother	18
Mother *	47	Sister	23
Sister	27	Brother *	56
Brother *	67	Case 5 *	54

* Had severe rickets.

glutamic acid). The paper chromatograms have not suggested the presence in the urines of any amino-acids not normally found there.

It is known that in rickets some of the renal functions are not normal, for the reabsorption of phosphate is diminished (Harrison and Harrison 1941). According to some investigators (Albright and Reifenstein 1948) this is caused by a secondary hyperparathyroidism, which may in its turn be the result of a deficiency of serum-calcium. Zetterström (1951) holds that the defect in the reabsorption of phosphate is a primary result of the vitamin-D deficiency. Possibly the defective reabsorption of phosphate and that of amino-acids, peptides, and conjugates are interrelated and may even be due to a fault in the same part of the trouble. Under treatment, however, the phosphate in the blood of rachitic children reaches its normal level before the amino-acid excretion does (table III), and the fall in the latter has a time-relation more in keeping with that of the alkaline-phosphatase activity.

Until now simple rickets has not been thought to be heriditary, although resistant rickets has long been known to be so (Gill 1939, Freeman and Dunsky 1950). The present results suggest that there may be important hereditary factors in the genesis of uncomplicated rickets, and further study may throw light on the mechanisms of this inheritance.

SUMMARY

Children with rickets excreted much more amino-nitrogen in free and bound form than did normal children.

Within a month after treatment with calciferol the excretion was reduced, but not as a rule to a strictly normal level.

Members of a family with rickets or signs of old rickets excreted more amino-acids than did the others.

This work was done with the financial help of Zuiver Wetenschappelijk Onderzoek.

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Preliminary Communication

ESTIMATION OF BLOOD-DEXTROSE BY A RAPID OPHTHALMOSCOPIC METHOD

THIS note describes a method of estimating the blood-dextrose by means of an adapted ophthalmoscope. This method gives an approximation to the blood-dextrose within ± 20 mg. per 100 mg. per 100 ml.

The ophthalmoscope is fitted with a device for measuring the intensity of illumination of the retina when a beam of light is shone through the pupil. Originally the ophthalmoscope was fitted with two polaroid screens, one of which could be rotated over a scale, and a monochromatic light filter to give a sharp cut-off. The red reflex was observed and the analyser rotated till extinction occurred. An alternative device achieves the same end using neutral graded wedges, but the polarising ophthalmoscope is more accurate.

The unit area illumination intensity of the retina so measured, using the pupil as a stop, is found to vary quantitatively with the blood-dextrose. This illumination change is probably due to alteration in the refraction of the eye. It is already known that eye refraction is affected by changes in blood-dextrose.[1] This is in keeping with the observation of many patients that their vision is impaired when the blood-dextrose changes. Experiments are proceeding to investigate the nature of this alteration which may be due to a physicochemical effect on the lens protein.

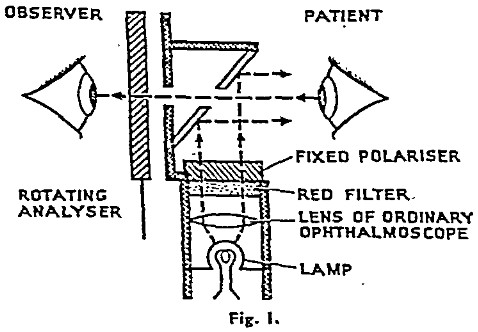

Fig. 1.

When suitable corrections for diffusion-rate of dextrose, pupil size, and refractive error are applied, a reading of the blood-dextrose can be given from the analyser rotation and a calibration curve, within ± 20 mg. per 100 mg. per 100 ml. of the laboratory finding in the Folin-Wu tube. A reading takes 45 seconds to complete. The correlation coefficient of 100 readings with the laboratory estimations is 0·954.

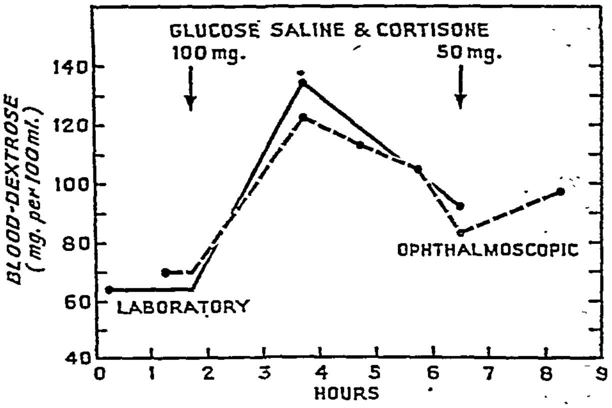

Fig. 2—Comparison between Folin-Wu and optical methods. The 100 mg. and 50 mg. refer to oral doses of cortisone.

This method has an obvious practical value, since in the diabetic clinic an approximate estimation of the blood-dextrose can be made within one minute of the patient's arrival, or at the bedside serial readings can be taken at short intervals, without taking blood. The necessary attachments are readily mounted on an ordinary ophthalmoscope.

Fig. 1 illustrates the principle of the instrument. Fig. 2 shows a comparison between Folin-Wu and optical methods under conditions of varying blood-sugar in a patient during an addisonian crisis.

It must be emphasised that this device is still experimental and that its use requires care and practice.

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Research in General Practice

AT a meeting on Oct. 27 of the Manchester Medical Society's section of general practice, Prof. ROBERT PLATT discussed Opportunities for Research in General Practice. He regretted the lack of articles by general practitioners in medical journals. This was partly due, he thought, to a wrong attitude towards research which assumed that it could only be carried out by whole-time workers with special facilities. The conventional idea of a research-worker was of an austere man in a white coat with a background of complicated glassware. His idea of a research-worker, on the other hand, was of a man who cleaned his teeth only on the left side so as to use the right side as a control to see if tooth-brushing had any effect on the incidence of caries. In other words, research depended largely on an attitude of mind. It need not be time-consuming but involved the design of a policy in order to answer a question. With very little added work one could plan a campaign—for use, for instance, in an influenza epidemic, when it could be quickly proved whether a certain line of treatment had any effect in reducing complications. In a dysentery epidemic during the late war he had done a similar research which had demonstrated the uselessness of sodium sulphate and the value of sulphaguanidine. Such observations could not be made in hospitals; for cases were highly selected before admission. It was important to think statistically; but this did not mean that one had to be highly trained in statistical theory.

Certain subjects particularly lent themselves to investigation by general practitioners—for instance, the incidence of common diseases such as migraine and hypertension, and the treatment of common disorders including neuroses. Other disorders in which plenty of problems awaited solution included rheumatism, obesity, sciatica, emphysema, and constipation. Every attempt at therapy was in fact an experiment. All who had the necessary attitude could engage in research.

New Inventions

A STRETCHER CHAIR WITH MANY USES IN HOSPITAL AND HOME NURSING

PREVIOUSLY we used the "Swedish chair"[1] on the neurosurgical ward, and this made bathroom privileges easier for hemiplegic, paraplegic, and other crippled patients. However, it was still a great feat of strength and ingenuity to lift a heavy paralysed patient into the Swedish chair. In addition, we looked for a contrivance that would hasten early convalescence. In the first two models (aided by a research grant from the Department of Veterans Affairs) we converted a stretcher into a chair by an elevator mechanism.[2] Later it was suggested that a mobile parallelogram might be the solution to the problem. This required balancing the stretcher with heavy weights. A sliding plane was then introduced into the parallelogram. With this third model we met with continued enthusiasm from many different groups of nurses and medical people who hope to discard the bedpan in modern nursing.[3] Many other uses were suggested—as a reading-chair, in the X-ray department for evacuation of enemas, as an X-ray stretcher, as a demonstration chair in amphitheatre clinics, and as a Swedish chair or hospital commode.

The stretcher chair is 6 ft. long. In the stretcher position it is 20 in. wide. In the sitting position the seat drops to 18 in. from the floor. The frame is of welded aluminium tubing, which rides on ball-bearing swivel wheels 5 in. in diameter with foot locks. The foam-rubber cushions are covered with sturdy 'Fabricoid' of good quality. Two handles, one on either side of the frame, are conveniently located. Thirty-five turns of the handle will raise or lower the chair from a sitting position at normal chair height (18 in. from the floor) to a stretcher position at hospital-bed height. The smooth action of the gearbox, located in the back of the frame, and the durable stainless-steel cables operate a parallelogram. The gearbox is self-locking; its action can take place by turning the handle in a clockwise or an anticlockwise direction. This mechanism effects the change of position of the back rest, the seat rest, and the leg rest. It is possible to stop the motion of the chair at any position between the full stretch and the sitting position or to provide a reclining position. A removable foot rest is provided for comfort in the sitting position; it is adjustable and designed to suit both very short and very tall people. The seat cushion is removable. There is a slide under the toilet seat where a stainless-steel bedpan can be inserted.

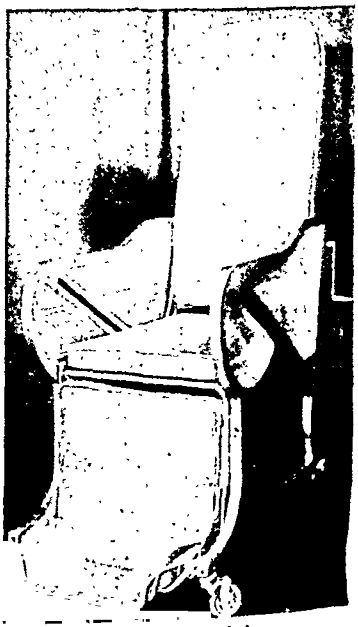

Fig. 2—As chair.

Under the name of the 'Stretchair,' the chair can be obtained from the Robert Mitchell Co., Ville St. Laurent, Montreal, who have made its construction possible. We are particularly indebted to Mr. St. C. Holland and Mr. G. A. Johnson of their research division.

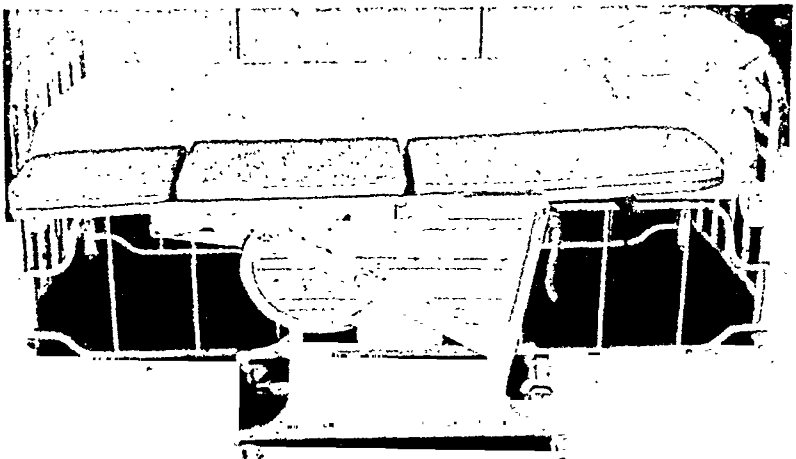

Fig. 1—As stretcher.

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Reviews of Books

Westminster Hospital 1719-1948

JOHN LANGDON-DAVIES. London: John Murray. 1952. Pp. 274. 21s.

ON Jan. 14, 1716, four citizens, Henry Hoare, Robert Witham, William Wogan, and Patrick Coburn, met at St. Dunstan's Coffee House to discuss their concern over the sick poor of Westminster. A banker, a brewer, a writer on religious subjects, and an ex-curate, they were a strange quartet with only vague conceptions of how to reduce the human misery in their midst. Yet from that meeting came eventually the founding of the first modern voluntary hospital in London. Starting with the nucleus provided by the four Westminster philanthropists, Mr. Langdon-Davies traces the development of research and therapy through the dark days of insanitation and all the evils consequent upon ignorance and poverty, step by step to the present day. If in dealing with such advances as antisepsis, anæsthesia, and nursing reforms he emphasises the part played by Westminster this is natural in the writer of a hospital history. He has had access to the complete set of minutes preserved by the hospital authorities and to the comprehensive outline of the hospital's history contributed by Mr. Walter Spencer to the Reports in 1924. His other sources included manuscripts in the Wellcome Medical Museum Library and the files of THE LANCET, and his biographical details include THE LANCET's venomous attack upon Sir Anthony Carlisle in 1838. The animosity displayed towards their colleagues by members of a staff makes strange reading today. Mr. Langdon-Davies's biographical sketches end in 1893 with an account of Mr. Spencer's attempt to ensure surgical efficiency; and, while recognising the difficulties, one cannot help regretting the lack of references to later members of the staff, some of whom have made substantial contributions to medicine. Apparently, too, the medical school was regarded as outside Mr. Langdon-Davies's terms of reference, for he says very little about its interesting vicissitudes and remarkable development. His book, however, has the advantage of being the work of a skilled journalist, able to grasp essentials and present them attractively. In describing the new hospital building it pays well-deserved tribute to the "key men on the Executive Building Committee," Mr. Charles Power with his great experience of hospital organisation and administration, and Sir Ernest Rock Carling with his genius for understanding other people's techniques.

Diabetes and Pregnancy

RALPH A. REIS, M.D., F.A.C.S., professor of obstetrics and gynæcology, Northwestern University Medical School; EDWIN J. DECOSTA, M.D., F.A.C.S., assistant professor of obstetrics and gynæcology, Northwestern University Medical School; M. DAVID ALLWEISS, M.D., associate in medicine, Northwestern University Medical School. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 78. 18s.

IN this addition (no. 158) to the American Lecture Series the authors express what they term the "in between view" on strict control of diabetes during pregnancy and induction of labour; but analysis suggests that their standards of diabetic control are as high as any in this country. They conclude that the only proven way in which diabetes may affect pregnancy is by giving rise to an oversize fœtus. Their figures do not support White's view that fœtal malformations are prevalent in pregnancies associated with diabetes. They ascribe their unusually low incidence of toxæmia to their custom of warning patients with vascular and renal complications against bearing children, and to the small proportion of their patients who had been juvenile diabetics. They deny that, with our present knowledge, hormones other than insulin can be usefully given to pregnant diabetics. The monograph draws attention to the danger of early postnatal hypoglycæmia in the infants of diabetic mothers. The authors are on less firm ground when they attempt to state the probabilities of diabetes developing in the children of diabetic mothers as precisely as if dealing with the inheritance of hæmophilia.

Handbook of Tropical Dermatology and Medical Mycology

Vol. I. Editor: R. D. G. Ph. SIMONS, M.D., senior lecturer, dermatological clinic, University of Leyden, Netherlands. Amsterdam and London: Elsevier Publishing Co. 1952. Pp. 845. £5.

IN this work a team of 80 contributors have attempted to cover every tropical skin affection with a completeness never before achieved; and it can be said straight away that they have succeeded. Not only have they dealt with an extensive range of subjects, but they have given a balanced picture of the many diseases involving other systems besides the skin. The subject matter has been critically selected, and the work is up to date, authoritative, and well documented. The lavish illustrations are all excellent.

To translate into homogeneous English contributions from so many Continental and other authorities was a formidable task, which has been carried out well, though the inevitable occasional error has slipped in here and there. Dr. Simons hopes that the volume will be of use to dermatologists and physicians in all parts of the tropics. It may well be more than this, for those practising in the temperate regions will also find it a valuable work of reference.

The Forgotten Language

ERICH FROMM. London: Gollancz. 1952. Pp. 224. 16s.

AS an elementary introduction to dream interpretation this book fulfils its purpose; it takes from well-known sources historical and expository quotations, links them together with an easy commentary, and persuades the ingenuous reader that the language of symbolism in dreams can be learnt without great effort: indeed, the author urges that the understanding of symbolic language should be taught in schools "just as other 'foreign languages' are part of their curriculum."

He appends a lengthy final chapter on symbolism in myths, fairy-tales, and ritual: the Œdipus myth is reconsidered in the light of Bachofen's theory of the transition in ancient religions and societies, with the result that Dr. Fromm discerns in Sophocles's trilogy not the theme of incest and hate through jealousy which Freud has stressed, but a tragic fight between the matriarchal and the patriarchal principle, exemplified in the hostility between father and son. This excursion, and others that examine the creation myth, Little Red Riding Hood, the Sabbath, and Kafka's *The Trial*, has less coherence and point than general readers might expect in a primer of the universal symbolic language which Dr. Fromm is convinced we should all learn to understand.

International Review of Cytology

Vol. 1. Editors: G. H. BOURNE, D.SC., London Hospital Medical College; J. F. DANIELLI, D.SC., zoology department, King's College, London. New York: Academic Press. 1952. Pp. 368. $7.80.

THIS volume has been issued under the auspices of the International Society for Cell Biology, and the editors hope to publish succeeding volumes annually. They intend to keep the scope of the review as wide as possible so that all aspects of cell biology may in due course be represented. The growth of new physical and micro-techniques during the last few years has led to many advances in knowledge of cytochemistry and micro-structure of cells.

A. F. Hughes briefly relates the history of cell biology. C. L. Huskins deals with nuclear reproduction. G. W. Kidder reviews enzyme capacities and their relation to cell-nutrition in animals; and L. G. E. Bell contributes a valuable article on the application of freezing and drying techniques to cytology. The chapter by Rosenberg and Wilbrandt on enzymatic processes in cell-membrane penetration is mainly physiological; yet, since it may throw light on the cell-membrane, this work also extends the range of cytology. Bisset's review of bacterial cytology is also valuable. R. Brown gives a short account of the problems of absorption of sugar by plant tissues in relation to protoplast surface enzymes. A. D. Hershey's excellent account of the reproduction of bacteriophage, in which the genetical, cytological, and chemical aspects are related to each other, is some indication of the intrinsic value of the whole volume and of the wisdom of the editors in keeping the range of subject-matter as wide as possible. Goldacre's article on the folding and unfolding of protein molecules as a basis of osmotic work is one of the few misfits of the volume. The ideas presented may be valuable; but they are not at present fully substantiated. Fankhauser's useful paper on nucleo-cytoplasmic relations in amphibian development gives an important place to embryological cytology. Swann discusses structural agents in mitosis, chiefly from the evidence of polarised light experiments. M. Singer's informative account of the factors which control the staining of tissue sections with acid and basic dyes is restricted to colouring proteins, and leaves out the attempts at rationalising staining reactions and cytochemistry. The method of estimating the iso-electric point of a tissue protein by finding the pH of minimal retention of acidic and basic dyes is interesting.

Lord Rothschild describes the behaviour of spermatozoa in the neighbourhood of ova. W. Montagna's conscientious review of the cytology of mammalian epidermis and sebaceous glands will probably be of more interest to the cytologically minded medical histologist than to general cytologists. L. H. Bretschneider's contribution on the use of the electron microscope in the investigation of tissue sections is of dubious value; fig. 3 (p. 312) is a good example of maltreated cells, and many of the objects shown could have been photographed with a higher numerical aperture light or ultraviolet microscope to show the same features. Glass knives are not mentioned. G. Gomori ends the book with a valuable account of the histochemistry of esterases. The index is useful though incomplete.

Physiologie normale et pathologique du métabolisme de l'eau

JEAN HAMBURGER, professeur agrégé à la Faculté de Médecine des Hôpitaux de Paris; GEORGES MATHÉ, interne médaille d'or des Hôpitaux de Paris. Paris: Flammarion. 1952. Pp. 502.

THE first half of this book is a well-written and up-to-date account of the amount and distribution of water in the body, and the regulation of water-balance, and can be recommended to the general reader as well as to the specialist. The second part, although equally lucid and well written, is more alien to prevalent notions on body-fluid imbalance.

Excellent features of the physiological section are the clear diagrams, adequate accounts of experimental methods, and a useful conversion table from mg. per 100 ml. to m.eq. per litre, and milli-osmols per litre for the different ions. The authors are aware that osmotic forces are not the sole determinant of water distribution, and they describe interesting experimental work showing that depression of cell metabolism leads to an accumulation of water in the cell. Perhaps the title of the book, with its stress on water, has led to some disproportion of emphasis, for little space is given to electrolyte balance, which often determines water-balance.

In the second half of the book, dealing with pathological water metabolism, we become more conscious that in France they order this matter, if not better, at least differently. Cellular dehydration and overhydration are contrasted with extracellular dehydration and overhydration; whereas in the English and American literature the emphasis is either on electrolyte deficit and excess, or on water depletion or excess which affects extracellular and intracellular fluid alike. Our more detailed analysis perhaps gives more definite guidance to treatment. The authors discuss therapeutic principles, but they have not found space for details, and there are some omissions, such as the use of sodium lactate in patients with diarrhœa, and osmotic diuretics in the treatment of œdema. The international bibliography contains 2536 references.

Spread of Tumours in the Human Body

2nd ed. R. A. WILLIS, M.D., D.SC. Melb., F.R.C.P., professor of pathology, Leeds University. London: Butterworth. 1952. Pp. 447. 63*s*.

THE first edition of this book when it was published in 1934 established Professor Willis's reputation as an authority on neoplastic disease. In its new form the work is a companion volume to his *Pathology of Tumours.* The general arrangement of the subject-matter is the same as in the first edition, but many sections have been revised and some rewritten. About 260 references have been added to the bibliography; and the appendix of case-notes on necropsies which Professor Willis has performed is increased by 177. The figures, mostly photomicrographs, are fewer and they are now collected at the end of the book. There seems little advantage in this. Many of them have suffered less reduction than in the first edition, and their reproduction is correspondingly clearer. The book will prove of great value and interest to all students of neoplastic disease.

Problems of Aging

Transactions of the Fourteenth Conference. Sept. 7-8, 1951. Editor: NATHAN W. SHOCK, M.D., chief, section on gerontology, National Heart Institute, New York. Josiah Macy, Jr., Foundation. New York: 1952. Pp. 138. $3.

THIS verbatim report of a two-day conference between American, British, Danish, and Swiss representatives shows how indivisible are the problems of ageing. The care of the aged is so intimately bound up with the causes of ageing and with the prevention of the disabilities of the aged that any serious discussion of the subject must range over medicine, biology, and sociology.

The colloquial form makes the report difficult to read, and the significance of some of the physiological experiments in the biological section may escape the general reader. The discussion section on sociology, psychology, and education produced no concrete suggestions, apart from a vague wish to arrive at a "longitudinal study of ageing." But the facts given by the representatives of the different countries in the sections on economics, welfare, and employment, and on medical services show what can be done to ensure that the life of the old can be useful to the world and pleasant to themselves.

The conference were in favour of the elderly continuing at work in some employment suitable to their age. The drawback to this policy is that many, if not most, elderly people have an overwhelming desire to retire at about the age of 65. But delegates remained convinced of the importance of retaining the aged as normal members of the community. The growing appreciation of this fact is one of the justifications for a conference such as this.

A Method of Anatomy (5th ed. London: *Baillière,* Tindall, & Cox. 1952. Pp. 870. 54*s*.).—Here, from Toronto, is the new edition of Prof. J. C. Boileau Grant's delightful textbook, where the text dangles fly-papers in the track of wayward memory, and the diagrams all but speak. It has been revised, clarified, rearranged, and shortened in some places, amplified in others; and it has acquired 78 new illustrations. Thus it remains the same good friend, only better. We still have to regret that Professor Grant has not included the central nervous system.

Surgical Instruments and Appliances used in Operations (14th ed. London: Faber & Faber. 1952. Pp. 160. 8*s*. 6*d*.).—In 1905, Mr. Harold Burrows produced the first edition of this useful little book. Mr. Ronald Raven, his collaborator, points out in the preface to this new edition that the text has been radically revised in order to bring in the many important advances since the publication of the 13th edition three years ago. The book is intended to help house-surgeons, theatre sisters, and surgical nurses; and it is fully qualified to do so.

The Science and Practice of Surgery (9th ed. London: J. & A. Churchill. 1952. Vol. I. Pp. 872. 32*s*. Vol. 2. Pp. 1019. 36*s*.).—Mr. W. H. C. Romanis and the late Mr. Philip Mitchiner, with the help of collaborators on many special subjects, present again this well-tried textbook. Principles in surgery, as they point out in their preface, have altered little in the quarter of a century of this book's life; but the increased scope of the science of surgery has led to extensive specialisation. Students, however, need principles; and this book, despite its title, aims as ever at teaching them the roots and trunk of principles rather than the twigs and efflorescence of science and practice. New material has been included only when it has been thoroughly established, and when the authors have convinced themselves it has real value. The result is perhaps more sober and trustworthy than lively and stimulating, an impression which is fortified by some rather elderly illustrations. The authors note that several of the older ones have been replaced, and some new ones have been included; but we hope to see the process carried further.

THE LANCET

LONDON: SATURDAY, NOV. 22, 1952

The Extracorporeal Heart

With their new-found power, cardiac surgeons look ambitiously to the day when they can work in a dry field while the circulation is sustained through a by-pass by means of a pump and oxygenator. Circulatory pumps of the Dale-Schuster and other types have long been used in physiological laboratories, and much basic work has been done on oxygenators. Kolff,[1] working with the artificial kidney in Holland in the dark days of enemy occupation, showed that it was feasible to make blood circulate outside the body, "wash" it clear of uræmic constituents, and return it to a vein; but only a small rate of blood-flow was necessary in this extra circulation.

For cardiac surgery in adults the pumps will have to handle 5 litres per minute, and Dodrill and his associates[2] have found that this is mechanically possible. The machines themselves present a difficult problem in sterilisation. Autoclaving or formalin sterilisation seems to be best, but these methods are not easily applied to a complex system of tubing, connections, and moving parts. Furthermore, small traces of blood residues from previous use may be a troublesome source of toxic material. The next difficulty is to prevent clotting. Heparinising the patient may lead to oozing unless dosage is very carefully gauged; at the end of the pumping period the action of heparin has to be terminated by giving a large dose of protamine sulphate, which induces severe hypotension.[3] Another problem connected with heparin is that of small fibrin threads which have to be filtered out in the machine. Renal infarcts and other embolic troubles have been noted in dogs after use of the extracorporeal heart.[3] The Scylla of clotting and the Charybdis of bleeding caused Mustard and Chute[4] to abandon artificial oxygenators in favour of an animal lung, but even then only 10 of 45 dogs survived circulatory by-pass experiments. Suction-cannulæ can be placed in the atrium, from which blood is drawn for oxygenation and later returned to the aorta, perhaps by a cannula up the femoral artery. If the atrium is opened before the pump is emptying the heart completely, hæmorrhage will occur; alternatively air may be sucked into the pump with rapidly fatal consequences. In devices where blood is oxygenated under high pressure and is then forced into the arterial system under the high pressure necessary when plastic catheters are used, dissolved gases may reappear as bubbles in the circulation unless this danger is guarded against. The biological problems are no less troublesome. Emptying of the right auricle is apparently accompanied by severe reflex hypotension and bradycardia[2]; and leucocytes may be trapped in the extracorporeal circuit with consequent leucopenia. Fischer and his associates,[5] who used dog lungs as the oxygenator for experiments in dogs, plaintively remark: "It hardly seems possible that so many pitfalls could present themselves in the performance of these seemingly simple experiments."

Mustard and Chute[4] used a monkey lung as the oxygenator in dealing with blue babies; they were kept alive for as long as three hours,[6] but the conditions operated on by the surgeon proved intractable, and there was thus no opportunity to observe any subsequent complications from this device. Dodrill and his co-workers[7] by-passed the left ventricle in a case of mitral valve disease, taking blood from the left auricle to the aorta via a cannula inserted up the left subclavian artery. By this means they avoided oxygenator troubles and also hypotensive reflexes from the empty right heart.[2] The patient recovered after fifty minutes of circulatory substitution at a rate of $4^1/_2$ litres of blood per minute. In Cincinnati a machine has been used to assist oxygenation in a patient with severe pulmonary fibrosis and cor pulmonale.[8] Blood was drawn from the inferior vena cava by a long catheter threaded up from the saphenous vein on one side. After oxygenation blood was returned via the opposite saphenous vein. As much as 1280 ml. per minute was passed through the machine; arterial oxygen saturation improved from 43 to 58–65%, and respiration became quieter. In this instance no leucopenia developed. There was, however, no sustained improvement and the patient died two weeks later. Necropsy showed no untoward effects from the extracorporeal circuit.

We still seem to be some way from the useful application of all this work. The problems are still formidable, and until some of these are solved its practical value will remain doubtful. Gross and his associates[9] have shown that atrial septal defects can be tackled by another means. When the patient is laid on the left side and a rubber bag or well is attached to the auricular wall, hardly any blood spills from the open auricle, since the pressure is low, and the hole can be repaired at the bottom of the pool of blood.

Latter-day Pilgrims

Few problems so tantalise man as human behaviour. Addressing the New York Academy of Medicine last month, Prof. Franz Alexander suggested that this was governed by two impulses: one was to seek security, and the other to embark on creative venture. These were essential and complementary aspects of life, but the second became manifest only if mankind had at its disposal a surplus of energy after ensuring self-preservation.

In the past, American civilisation had been characterised by a spirit of self-confidence and adventure, but a trend towards seeking security above all things

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1. Kolff, W. J. The Artificial Kidney. Kampen, Holland, 1946.
2. Dodrill, F. D., Hill, E., Gerisch, R. A. *J. thorac. Surg.* 1952, 24, 134.
3. Helmsworth, J. A., Clark, L. C., Kaplan, S., Sherman, R. T., Largen, T. L. *Ibid*, p. 117.
4. Mustard, W. T., Chute, A. L. *Surgery*, 1951, 30, 684.
5. Fischer, H. W., Albert, H., Riker, W. L., Potts, W. J. *Ann. Surg.* 1952, 136, 475.
6. Jahes, R. M. *Ibid*, p. 482.
7. Dodrill, F. D., Hill, E., Gerisch, R. A. *J. Amer. med. Ass.* 1952, 150, 642.
8. Helmsworth, J. A., Clark, L. C., Kaplan, S., Sherman, R. T., Largen, T. L. *Ibid*, p. 451.
9. Gross, R. E., Pomeranz, A. A., Watkins, E., Goldsmith, E. I. *New Engl. J. Med.* 1952, 247, 455.

was becoming evident in the young generation. Dr. ALEXANDER cited an inquiry in 1948 which disclosed that half the young men in a representative sample preferred a safe job, even if it were relatively poorly paid. A similar opinion poll conducted by *Fortune* Magazine[1] in 1949 showed that only 2% of college students intended to go into business on their own: most of the students wanted to work for large firms, which they thought would be more "depression-proof" than small concerns. Much of this quest for security was, no doubt, the aftermath of two world wars and the depression of the '30s; but, as in all mass social phenomena, there had been a considerable over-reaction. Probably, Dr. ALEXANDER continued, many people in the Western world lived nowadays in a state akin to panic, owing not only to the catastrophes that had befallen them but to their feeling that the complex and rapidly changing social and economic conditions of the modern world were beyond the individual's comprehension or control. When the mass of people felt that their world was frighteningly chaotic, they yearned for strong, authoritative leadership; and security became the boon which they craved above all else. Prof. ARNOLD TOYNBEE's[2] conclusion that civilisations made their greatest progress in an unfavourable environment should correct extreme pessimism: within limits, unfavourable conditions stimulated men not only to make the effort necessary for survival but to go beyond this and excel in cultural creativeness. Nevertheless it was obvious that impossibly difficult conditions could have a paralysing effect, with all available energy spent in the struggle to survive: at present half of America's resources were being devoted to rearmament. There was a danger that an emotional reaction, due to continued frustration, might explode in the Western community, as in an individual goaded to rage. Perhaps, too, Western civilisation was entering a period of decline; in TOYNBEE's view this began with the tendency towards centralised and solidified government. This development had led earlier civilisations to eventual disintegration, for two reasons: first, the governed fell more and more out of sympathy with their rulers, who necessarily became more harsh and impersonal as their sphere of authority extended; and secondly, they became more liable to military defeat, since rigidly centralised régimes were apt to cling to obsolete, traditional weapons in warfare. In this respect, said Dr. ALEXANDER, the Western world might have an advantage. The problem before us was to organise our society for a reasonable measure of security, so that creative energies might once more be set free.

In this country the series of Reith lectures now being broadcast by the B.B.C. will perhaps enable us to see ourselves as others see us; for in this series Professor TOYNBEE is discussing the impact of the West on other civilisations. Conceivably Western man's quest for security, though it may lead to a period of stagnation and decline, reflects a deeply unconscious need for a breathing-space from his fiercely competitive, extraverted society, so that he may become acquainted with himself.

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1. *Fortune*, June, 1949, p. 170.
2. Toynbee, A. J. A Study of History. London, 1934.

Oral Contraception

IN his presidential address this year to the British Association, Prof. A. V. HILL, F.R.S., spoke of the ethical dilemma for preventive medicine in the prospect that "the pressure of increasing population, uncontrolled by disease, would lead not only to widespread exhaustion of the soil and of other capital resources but also to continuing and increasing international tension and disorder, making it hard for civilisation to survive." A reliable contraceptive that could be taken by mouth would have revolutionary implications; it would hold out the hope that men and women might exercise that control over the numbers of their children which, in the words of the Royal Commission on Population, "is one of the first conditions of their own and the community's welfare." It is precisely this discovery that is claimed by SIEVE[1] in a preliminary report on a trial of phosphorylated hesperidin. This substance is said to act by inhibiting hyaluronidase, the enzyme that may assist the spermatozoa to penetrate the gel surrounding the unfertilised ovum.

There has been much previous work in this field. In 1929 DURAN-REYNALS[2] described a factor in aqueous extracts of mammalian testicle that enhanced the lesions of vaccinia in the skin. McCLEAN[3] reported that this action was due to a dramatic increase in the permeability of the dermis, and that the factor was associated with the spermatozoa. He found that the immediate diffusion of injected material containing the factor "is so striking that it can be compared to the different behaviour of a drop of water when placed upon glazed and upon blotting paper." This action on the tissues was confirmed by HOFFMAN and DURAN-REYNALS.[4] The enhancing action of this factor was studied in other viral and bacterial infections, and factors with similar diffusing properties were obtained from the most diverse sources—for example, from culture-filtrates and extracts of many species of invasive bacteria,[5] from snake and spider venoms,[6] and from leeches.[7] Meanwhile other workers[8] in the U.S.A. were studying the nature of the viscous polysaccharides in such mesodermal tissues as vitreous humour, synovial fluid, and umbilical cord; and they reported that these polysaccharides were hydrolysed, and their viscosity was destroyed, by a group of enzymes produced by such invasive organisms as pneumococci and *Clostridium welchii*. It remained for CHAIN and DUTHIE,[9] working in Oxford, to make the observation that elucidated the nature of spreading factors and which, at the same time, suggested the possible significance in infection of the enzymes that had been studied by the American workers. CHAIN and DUTHIE reported a remarkable mucolytic activity of spreading factors derived both from testis and from other sources; this activity was associated with a rapid fall in the viscosity of synovial fluid and the liberation of reducing substances; and they showed that there was a significant correlation between "spreading" and "mucolytic" activity. In 1933 McCLEAN and MORGAN[10] had reported that the addition of purified testicular extract to diphtheria antitoxin injected subcutaneously approximately

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1. Sieve, B. F. *Science*, 1952, 116, 373.
2. Duran-Reynals, F. *J. exp. Med.* 1929, 50, 327.
3. McClean, D. *J. Path. Bact.* 1930, 33, 1045; *Ibid.* 1931, 34, 459.
4. Hoffman, D. C., Duran-Reynals, F. *J. exp. Med.* 1931, 53, 387.
5. Duran-Reynals, F. *Ibid.* 1933, 58, 161; McClean, D. *J. Path. Bact.* 1936, 42, 477; *Ibid.* 1941, 53, 13.
6. Duran-Reynals, F. *J. exp. Med.* 1939, 69, 69.
7. Claude, A. *Ibid.* 1937, 66, 353.
8. Meyer, K., Dubos, R., Smythe, E. M. *J. biol. Chem.* 1937, 118, 71; Meyer, K., Palmer, J. W. *Ibid.* 1934, 107, 629; *Ibid.* 1936, 114, 689; Robertson, W. van B., Ropes, M. W., Bauer, W. *Ibid.* 1940, 133, 261.
9. Chain, E., Duthie, E. S. *Brit. J. exp. Path.* 1940, 21, 324.
10. McClean, D., Morgan, W. T. J. *J. Path. Bact.* 1933, 36, 193.

oubled its rate of absorption; subsequent work[11] showed hat this action was due to hyaluronidase, which has ince been used clinically.

The work of Long,[12] Yamane,[13] and Pincus and nzmann[14] had demonstrated that a substance present n semen dissolved the viscous gel cementing the cumulus ells around freshly ovulated rat ova. In 1942 McClean nd Rowlands[15] showed that hyaluronidase from any ource—testicular, bacterial, or from snake venom—ould disintegrate the cumulus cell mass of rat ova, nd that this was due to the specific activity of the nzyme since the rate of dispersal was directly proportional to the concentration of hyaluronidase in the arious preparations. They suggested that for fertilisation large numbers of sperms had to be in the vicinity f the ovum so as to produce a high enough concentration f enzyme to liquefy the gel and allow penetration by he single effective sperm. Fekete and Duran-Reynals[16] confirmed this with mouse ova. Later, Rowlands[17] observed an increase in the fertilising apacity of dilute rabbit-sperm suspensions on the ddition of hyaluronidase. The hyaluronidase content of semen and its release from spermatozoa was studied by Swyer,[18] who concluded that in men, rabbits, bulls, and boars there is a close correlation between concentration of sperm and enzyme; the spermatozoa do not actively produce hyaluronidase—they liberate the preformed enzyme at a rate which depends on its concentration in the plasma. This explains the release of sufficient enzyme in the fallopian tubes to bring about disintegration of the cumulus surrounding freshly ovulated ova. In 1948 Pincus et al.[19] reported that various substances which inhibited the viscosity-reducing activity of hyaluronidase in vitro also inhibited the follicle-cell-dispersing activity of semen-hyaluronidase in vitro, and that when the inhibitors were added to sperm suspensions artificially inseminated in rabbits, the number of ova fertilised was significantly reduced. These substances were also contraceptive when introduced in sufficient concentration into the vagina of naturally mated females. Martin and Beiler,[20] having found that phosphorylated hesperidin is a powerful non-toxic inhibitor of hyaluronidase, administered this substance either intraperitoneally or orally to groups of rats with suitable control groups and observed the results of mating. They claimed approximately 80% reduction of conception in the treated rats, which, moreover, mated successfully after hesperidin was discontinued. The action appeared to be specifically on the female, although the œstrus cycle remained normal during treatment. Meyer[21] had shown that hesperidin preserves the coronal cell layer round the ovum in the presence of spermatozoa.

In his preliminary report Sieve[1] records the trial of a hesperidin derivative in 300 married couples. Each had had at least one normal child, and 41% had a period of fertility control followed by a normal pregnancy and repeated therapy for a second period of control. There was no evidence that this drug impaired fertility after treatment was stopped. The period of fertility control varied from three to thirty months, but 61 couples (20%) were controlled continuously for thirty months; an undertaking was obtained that during the period of control no other contraceptive device would be employed. Phosphorylated hesperidin was given by mouth to both the male and female partners in divided doses on the basis of 5 mg. per kg. body-weight per day, plus about 20% to allow for missed doses. Thus people of normal weight took about 500 mg. per day in five tablets at meal-times. Sieve emphasises the importance of maintaining the blood-saturation level, but it is not clear why the males were treated as well as the females, since preliminary animal experiments had not indicated that this influenced the results significantly. Continuous treatment for ten days is believed necessary before fertility is controlled, but a lapse of forty-eight hours restores fertility. This hesperidin derivative caused no toxic signs or symptoms, and 15 couples were given twenty-five times the normal dose for up to fifty days without any apparent ill effects. Only further experience, however, can demonstrate whether this substance is really free from danger. The report shows only 2 failures in the whole series of 300 couples, and these 2 couples admitted to having failed to take the tablets. 280 couples followed the instructions precisely, and the other 18 missed only occasional doses.

These results are so astonishingly good compared with those in most biological experiments that scepticism is natural. If, however, the claims were to be confirmed, they would be of vast importance. As we recalled last week, Pirie[22] has pleaded in our columns for intensive research into "the metabolism of gametes and zygote with special regard to methods of interfering with it." As he said: "Until we know as much about the biochemistry of human gametes as we do about rabbit liver there is little chance of discovering those biochemical anomalies on which differential inhibition—i.e., rationally based contraception—must depend." Sieve's work on phospho-hesperidin may at least provide the stimulus needed to fulfil Pirie's hope.

Annotations

LESSONS FROM HISTORY

The creation of the Emergency Medical Service was one of the most interesting events of the late war. It was something new; it was an attempt at a comprehensive organisation; and it was the foundation on which the National Health Service was later built. The *Medical History of the War* is rightly giving two volumes to this valuable by-product of the conflict. The first, which has just appeared,[23] describes the origin, as far back as 1923, of what grew into the E.M.S. and how it was run when the emergency came. This volume deals only with England and Wales; the arrangements in Scotland and Northern Ireland will be described in the first parts of the next volume.

The story of the air-raids has also been reserved for the next volume, which for the general reader may be the more exciting of the two: but the doctor, consciously living in contemporary history, will find in this volume the subjects of the greatest interest. Colonel Dunn has fortunately made it eminently readable. It is not an orthodox official document: adverse comments on what happened have not been by any means omitted. But what will immediately strike any reader is the vastness and complexity of the organisation, and the success with which it was both built up and administered. Critics

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11. Gaisford, W., Evans, D. G. *Lancet*, 1949, ii, 505; Evans, D. G. Perkins, F. T., Gaisford, W. *Ibid*, 1951, i, 1253; Hechter, O., Dopkeen, S. K., Yudell, M. H. *J. Pediat.* 1947, 30, 645; Schwartzman, J. *Ibid*, 1949, 34, 559; Schwartzman, J., Henderson, A. T., King, W. E. *Ibid*, 1948, 33, 267.
12. Long, J. A. *Univ. Calif. Publ. Zool.* 1912, 9, 105.
13. Yamane, J. *Cytologia, Tokyo*, 1930, 1, 394.
14. Pincus, G., Enzmann, E. V. *J. exp. Med.* 1935, 62, 665.
15. McClean, D., Rowlands, I. W. *Nature, Lond.* 1942, 150, 627.
16. Fekete, E., Duran-Reynals, F. *Proc. Soc. exp. Biol., N.Y.* 1943, 52, 119.
17. Rowlands, I. W. *Nature, Lond.* 1944, 154, 332.
18. Swyer, G. I. M. *Biochem. J.* 1947, 41, 409; *Ibid.* p. 413.
19. Pincus, G., Pirie, N. W., Chang, M. C. *Arch. Biochem.* 1948, 19, 388.
20. Beiler, J. M., Martin, G. J. *J. biol. Chem.* 1948, 174, 31; Martin, G. J., Beiler, J. M. *Science*, 1952, 115, 402.
21. Meyer, K. *Physiol. Rev.* 1947, 27, 335.
22. Pirie, N. W. *Lancet*, 1952, i, 54.
23. Medical History of the Second World War. Editor-in-Chief: Sir Arthur MacNalty, F.R.C.P. The Emergency Medical Services. Editor: Lieut.-Colonel C. L. Dunn, C.I.E., I.M.S. retd. Vol. 1. England and Wales. H.M. Stationery Office, 1952. Pp. 460. 50s.

of the Civil Service—and there are plenty of them among doctors—will agree that Government departments on the whole did a good piece of work. Such lapses as there were, both recorded and unrecorded (for example building X-ray departments which could only be reached through operating-theatres, without showing the plans to the radiologists or surgeons), were due to that ubiquitous infirmity of the administrative mind, the tendency to save trouble by making decisions without consulting the expert. On the other hand some of the most brilliant successes were due to handing over control to those who understood. For instance real power was entrusted to the sector officers, who were all men who had been familiar with hospital practice all their lives. Is that not an example of the wisdom of giving day-to-day control to the expert and reserving policy-making for laymen? And is there not another lesson to learn here? Of course, a sector officer was an officer and not a committee, and democracy is not a prime necessity in war-time. But it is becoming evident, in the National Health Service, that public control and public auditing and democratic theory can become objectives on their own account, fetishes divorced from necessity. To balance efficiency and liberty is a proper aim, but is the sacrifice of efficiency and liberty to ideology as desirable?

The relation under the E.M.S. of the social and positive health services to the service for the treatment of disease, inevitably raises the question of the possibility of greater unification in the future. What might have been the result, if, as might easily have happened, we had set up a national medical service, including the medical branches of the three fighting Services, responsible for the treatment of both Service and civilian casualties and for the general medical care of the population? Such a combined service would have been a relatively small step further than the E.M.S. It would have made transfers of man-power and equipment simpler, and it would have prevented overlap, duplication, and waste. What would have been the history of the National Health Service if this had been done? The service would already have been there, in military guise. Would a conversion to a civilian form have been made easier by pre-existence, or would the reaction against discipline, combined with the shortcomings of a rapidly evolved scheme, have turned the profession against it?

IMMUNOLOGICAL PROCEDURES

UNFORTUNATELY many students pass their final examinations knowing more of the biochemical activities of *Salmonella typhi* than of the steps to immunise against infection with this organism. H. J. Parish's admirable book,[1] published in 1948, is well designed to fill this gap; a well-known work published by the American Public Health Association[2] is more inclusive since it is intended for use the world over, but it lacks the details of procedure which are so useful to the novice. A third book,[3] just published, is intended to provide administrative and professional guidance to medical officers in the Army; but it will be equally valuable to their colleagues in civil life. It is hard to praise this work too highly.

The recruit, unless he raises strong objections, is immunised against smallpox, diphtheria, tetanus, and the enteric fevers. If he goes to tropical Africa vaccination against yellow fever will be added to the list; and on occasion it may be thought wise to protect him against typhus, cholera, plague, and rabies. The older soldier must have his immunity maintained, and his wife and children may or must share his protection. B.C.G. vaccination against tuberculosis is available for members of the R.A.M.C. and Q.A.R.A.N.C. To detailed and lucid guidance on all these procedures the book adds instructions on the techniques of inoculation, single and in mass, and on the sterilisation of syringes. We know of no better examination of the pros and cons and caveats attached to the different methods of sterilisation, and we are glad to see the hot-oil method for needles given its due. It is odd, however, that an Army which standardises its ordnance and its boot-brushes cannot do the same with needles, syringes, and sterilisers.

We feel that this book might have placed more emphasis on the value of passive immunisation for controlling epidemic diphtheria in a closed community. On the other hand, the account of serum reactions is clear and accurate; and the exhaustive directions for the storing of serological products in temperate and tropical climates will undoubtedly help to reduce the proportion of condemned stores and unsuccessful vaccinations. At the price of two shillings this work is as good a bargain as we have met in years.

THE DELINQUENT'S BACKGROUND

> "The seriousness of the situation is plainly seen from the figures. . . . There is need for energetic action by all who may be in a position to help."

THIS statement, from the Memorandum on Juvenile Delinquents issued jointly by the Home Office and Ministry of Education in 1949, is quoted by Dr. Edelston[1] as a justification for "yet another book" on delinquency. Professor Ferguson[2] also apologises "for yet another book"; but they both rightly emphasise that there is still much to be said and much to be found out, which is supported by the fact that their two books hardly overlap at all. Dr. Edelston writes as a clinician, and is particularly concerned with the psychological make-up of the child. "In the [illegible] only thing that can account for the [illegible] is his own personality" and each one is unique. He gives 30 case-histories, in 25 of which stealing was a prominent feature; and he says that no two were alike and that even the stealing had a different significance in each case. Professor Ferguson takes the complementary approach. Making use of material already collected on a group of ordinary boys, a group of physically handicapped boys, and a group of mentally handicapped boys, he now studies the prevalence of delinquency among them and examines the circumstances in the home, school, and social environment which appear to induce it.

Professor Ferguson has collected a great deal of valuable material and sets it forth in a way that makes it readily assimilable; it has already been much quoted and it is bound to carry great weight. Nevertheless his selection of data and his interpretation of them are sometimes open to statistical question. Thus he says that "in broken homes delinquency rates were worse when family disruption was due to a cause other than death"—a statement based on the finding that when disruption was due to death, the delinquency-rate was 12·5%, whereas when disruption was due to other causes the rate was 15%. But the numbers at risk were respectively 192 and 179, and the statistician would say that these percentages are not significantly different. There are other cases where the difference shown may have been due to chance, but this cannot be discovered from the figures given, without additional work. Anyone who as attempted this sort of survey will know that an normous amount of arithmetic has already been done o produce the figures Professor Ferguson offers; but hose who will make most use of his book would have een glad of even more.

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[1] Parish, H. J. Bacterial and Virus Diseases. Edinburgh, 1948.
[2] The Control of Communicable Diseases in Man. 7th ed., New York, 1950.
[3] Memorandum on Immunological Procedures. H.M. Stationery Office. 1952. 2s.

[1] The Earliest Stages of Delinquency. By A. Edelston, M.B., D.P.M., psychiatrist and director, Bradford Child Guidance Clinic. Edinburgh and London: E. & S. Livingstone. 1952. Pp. 200. 10s. 6d.
[2] The Young Delinquent in his Social Setting. By T. Ferguson, professor of public health and social medicine, University of Glasgow. London: published for the Nuffield Foundation by the Oxford University Press. 1952. Pp. 155. 16s. 6d.

His most important observation is, perhaps, the extent o which dullness of intelligence is associated with elinquency. It seems that the lowest 10% on the ntelligence scale contribute at least half as many delinuents as the remaining 90% of the juvenile population. Moreover, there is a tendency for adverse factors to luster: the dull boy tends to come from a bad and vercrowded home, and to have other delinquents in his amily; he tends to take a blind-alley job and keep it or a short time only; and he is likely to be rated by his eachers as of poor personality, lacking in reliability, nitiative, and perseverance. This last proposition is of nterest because it is contrary to accepted psychological heory, which holds that "intellectual" and "personality" factors are independent. Could it be that the ssessment is at fault? Teachers are not objective scientific observers; they cannot easily dissociate the child from the setting in which they see him. A boy trying to cope with tasks at or above the limit of his capacity will be likely to reveal such defects as his personality may have; whereas the brighter child, who achieves the same task without effort, may be just as deficient in the sterling virtues but able to conceal this from his teachers.

PROCAINE AMIDE

THE precise status of procaine amide as a substitute for quinidine in the treatment of cardiac arrhythmias is still a matter of controversy among cardiologists. Last year[1] we suggested that procaine amide was the drug of choice in the treatment of paroxysmal ventricular tachycardia, and that it was of value in abolishing troublesome ventricular extrasystoles, but that there was no evidence that it was of value in the treatment of auricular arrhythmias. Some reports which have been published since then suggest that side-effects may be commoner than was originally appreciated. In dogs, for instance, Harris et al.[2] found procaine amide to be "very effective" in reducing the frequency of severe ectopic ventricular tachycardia associated with myocardial infarction, but, in view of 3 fatalities, they recommend that "in all cases of severe ectopic ventricular tachycardia only that amount of drug which is required to reduce the ectopic rate to a safely low range and to maintain it at a low level should be administered." They also advise that in such cases the drug should be given under simultaneous electrocardiographic control. Charlier[3] came to the same conclusion from his experience with the drug in anæsthetised dogs in which ventricular arrhythmia had been induced by aconite nitrate.

Although there is still some uncertainty as to whether or not procaine amide is of value in the treatment of auricular arrhythmias, the balance of opinion favours the view that it is not. On the basis of his findings in 2 patients with ventricular arrhythmia and one with auricular arrhythmia, Schaffer[4] does not believe that it has "a preferential effectiveness on ventricular as compared to auricular arrhythmias," while Miller and his colleagues[5] report restoration of normal rhythm following its use in each of 7 cases of paroxysmal auricular fibrillation, in 6 of 13 cases of chronic auricular fibrillation, and in 2 of 3 cases of auricular flutter. They emphasise that such patients should be digitalised before procaine amide is given. On the other hand, Zapata-Diaz et al.[6] conclude from their clinical and experimental work that in auricular flutter the use of procaine amide is "dangerous because it can lead to a 1 : 1 atrioventricular response," and that, while it may restore sinus rhythm in paroxysmal auricular fibrillation, "it does not seem to be devoid of danger." Bellet et al.[7] found that auricular fibrillation did not respond to procaine amide in the 11 patients they treated with it; and Schreiner and Kelley[8] describe the onset of ventricular tachycardia following the use of procaine amide in a patient with auricular fibrillation. Schack et al.[9] found that auricular fibrillation and flutter of over three years' standing were unaffected, though some auricular arrhythmias that had resisted quinidine responded to the drug by mouth. However, reports of its efficacy in controlling ventricular arrhythmias continue to appear.[10–12] Another use suggested for procaine amide is to give it before cardiac catheterisation, as a means of preventing induced arrhythmias,[13] but Lucas and Short[12] could not confirm its value for this purpose.

The toxic effects which have been reported may be divided into those involving the heart and those of non-cardiac origin. The latter include a case of agranulocytosis,[14] a generalised reaction,[15] and an allergic reaction involving the skin.[16] In all 3 cases the procaine amide was given by mouth, and all 3 patients recovered. Among the cardiac side-effects are ventricular fibrillation[17 18] and ventricular tachycardia,[19] and here the drug was given intravenously. This question of how to give procaine amide is one of the major difficulties in its use. Oral administration is unreliable in its effect, except for maintenance doses, and it is liable to produce nausea and vomiting. The intravenous route is potentially dangerous unless the drug is given by what almost amounts to a drip technique and under electrocardiographic cover; it can therefore be considered only in emergencies. Fortunately, evidence is now accumulating that the intramuscular route may prove relatively safe and effective. Bellet and his colleagues[7] have shown that an intramuscular injection of 1 g. of procaine amide raises the blood-level of the drug in five minutes; a peak is reached in fifteen minutes to one hour, and significant levels are still present after six hours. In spite of the relatively large volume of the injections given—up to 15 ml.—no irritation or swelling appeared at the site of injection. It may well be, therefore, that the safest and most effective method of using procaine amide is by the intramuscular route, reserving the intravenous route for cases of real urgency. The exact position about oral treatment is still in doubt, but it should probably be reserved for maintenance doses and, to a lesser extent, for initial trial in patients whose condition is not urgent. In a certain number of these patients it will be effective, and so remove the need for intramuscular injection. But, however it may be used, procaine amide must only be given under strict supervision and, certainly in the early stages of treatment, this means in hospital.

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1. *Lancet*, 1951, ii, 870.
2. Harris, A. S., Estandia, A., Ford, T. J. jun., Smith, H. T., Olsen, R. W., Tillotson [illegible] 1952, 5, 551.
3. Charlier, R. *Arch. int.* [illegible] 442.
4. Schaffer, A. I. *Amer. H* [illegible]
5. Miller, G., Weinberg, S. L., Pick, A. *Circulation*, 1952, 6, 41.
6. Zapata-Diaz, J., Cabrera, C. E., Méndez, R. *Amer. Heart J.* 1952, 43, 854.
7. Bellet, S., Zeeman, S. E., Hirsh, S. A. *Amer. J. Med.* 1952, 13, 145.
8. Schreiner, G.E., Kelley, R. T. *Amer. Heart J.* 1952, 43, 749.
9. Schack, J. A., Hoffman, I., Vesell, H. *Brit. Heart J.* 1952, 14, 465.
10. Hanenson, I. B., Kayden, H. J., Messinger, W. J. *Amer. Heart J.* 1952, 43, 293.
11. Antzis, E., Dunn, J. J., Schilero, A. J. *Ibid*, p. 911.
12. Lucas, B. G. B., Short, D. S. *Brit. Heart J.* 1952, 14, 470.
13. Zinn, W. J., Cosby, R. S., Levinson, D. C., Miller, H., Dimitroff, S. P., Cramer, F. B., Griffith, G. C. *Amer. Heart J.* 1952, 43, 451.
14. Inouye, M., Millar, J., Townsend, J. H. *J. Amer. med. Ass.* 1951, 147, 652.
15. Bakos, A. C. P., Askey, J. M. *Ibid*, 1952, 149, 1393.
16. Hellman, E. *Ibid*, p. 1393.
17. Miller, H., Nathanson, M. H., Griffith, G. C. *Amer. Heart J.* 1952, 44, 432.
18. Read, J. M. *J. Amer. med. Ass.* 1952, 149, 1390.
19. Denney, J. L., Miller, H., Griffith, G. C., Nathanson, M. H. *Ibid*, p. 1391.

ACCIDENTAL POISONING IN CHILDREN

ALTHOUGH poisoning is relatively uncommon among children, some recent reports [1-3] suggest that it is on the increase. This increase is probably due to the large number of medicines and other potential poisons which are now brought into the home, and to overcrowded living conditions which increase the risk of these substances being left where children can get at them.

The child may be brought to the doctor with a story of having taken a known or, more commonly, an unknown quantity of some known substance; or he may have been found with a bottle or container whose contents are unknown; or he may have symptoms which the parents do not suspect to be the result of poisoning. Such symptoms may be vomiting, diarrhœa, cyanosis, drowsiness, loss of consciousness, convulsions, or collapse—any of which should suggest to the doctor the possibility of poisoning. The diagnosis may be made in some cases by smelling a volatile substance in the child's breath, or by recognising a characteristic set of symptoms and signs; but it may be necessary to analyse the vomit, urine, or blood to identify the poison.

If the nature and quantity of the poison are unknown, it is hard to decide how energetically to treat an apparently well child, but the fatal cases reported by Dr. Slade [4] indicate that it is always wise to assume that a dangerous amount has been taken. First-aid treatment with a salt or mustard and water emetic may safely be advised over the telephone, except when the poison is a corrosive or a volatile hydrocarbon. The parents should also be instructed to save any material vomited or urine passed.

Gastric lavage has long been considered a more effective method of removing poisons from the stomach than emesis, but there are certain objections to its use in children. Passing a stomach-tube can be a harmful business both physically and psychologically, and it may provoke a fatal convulsion. Moreover, solid objects, such as berries and tablets, may not be returned through the tube. The procedure is often ineffective in other ways,[5] and the introduction of fluid into the stomach may cause the pylorus to open and actually hasten the absorption of a poison. It is probably better to rely on emetics in children, and of these the best for the doctor's use is apomorphine, which should be given by subcutaneous injection. This drug has the advantages of diminishing intestinal motility and acting as a sedative, but it is, of course, contra-indicated in poisoning by opium alkaloids, or when the child is semi-comatose from any other cause. Another line of treatment which has long been followed, but whose value is doubtful, is the administration of purgatives: so far from promoting excretion of the poison, purgatives may hasten absorption by increasing intestinal motility, and syrup of figs was thought to have done so in one of Slade's cases. There is, however, no such objection to the use of daily enemata. In the case of poisons affecting the central nervous system, further elimination may be achieved by lumbar puncture.

When all possible steps have been taken to remove the poison from the body, an appropriate antidote can be given or, if the poison is unidentified, a universal antidote of charcoal, tannic acid, and magnesium oxide. Too much should not be expected from such treatment, however, and it should not be relied upon while action against the systemic effects of the poison is neglected.[2] Such action consists in counteracting loss of fluid and electrolytes, treating circulatory and respiratory failure, and giving physiological antidotes to neutralise the effect of the poison *after* it has been absorbed—e.g., methylene blue in toxic methæmoglobinæmia,[6] and dimercaprol (BAL) in poisoning by arsenic and certain metals. When the nature of the poison is known, the appropriate substance should be given before the onset of symptoms. The danger of convulsions in young children is very great, and it is advisable to give a barbiturate sedative in all cases of poisoning not caused by hypnotics.

Of course, the best treatment of all is preventive, and the old lessons must be put before parents (and others) as often and as forcibly as possible, especially when highly coloured or sugar-coated preparations are being prescribed. Nevertheless, dangerous drugs will continue to come by accident or oversight into the hands of children, and there seems little justification for continuing to manufacture potentially lethal substances in such an attractive form.

PHOTOSENSITISING SUBSTANCES

PHOTOSENSITISATION of the animal skin is exactly analogous to the action of the dye added to a panchromatic plate to extend its sensitivity-spectrum: it occurs when the tissues contain a substance converting light into chemical energy, which in turn produces local cell damage. In man the only well-known form of photosensitisation is that in congenital porphyria, where the photosensitising agent is probably uroporphyrin. In animals, however, several agents in addition to porphyrins may give rise to similar syndromes. These veterinary conditions have been reviewed by Clare [7] in a little book which might well be read by medical biologists.

Veterinary diseases giving rise to photosensitivity fall into three groups: (1) those in which the sensitising substance comes from an error of metabolism, as in cattle porphyria; (2) those in which it is ingested directly in the diet; and (3) those in which the primary disorder is a blocking of liver metabolism which prevents the destruction of chlorophyll derivatives. The most important substances in the second group are hypericin, a complex polyhydroxy-polycyclic compound from many species of St. John's wort, and fagopyrin from buckwheat. Of greater interest to human medicine is the photosensitisation due to phenothiazine used as a vermifuge. In man drug photosensitivity is uncommon; but it might lead to unpleasant side-effects in a first test, under tropical conditions, of material which had passed toxicity tests on clothed volunteers in a temperate climate.

In hepatogenous photosensitivity the sensitiser is phylloerythrin. This pigment is normally detectable in the bile and fæces of herbivores, though it may appear in other animals given large amounts of chlorophyll. In liver derangement due to various plant poisons the blood-phylloerythrin rises to a photosensitising level, and necrotic skin lesions appear. In some strains of sheep the inability to deal with this pigment appears to be congenital. Phylloerythrin has never been demonstrated, it appears, in human plasma; but possibly the chlorophyll fad, combined with a hot summer and a hobnailed liver, may yet yield an unsought demonstration of its presence.

In addition to the possible action of drugs or plant poisons, the study of photosensitivity in animals has a further bearing on porphyria in man. The episodic type of porphyria has at least some of the characters of a hepatogenous photosensitivity, in which an inborn metabolic error gives rise to the sensitising substance, a high concentration of which appears in the blood during a hepatic crisis. Photosensitivity is now increasingly recognised in some of these episodic porphyrias as well

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[1] King, A. L. *Permanente Fdn. med. Bull.* 1950, 8, 20.
[2] Ryan, D. C. *Med. J. Aust.* 1951, ii, 702.
[3] Craig, J. O. *Arch. Dis. Childh.* 1952, 27, 303.
[4] Slade, D. A. *Lancet,* Oct. 25 1952, p. 809.
[5] Harstad, E., Moller, K. O., Simesen, M. H. *Acta med. scand.* 1942, 112, 478.
[6] See *Lancet,* 1951, i, 1062.
[7] Photosensitisation in Diseases of Domestic Animals. By N. T. CLARE, M.SC. Review series no. 3, Commonwealth Bureau of Animal Health. Farnham Royal, Bucks: Commonwealth Agricultural Bureaux. Pp. 58. 7s. 6d.

as in the congenital form. There is also the striking observation of de Mello[8] that photosensitivity can itself induce porphyria. Rabbits sensitised with rose bengal and irradiated with ultraviolet light were found to have a grossly increased coproporphyrin output. This observation cannot yet be fitted into the general pattern of our knowledge of porphyrin metabolism, though it may prove important. Coproporphyrin itself has never been convicted as a sensitising material—probably the mechanism of its excretion is too efficient.

The whole subject of photosensitivity in its toxic, congenital, and hepatogenous forms is one where veterinary and human medicine could usefully converse occasionally—the knowledge obtained from animals might explain some of the obscure dermatological conditions, especially in the tropics.

SOCIETY FOR SPASTICS

THE National Spastics Society has been set up by the parents of children suffering from cerebral palsy, and its membership is entirely confined to them. The aim of this society,[9] under the presidency of Prof. J. M. Mackintosh, is to spread information and encouragement about spastic children to parents and others. In order to do this it must try to discover more parents of spastic children and adult spastics and bring them into the association. It must also try constantly to increase the number of local associations so as to cover the whole country and ensure a widespread interest in meeting this difficult problem. There are now parents' associations in nearly fifty towns in England and Wales; but all who are interested need to do much more work in starting new centres, in collecting funds for development, and in approaching local authorities for their help in providing education and medical care. The child with cerebral palsy is an outstanding example of the need for effective coöperation between voluntary effort and the State.

The total number of spastic children in this country is not known, but investigations have shown that the total cannot be far short of 30,000. Of these some 10% are of high average or superior intelligence, and a further 50% are educable. Of the remainder a substantial proportion may greatly benefit from new methods of training; wherever schools have been established for spastic children a surprisingly large number have clearly been helped by education combined with therapy. There is great need for various types of provision for such children; and experiment and assessment are necessary in order to find the right combination of services. The traditional view was that a spastic child could not develop mentally beyond the limits of his motor experience, because he had to translate his ideas into muscular activity in order to grasp anything. Thus the first object in treating a spastic was to educate his muscles until some control was secured. Until this goal was reached, academic instruction was deferred, and it might be neglected for ever. Only lately has it been realised that mental growth brought about through academic education promotes physical control as well as skill in circumventing a physical difficulty. As Carlson has said: "The spastic is ordinarily a badly spoiled child, completely lacking in self-discipline and the power of concentration. Yet it is only through the acquisition of these qualities that he can overcome his handicap. As a school is obviously the best way to develop his powers, it is also the best means of taking the child's mind off his own difficulties and thus increasing the benefits of physiotherapy, which cannot stand by itself as a form of treatment."

The diagnosis of cerebral palsy in a small child is by no means easy, but this is not the most serious difficulty. In the past the trouble has been rather that a hasty diagnosis was made by someone strange to the child, who, after comparatively superficial assessment, was assumed to be mentally defective and was relegated to the tragic ranks of the ineducable. It is now quite clear that no child should be regarded as ineducable until his condition has been thoroughly assessed; and the investigation should include an expert examination of sight and hearing and careful estimation of intelligence against the background of age and physical capacity.

The primary service to a spastic child is educational, and the special needs are as follows:

Day-nursery clinics where children may be brought for observation, proper assessment of their handicaps, treatment, and the all-important social contacts with other children: where parents can learn what treatment to carry on at home and understand better how to adjust themselves to having a handicapped child.

Day special schools or cerebral-palsy units in existing schools for physically handicapped children aged 5–16 years, in large cities; and special provision for children of lower mental grade, who tend to be ignored because of the great difficulty of finding the right type of occupational care.

Residential special schools which will provide for spastic children from the smaller towns and rural areas.

A residential special secondary school to take children of above-average intelligence whose handicap is such that they are unlikely to get jobs needing physical dexterity and whose brains must therefore be their main asset.

Residential homes for the very badly handicapped who have little or no hope of being trained for a vocation. There is seldom a vacancy for these children in other homes or institutions.

Training centres where adolescents and adults may receive treatment, be trained for a job, and get equipment that will make the job easier to do.

TREATMENT OF BENIGN TERTIAN MALARIA

BENIGN tertian malaria is not usually dangerous in itself, but it is an intractable and highly incapacitating nuisance, unworthy of the term "benign"; it would better be known as *Plasmodium vivax* malaria. In one way it is not intractable, for individual attacks respond readily enough to all the recognised drugs—quinine, mepacrine, proguanil, or chloroquine—but none of these can be relied on to prevent relapse. In the tropics *P. vivax* malaria has a short incubation period, and the primary attack takes place soon after the infective mosquito bite; the tissue phase persists and relapses are common. The archetype of *P. vivax* causing this form is the Chesson strain, which originated in the South-west Pacific area. But in temperate climates in Europe and America, and now notably in Korea, there exist strains of *P. vivax* which behave quite differently: there is either a long incubation period lasting several months or, after a primary attack at the end of a short incubation period, a latent period of six to nine months after which relapses tend to occur. The archetype of this form of *P. vivax* is the St. Elizabeth strain, which originated in the United States. Late relapses have been noted in American troops after returning from Korea, even though they had taken chloroquine regularly in the transmission season and, in many cases, had not had any primary attack in Korea. Chloroquine did not prevent infection and relapse; it did suppress the clinical manifestations of infection so long as it was taken regularly, but when it was discontinued the blood forms developed unhindered from the tissue phase, which had evidently persisted unharmed by the suppressive drug.

It has long been known that drugs of the 8-aminoquinoline series (pamaquin ['Plasmoquine'], pentaquine, isopentaquine) may prevent relapses if taken at the time of, or shortly after, the curative courses of quinine, mepacrine, or chloroquine; but drugs of this series may produce toxic effects in amounts not far removed from the minimum effective doses. The U.S. Council on Pharmacy and Chemistry reports work[1-4] done on a little known 8-aminoquinoline—primaquine (8-[4-amino-1-methylbutylamino]-6-methoxyquinoline)—which appears to be as effective as pamaquin but less toxic. Primaquine was synthesised at Columbia University during the great anti-malaria programme in the late war, and was tested on volunteers and in the field. It has now been used on a large scale in troops returning from Korea.

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[8] de Mello, R. P. *Proc. Soc. exp. Biol., N.Y.* 1949, 72, 292.

[9] The society's headquarters are at 20, Pembroke Road London, W.8.

The first test[1] was made to find out if primaquine could safely be given to large numbers of men. The plan was to administer 15 mg. of primaquine base each day for two weeks, starting at the time of arrival at the military depot in Japan, and ending usually during the voyage home. During the malaria season in Korea the men had received chloroquine as a routine suppressive measure, but this was discontinued before primaquine was administered. In one combined test 2060 officers and men received 12–20 pills of primaquine (15 mg. of base), and 725 men received a placebo. This test showed that the drug could be handled effectively with large numbers of men, and was not toxic.

Garrison et al.[2] report that, of 232 men with first attacks of *P. vivax* malaria after a long latent period who were treated with chloroquine alone for three days, 27·6% had relapsed after four to eleven months; of 246 given chloroquine for three days and pamaquin (27 mg. of base daily) for fourteen days 0·4% relapsed; and of 231 given chloroquine and primaquine (15 mg. of base daily) none relapsed. Neither pamaquin nor primaquine, however, is effective against the erythrocyte stages of the parasite, and these drugs should therefore not be relied on for treating the acute attack; they should, according to Garrison et al., be given together with chloroquine. Pamaquin, and probably primaquine, should not be given at the same time as mepacrine.

Clayman et al.[3] describe toxicity studies in a large number of white volunteers. Primaquine was given in a daily dosage varying from 10 to 240 mg. of base, in single or divided doses, for five to fourteen days, alone or with other drugs, either for the treatment of clinical malaria or in the absence of clinical malaria. It was also given in a dosage of 30 mg. of base once or twice weekly for a year, together with chloroquine. It seems that at a daily dosage of 15 mg. of base, primaquine may safely be administered continuously for two weeks without special medical supervision, and adult white patients receiving as much as 30 mg. a day may remain up and about as outpatients. But at higher doses supervision in hospital is advisable; methæmoglobinæmia and abdominal symptoms, including vomiting, have been observed. Thus in white people the drug is fairly safe; but in Negroes this is not so, and Hockwald et al.[4] recall that the 8-aminoquinolines sometimes give rise to very severe hæmolytic crises resembling blackwater fever, and that these are especially common in Negroes. Primaquine in a daily dose of 30 mg. (base) gave rise to anæmia in 17 of 105 Negroes; and in 5 of these there was hæmolysis. With 30 mg. of pamaquin (base) these 5 men showed similar severe anæmia. They tolerated 15 mg. of primaquine daily, however, and Hockwald et al. conclude that 15 mg. of base can safely be given daily for two weeks to Negroes. It may be given with quinine or chloroquine, but never with mepacrine.

Primaquine is therefore a useful addition to the drugs we use for *P. vivax* malaria; it is, dose for dose, more effective and less toxic than pamaquin.

YESTERDAY IN TODAY

THE medical man is apt to think of history as a harmless hobby which collects the amusing superstitions and bric-a-brac of the past. Twentieth-century medicine is dizzy with the speed of its own advance. Scientific change is so rapid that the historic may be thought synonymous with the out of date, and to be out of date is to be guilty of the unforgivable sin. We sometimes forget that medicine is always a by-product of its times, not only in its scientific equipment but in its philosophy and objectives. In community medicine, as in other fields of policy, every situation is the result of historical developments, and only if these are understood can we plan properly for the present and future. We must know where we have come from to see where we should go next.

Dr. Henry Sigerist has done more than anyone in our time to teach medical men the importance of historical approach. He has brought immense learning to the study of the history of medicine; but to him historical study is not an end in itself, it is a lesson for today. It is not only a necessary instrument of policy, it is an important discipline in medical teaching.

In his Heath Clark lectures at the London School of Hygiene and Tropical Medicine, Dr. Sigerist ranges from Galen to the present time, using a cavalcade method to demonstrate medicine and medical policy as one aspect of the contemporary culture. Thus Galen's teaching on hygiene was an expression of the fact that for the Roman patricians to whom it was directed, the cult of the body was an end in itself. The Galenical philosophy on which the teaching was based lingered on in the Middle Ages, but its impact was quite different because Christianity had taught a different view of the body through whose suffering redemption might come. In the field of State medicine it is significant that the first major work comes from the eighteenth-century search for the philosophy of good government for the masses under benevolent despotism. Johann Peter Frank (*System einer vollständigen medicinischen Polizey*, 1779) in the period of the enlightened man had no less an ambition than the study of the health needs of man in his total environment, physical and social, and his policies were to be enforced by the enlightened despot.

The dominating events leading up to our own epoch were the rapid expansion of industry and the breakdown of the traditional supports of the static agricultural society. Established methods of dealing with the sick and infirm could not cope with the fast-growing new communities of wage-earners precariously poised on the edge of destitution and pestilence. The survival of the new society depended on certain public-health measures against epidemic disease. Slowly these measures of environmental control were put into effect. But the problem of providing medical care to the sick individual was still unsolved. Tsarist Russia sought a solution through a public State medical service, and this was taken over and developed by the Soviets. In Germany Bismarck tried another way: his intention partly paternalistic, partly to dish the rising Socialist party, he evolved the insurance method of social security provision which became a model for other Western countries. In our own day medicine is hoist with its own scientific and technical advance. The immense costliness of medical care today puts it beyond the means of the great majority to afford for themselves or for private charity to provide. Sigerist is doubtful whether the insurance method can solve the problem and he sees in our National Health Service, for all its imperfections, a great step forward, and an experiment watched by the rest of the world.

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1. Alving, A. S., Arnold, J., Robinson, D. H. *J. Amer. med. Ass.* 1952, 149, 1558.
2. Garrison, P. L., Hankey, D. D., Coker, W. G., Donovan, W. N., Jastremski, B., Coatney, G. R., Alving, A. S., Jones, R. jun. *Ibid.* p. 1562.
3. Clayman, C. B., Arnold, J., Hockwald, R. S., Yount, E. H. jun., Edgcomb, J. H., Alving, A. S. *Ibid.* p. 1563.
4. Hockwald, R. S., Arnold, J., Clayman, C. B., Alving, A. S. *Ibid.* p. 1568.

Special Articles

INITIAL PRACTICE ALLOWANCES

ARRANGEMENTS for paying initial practice allowances, in accordance with the recommendations of the Working Party on the distribution of remuneration among general practitioners, are announced this week by the Ministry of Health.[1]

These allowances will become payable from April 1, 1953, to certain doctors in areas classified as " designated" by the Medical Practices Committee. From the same date fixed annual payments will cease to be paid; but doctors receiving fixed annual payments immediately before April 1 will be entitled to a special payment for a temporary period in whatever type of area they are practising, subject to certain conditions.

In designated areas the following will be eligible to apply for an initial practice allowance:

1. Doctors who are genuinely setting up a new single-handed practice in a practice area new to them.
2. Doctors filling vacancies in small single-handed practices.

To qualify for the allowance a doctor must have been in general practice for not less than two years, whether as a principal or otherwise, or have been fully registered as a medical practitioner for not less than four years. The allowance will be payable for a maximum of three years at the rate of £600 in the first year, £450 in the second year, and £200 in the third year, subject to certain conditions in the second and third years.

NEW SINGLE-HANDED PRACTICES

First Year

Doctors should consult the appropriate executive council before making any final decision on whether to start a practice in an area which they believe to be classified as designated. If the doctor fulfils the necessary conditions payment of the allowance will begin from the date on which the practice is started following his admission to the medical list.

It may be necessary for the Medical Practices Committee to change the classification of some designated areas as soon as one or two additional doctors are admitted to the list. In such cases not all applicants may qualify for allowances. Doctors who apply for admission to the medical list in borderline designated areas would be well advised not to enter into any binding arrangements for acquiring practice premises before being informed that they have been granted an allowance, if their entry into practice in the area depends on this.

A doctor may apply for an initial practice allowance (and for admission to the medical list) before he has secured practice premises, provided that he indicates the district in which he proposes to secure surgery premises. He will then be admitted to the medical list provisionally. He may not, however, be provisionally included in the list for more than one area at any one time. Payment of the initial practice allowance and full admission to the list will be subject to his starting his practice within one month after provisional admission to the list; but this period will be renewable month by month up to a further two months at the discretion of the executive council.

If, after a payment has been started, the executive council considers that the doctor is not genuinely setting up in single-handed practice it will give the doctor three months' notice of intention to terminate payment.

Second and Third Years

The allowance for the second year will be conditional on the doctor obtaining 150 patients at the end of the first year, and will be the amount by which his gross professional earnings due for the first year, excluding the initial practice allowance in respect of that year, fell short of £1100, subject to a maximum payment of £450.

The allowance for the third year will be conditional on the doctor obtaining 500 patients at the end of the second year, and the amount will be that by which his gross professional earnings for the second year, excluding the initial practice allowance in respect of that year, fell short of £1000, subject to a maximum payment of £200.

If a doctor fails by a slight margin to reach the minimum numbers on his list to qualify for a continued payment the council may at their discretion, and in consultation with the local medical committee, regard the conditions as having been fulfilled. The minimum numbers to be reached may also be modified on other reasonable grounds—e.g., if the doctor has been ill or for other good reasons has been unable to carry on his practice duties for some part of the year.

If a doctor fails to qualify for a payment in his second year, either because his list does not reach the required size at the end of the first year or because his earnings exceed the limit, this will not debar him from a maximum payment of £200 in the third year if his list reaches 500 at the end of the second year and his earnings for that year are below the limit.

A doctor may not receive an initial practice allowance for more than three years even though he starts a practice in one area and then moves to start another practice in another designated area.

VACANCIES IN SMALL SINGLE-HANDED PRACTICES

Doctors filling vacancies in small single-handed practices in designated areas will be eligible for an initial practice allowance for three years. The allowance in the first year will be the sum required to raise the income calculated on the size of the list when taken over to a gross total of £1000, subject to a maximum payment of £600. Income for this purpose will be regarded as capitation fees and, where payable, additional " loadings " and mileage and dispensing payments. On this basis doctors taking over lists of up to 800–900 will be eligible to apply. A doctor filling a vacancy in a small practice who has previously received an initial practice allowance in respect of an effort to start a new practice elsewhere will not be eligible for payment for more than three years in all.

DOCTORS PREVIOUSLY RECEIVING FIXED ANNUAL PAYMENTS

Doctors in all areas who, when the scheme begins on April 1, 1953, have been in receipt of a fixed annual payment for less than three years, and whose applications for payment are received before Nov. 24, 1952, will receive a special payment at the appropriate initial practice allowance rate for the balance of the three-year period or for one year, whichever is the longer. The payment will be subject to the appropriate maxima on professional earnings during the preceding year (excluding the fixed annual payment and the percentage increase in respect of it paid as a result of the Danckwerts award). If payment is due for more than one year, its continuance will also be subject to the standard conditions relating to the size of the list to be secured at the end of each year.

A doctor who, when the scheme begins, is in receipt of a fixed annual payment which has continued for three years or more will receive a special payment for one year. The payment will be the amount by which his gross professional earnings due for the preceding year (excluding the fixed annual payment and percentage increase) fell short of £1100, subject to a maximum of £200.

Doctors receiving a fixed annual payment in areas other than designated and whose applications for payment are received by the executive council on or after Nov. 24, 1952, will receive a special payment for one year from April 1, 1953. The payment will not be continued in such cases after March 31, 1954.

No special payment will be made to a doctor in respect of his existing practice if he has never had a fixed annual payment in respect of that practice, or has had one and is no longer receiving it.

CHANGE IN CLASSIFICATION OF AN AREA

Doctors who after Oct. 18, 1952, and before April 1, 1953, have started a practice in an area which at the time of their starting the practice was classified as designated by the Medical Practices Committee will be eligible to apply for the initial practice allowance from April 1, 1953.

A doctor who after April 1, 1953, is receiving an initial practice allowance in an area whose classification is subsequently changed from designated will continue to be eligible for the payment for the remainder of the three years, subject to his satisfying the normal conditions. A doctor who is practising in an area which is not classified as designated will not be entitled to an initial practice allowance in respect of his existing practice if the classification of the area is subsequently changed to designated.

APPEALS TO THE MINISTER

Where the executive council has refused to grant or continue an initial practice allowance or special payment, or where the amount of payment is in dispute, the doctor will have a right of appeal to the Minister of Health.

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[1] E.C.L. 88/52; E.C.N. 112.

RESPIRATORY AIR CURRENTS

The Semon Lecture

THE more violent respiratory air currents emerge as the coughs and sneezes that are of such popular epidemiological significance; but the gentler currents in the upper respiratory tract can also be important, as Dr. A. W. PROETZ, of St. Louis, showed in the 1952 Semon lecture of the University of London, given at the Royal Society of Medicine on Nov. 6. Dr. PROETZ described some of the physical properties of air currents in general. If smoke from a cigarette is blown through a straight glass tube of uniform bore, no particles are deposited on the tube; but if the tube is bent or constricted, there is a turbulence in the smoke and a deposit is rapidly formed just beyond the bend or constriction. A homely example of this may be found in the smoker who has an obstruction in one side of his nose. If he blows the smoke out through his nose there is a deposit of particles beyond the constriction, and the vibrissæ (or long hairs) just inside the nostrils become stained brown.

If the nose is healthy, the air currents pass into the nasopharynx without obstruction. The nasal airway in man is normally only about 1 mm. in width, and the nose gets its capacity through height rather than width. The air currents in the nose are affected by three things: the size and direction of the external nares; the general shape of the nose; and the difference in size between the anterior and posterior nares, the latter being larger than the former. Normally the nares are directed downwards so that, on inspiration, the air first of all passes straight upwards; it then passes through the upper part of the nose in a gentle curve; and it leaves the nose through the posterior nares to enter the nasopharynx. This inspired air does not come into contact with the ostia of the sinuses in the middle or the superior meatus. As the air passes downwards from the nasopharynx to the larynx, there are turbulent areas at the back of the mouth, under the palate, and round the epiglottis; and it is interesting to note that these are the very situations where aggregations of lymphoid tissue are found. During expiration there are in the normal nose eddies of air under the middle turbinates, and the ostia of the sinuses are, therefore, reached by this air alone, after it has been moistened. There is very little air exchange in the sinuses themselves.

Abnormal air currents may be caused by various lesions—by deviations of the nasal septum, by polypi, by swelling of the turbinates, by enlarged plicæ septi, or by adenoids. The air currents in the nose normally pass through its upper, and not its lower, part, and a swelling high in the nose, such as may occur in a common cold, will leave only a small passage for the air through the lower part of the nose. Air then passes straight back and impinges against the nasopharynx, where the adenoids are situated. This produces the dry spot at the back of the throat in the early stages of a cold. A deviation of the septum may often have to be corrected by surgery, but not always. Sometimes the turbinates will enlarge on the unobstructed side, and so adapt themselves to the abnormal condition of the septum. If a submucous resection is performed in such a case, there will be too much room on the unobstructed side when the septum comes to lie in the midline; and there will be a constriction on the other side where the straightened septum lies against the enlarged turbinate. In such a case, a dry area will develop, with subsequent stasis and liability to infection. The remedy is, therefore, not always surgical. When there is only a low spur on the septum, this is streamlined and air can pass above and below it. There is therefore no interference with the air currents and no harm is done. However, should the patient with a low spur catch a cold there will also be swelling in the upper part of the nose with considerable obstruction. Polypi in the superior meatus of the nose will interfere with the air currents, but polypi in the middle meatus, although they will have to be removed for other reasons, have an almost negligible effect on the air currents. If the middle turbinate is removed, there is practically no change in the air stream; but if both middle and inferior turbinates are removed, what is tantamount to atrophic rhinitis develops, and true atrophic rhinitis soon follows. Although there is then a much wider air space than normal, the patient complains of nasal obstruction, because there is eddying of air in the nose on inspiration, with deflection of the normal currents.

Dr. Proetz illustrated his remarks with two excellent films, which demonstrated the behaviour of smoke in various kinds of tubes; the mucus blanket being moved by the cilia; red cells being tumbled along at a great pace; the stasis that follows drying; and the normal air currents and their variation under different conditions.

Medicine and the Law

Doctor, Hospital, and Patient

IN the case of Payne *v.* St. Helier Group Hospital Management Committee and Another, reported in the *Times* (Nov. 12), the court placed upon a professional man the full responsibility for his professional actions. The casualty officer at the hospital was held to have been negligent; the management committee, as his employers, thus became liable also, since he was acting as their servant in the course of his duty as such. In awarding damages to the plaintiff, however, the judge made an order indemnifying the committee against the doctor in respect of the whole sum awarded as damages and in respect of two-thirds of the committee's costs.

The plaintiff, Mrs. Payne, was the widow of a horse-keeper employed by United Dairies. Early in the morning of July 10, 1950, the deceased was kicked in the abdomen by a horse. He consulted his doctor, who sent him to the hospital for examination. At the hospital the casualty officer examined him some nine and a half hours after the accident; this practitioner had been professionally qualified for two years. He observed an abdominal bruise, but, concluding that there was no internal injury, sent the patient home and told him to go to bed and to call in his own doctor if pain was felt. By July 28 the patient was very ill; he was readmitted to hospital where two operations were performed—first a lumbar incision, and secondly a laparotomy which showed general peritonitis. On Aug. 30 the patient died.

His widow alleged negligence as follows: the hospital system, she said, must be wrong if a patient, sent in by a general practitioner, was examined by a casualty officer only and not by a surgeon of consultant rank; the casualty officer must have been negligent in failing to heed that the bruising indicated a very severe blow, in failing to appreciate that a general practitioner's action in sending the patient for examination meant that a more experienced opinion was required, and in failing to keep the patient in hospital for observation or to have him examined by a consultant surgeon. For the defendant doctor (the casualty officer) it was contended that Mrs. Payne had not established that her husband's death from general peritonitis on Aug. 30, so long after the injury, was due to the negligence (if any) of the defendant on July 10, and that, even if the patient had been kept in hospital and examined by a consultant, there was nothing to show that his life would have been saved.

Mr. Justice Donovan found in favour of the widow. The clinical tests made by the defendant doctor were admittedly correct; but he must have, or ought to have liscovered that the patient was suffering from pain, hock, and rigidity of the abdomen; if these conditions vere present in addition to the bruising, then the diagnosis nd treatment represented less than the exercise of easonable care. It was wholly unjustifiable to send the nan home and not to detain him for examination by consultant. These findings amounted to a verdict of egligence; had the proper course been taken, his Lordship considered that the deceased would in all robability have survived. He awarded £2640 damages, lacing the liability substantially upon the defendant loctor in the terms already stated.

Parliament

Education of Blind Children

IN the House of Commons on Nov. 12, Mr. EDWARD SHORT called attention to the need for more facilities for the education of blind children. The National Institute for the Blind, with Government assistance, provided education for over 1100 young people, but owing to improved medical services the number of premature babies who survived was increasing. The prevalence of blindness was greater among premature babies than among normal babies. An increase in the incidence of blindness among children was therefore to be feared. Yet the only additional provision to be made this year for blind children seemed to be a share of 150 extra places to be provided in special schools for physically handicapped children. That, he thought, was inadequate to meet the probable increase in the present waiting-list of 150.

Mr. KENNETH PICKTHORN, parliamentary secretary to the Ministry of Education, claimed that the blind had got rather more than their share of accommodation compared with other handicapped children. He agreed that of the 1300 blind children who were the responsibility of the Ministry of Education about 170 were on a waiting-list to go to school. Most of these wanted to go to Sunshine Homes and not to the schools which had vacancies. Again many of them were under five years of age and their parents did not want to be parted from them. A considerable number had additional handicaps and were not eligible for the ordinary Sunshine Homes. Two Sunshine Homes did accept blind children with another defect. Deducting these two classes, he was left with the real waiting-list, and he did not believe they would have long to wait.

In the next ten years, he thought, about 200 additional places would be needed. But if the increase in the number of premature births surviving continued, then more than 200 places might be needed. A subcommittee of the Medical Research Council was inquiring into the problem of premature babies who are blind, especially into the geographical incidence of the condition which was oddly uneven. They could not say what further effect this particular kind of blindness—a new condition not earlier recognised or understood—might have.[1]

There were about 1800 partially sighted children, and according to the best opinion it was in their interests as well as those of the blind children to separate them in different schools. That was being done. He thought it was pessimistic to suppose that there was anything like a scandalous shortage of accommodation for partially sighted children.

QUESTION TIME

Lung Cancer among Gas-workers

Mr. S. T. SWINGLER asked the parliamentary secretary to the Ministry of Works, as representing the Lord President of the Council, on what lines it was intended to pursue research into the special causes of lung cancer in gas-workers, through the agency of the Medical Research Council.—Mr. A. H. E. MOLSON replied: The Medical Research Council has arranged for one of its expert committees to examine the possibilities. Until this committee has had time to consider the problem in detail, I shall not be able to indicate which lines of research are likely to be the most promising.

Mr. SWINGLER: Will the Minister consult the Minister of Fuel and Power, because one of the troubles is that two-thirds of the gas boards do not employ full-time medical staffs? Mr. MOLSON: The whole matter is under careful consideration. Investigations have already been made and the matter is still being followed up.

Medical Service in the Gas Industry

In reply to Mr. SWINGLER, Mr. GEOFFREY LLOYD, Minister of Fuel and Power, said he did not think it was necessary to establish in each area of the gas industry a full-time industrial medical staff as part of a comprehensive health service for the industry. He was in favour of developing a proper industrial health service, but for some boards with small and scattered installations it would not perhaps be the best plan to have a full-time medical officer; it might be better to rely on local medical practitioners. If they were to rely on a full-time medical officer, there was a danger that far too much of his time would be spent in travelling to the different installations over the whole area.

Hospital Expenditure

In answer to a question Mr. IAIN MACLEOD gave the following figures for the expenditure per head of population which it is estimated will be incurred by each regional hospital board in the current year:

Estimated hospital expenditure in 1952–53 per head of population

Regional hospital board	*Amount per head* £	s.	d.
Newcastle	4	6	3
Leeds	4	16	0
Sheffield	3	19	0
East Anglian	4	0	8
North West Metropolitan	5	5	4
North East Metropolitan	6	0	10
South East Metropolitan	5	17	5
South West Metropolitan	6	6	10
Oxford	4	17	10
South Western	5	10	0
Birmingham	4	5	2
Manchester	4	6	11
Liverpool	5	0	6
Wales	4	14	10

Incidence of Tuberculosis in the Regions

In answer to a question Mr. MACLEOD gave the following figures showing the percentages of the population suffering from tuberculosis in each region:

Regional hospital area	Number of notified cases on chest clinic registers at Dec. 31, 1951	% of population
Newcastle	19,706	0·68
Leeds	14,745	0·48
Sheffield	25,986	0·63
East Anglian	7449	0·51
N.W. Metropolitan	29,616	0·73
N.E. Metropolitan	21,750	0·72
S.E. Metropolitan	27,601	0·86
S.W. Metropolitan	30,471	0·67
Oxford	6474	0·45
South Western	16,839	0·61
Wales	21,831	0·84
Birmingham	26,013	0·58
Manchester	25,297	0·58
Liverpool	15,294	0·73

Special Grants during Preregistration Year

Sir GEOFFREY HUTCHINSON asked the Minister whether he would consider making special grants to doctors required to give one year's service as house-surgeons on qualification where doctors had served in H.M. Forces and for that reason were in a higher age-group than was normally the case, and where such doctors have family responsibilities.—Mr. MACLEOD replied: Such a house-officer may be eligible for a special grant from the Minister of Education, in addition to his salary.

School Dentistry in Scotland

Replying to a question Commander T. D. GALBRAITH stated that in Scotland the number of dentists in general practice taking part in the National Health Service had fallen from 1254 at the end of 1951 to 1210 at the end of last month. In the same period the number of dentists in the school service had increased from 104 to 131. There was no formal establishment of dentists in the school service, but he was advised that the present number, which was equal to the highest number ever before, was still far short of the total that could usefully be employed. The reason for the increase in the number of dentists now going into the school dental service was first of all the improved salary scales and also the reduction in the numbers attending the general dental service.

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[1] See *Lancet*, 1951, ii, 1173; Oct. 25, 1952, p. 818.

South-West Metropolitan Regional Hospital Board

Dr. REGINALD BENNETT asked the Minister of Health what had been the result of his consideration of the suggestion that a separate region and regional hospital board should be created for the western area of this region.—Mr. MACLEOD replied: After consulting all the parties concerned in this matter, and having carefully considered all the views expressed, I have reached the conclusion that no substantial advantage would be gained by the creation of a separate region and regional board for this area. It seemed to me that the criticisms made by those who wanted a new region could probably be met more economically, and without the loss of the advantages at present deriving from the existence of a single region, by delegation of powers more freely to the western area committee rather than by creating a new region and a new board. I therefore asked the regional board to consider how this wider measure of delegation might be achieved, and sought their views on a number of suggestions which appeared to me to be practicable. These suggestions were discussed by representatives of the board and the western area committee with officers of the Ministry and I understand that the committee are preparing detailed proposals indicating how, in their view, the suggestions might be implemented and they will submit their proposals for the board's consideration in due course. I now await the board's considered views.

Prescription Charge for Nurses

Mr. M. TURNER-SAMUELS asked the Minister if he was aware that it is a tradition that hospitals should care for the health of their staff, especially of nurses whose occupation was of the nature of a vocation and who were expected to put the care of patients before the strict interpretation of terms of service; and if he would therefore withdraw the instruction of his department contained in Circular H.M.C. (52)52 that nursing staff of hospitals, whether resident or not, shall be charged the fee of 1*s.* for prescriptions made up in the hospital pharmacy unless they were inpatients of the hospital.—Mr. MACLEOD replied: While I certainly do not wish to discourage the proper care of the health of nursing staffs, I am not satisfied that the payment of this charge, which is payable by all other members of the community in similar circumstances, has this effect, or that it would be justifiable to make an exception in their case.

Hospital Staffs

Mr. ARTHUR BLENKINSOP asked the Minister what fresh instructions he had issued limiting hospital medical staffs and proposing reductions in hospital domestic staff.—Mr. MACLEOD replied: None, Sir; though I have opened discussions with the boards of governors about the medical staff establishments of the teaching hospitals.

Corporal Punishment

Replying to a question Sir DAVID MAXWELL-FYFE, the Home Secretary, said that before corporal punishment was abolished as a judicial penalty in September, 1948, the only important offences for which it could be imposed on male adults by the courts were offences of armed robbery and robbery with violence contrary to section 23 (1) of the Larceny Act, 1916. In 1946 and 1947 there were, respectively, 804 and 842 offences of this nature known to the police in England and Wales; the corresponding figures for 1950 and 1951 were 812 and 633. The provisional figure for the first six months of 1952 was 359.

Most other crimes of violence against the person had increased in recent years. In 1948, 646 cases of felonious wounding were known to the police in England and Wales, whereas the figure for 1951 was 1078. For malicious wounding the figures for 1948 and 1951 were 3547 and 4445, respectively; for rape 252 and 335; and for indecent assault on females 5659 and 7287. Corporal punishment could not, however, be imposed as a judicial penalty for any of these offences before 1948.

In England Now

A Running Commentary by Peripatetic Correspondents

SNOW has fallen in the Pennines. The wireless forecasts cold or rather cold weather throughout the country, and already I have been called out to see a man who tells me that his black eye and broken nose are due to a fall on the ice, not to a family misunderstanding. These signs of winter depress me, especially as I am continually hearing how healthy cold weather is. Patients affirm it as they display their rheumaticky limbs and chilblained fingers. They insist upon it as they cough in my face. Between sneezes they murmur in husky voices that the cold destroys germs. Plenty of fresh air, though it kills you, seems to be the motto for today. But, come to think of it, those who live in hermetically sealed rooms, those who believe that cold water is dangerous, and those who hold that too much water of any temperature is best avoided in winter—they are the ones who live to be eighty or ninety and seldom bother the doctor. My old chap down the road, who will be a hundred next month, knows better than to send for me when he gets a cold on the chest. He merely puts on yet another layer of winter woollies, stuffs another sock in the crack under his bedroom door, and gets better.

* * *

The conflict between the art of medicine and the science of medicine schools recalls a lesser but equally intense conflict between the art of wine-making and the science of wine-making groups. The art of wine-making is described in many cookery books; but many otherwise reliable textbooks of bacteriology lack a chapter on the science of wine-making. Yet good wine of high alcohol content can be readily prepared from the simplest ingredients—fruit, sugar, and yeast—provided ordinary bacteriological techniques are applied.

It is best to use a culture of *Saccharomyces ellipsoideus*, which has been repeatedly shown to attain a higher alcohol content (up to 15%) than any other yeast. A suspension is prepared by growing in a large volume of glucose-broth, centrifuging, and depositing the yeast in a small volume of saline. The fruit and sugar mixture should be sterilised in its container by heating in the oven for one hour at regulo no. 5. After cooling, the yeast suspension is added and a gas trap inserted. Fermentation should be carried out in a warm room (70°-75°F) and preferably at an even temperature. When fermentation has ceased the wine is filtered through a clean handkerchief and bottled without screwing the corks home tightly. In place of the traditional wooden cask, a pinch of tannic acid will often improve matters. Finally, and most difficult of all, don't drink the wine until it has matured for at least six months and preferably a year.

Inquiries about Château Medresco should not be addressed to Old Queen Street but to our filiale at Mont Moulin.

* * *

District midwifery in Lahore is often complicated by the fact that very few of our mothers seem to know where they live and seldom give us their correct address. We often wonder how they find their own way home. It would be less confusing if they told us to turn right at the third buffalo, and then follow the white horse with the lame leg to the fourth water tap by the Pipul tree. Perhaps W.H.O. should only recruit public-health nurses with second sight.

Kaneez, with ten pregnancies to her credit and two children who managed to survive infancy, was perhaps our prize problem mother. Sweetly vague, with her hair hanging in wisps from under her burka, she attended our antenatal clinic from the earliest months, but unfortunately rarely on the right morning. She would send for UNICEF milk, but always an hour too late so that the poor health visitor had to dirty her pots and pans again and make some more. She was always demanding little dabs of gentian-violet and 'Vaseline' at the most inconvenient moments. Then suddenly she would desert us for weeks, and it would take hours of home visiting and offers of soap (bribery) to persuade her to come to the clinic again for examination. She was a lady of uncertain temper. Some days when we visited her she would not speak, but went on with the cooking, slapping the chappati angrily while giving us fierce looks. At other times she would be sweet and docile and do everything we asked, except of course prepare her things for delivery.

As her time drew near it became routine to ask the midwife who had been on night call: "Has Kaneez delivered yet?" Eventually, at five o'clock one morning she sent her booking card, and we rushed like mad, pinning up our hair as we drove through the gate. We arrived there just in time: the baby was born, of course, but the cord was not cut. Kaneez was lying on the bed looking faintly surprised, and the baby, which she had forgotten to pick up, was lying squalling naked in a puddle on the mud floor. An obliging neighbour, string and vegetable knife in hand, was about to cut the cord. No-one was at all pleased when we demanded water to boil the ligatures and instruments, but we quietly got on with it, and then bathed the mother and baby. Kaneez did not like the idea of feeding her baby at the breast; it was not her custom for the first three days, but we eventually persuaded her. We put the infant in her arms, and when it was sucking well turned our backs for a minute to strap up the delivery bags. When we looked again the same helpful neighbour had taken the baby and was giving it a drink of nice sweet tea, hot and strong, throwing it expertly into its mouth with her grubby fingers while our Kaneez looked on approvingly.

* * *

The staff table at lunch was discussing the Motor Show, and the Senior Anæsthetist put forward the view that cars had deteriorated each year since the war. Challenged to prove this, he suggested that as the Ophthalmic Surgeon was present the company should consider visibility as a sample of modern trends.

His theory received instantaneous support. The Orthopædic Surgeon and the Obstetrician vied with one another in deploring the common practice of curving the wind-screen, which caused distortion particularly at the sides where the curve was greatest. Night-driving, the Physician declared, was made more difficult by the secondary images of bright lights, and by the head-lamps of following cars, for rear-blinds are now usually omitted. The Pathologist pointed out that continual renewal of wiper-blades was necessary if the curved rubber was to clear the whole area wiped. He added that, to cut prices, most windscreen-wipers now had no auxiliary hand-control, and if the electric motor packed up, the driver had had it, particularly as the screen itself now seldom opens—a fatal fault in thick fog. The substitution of toughened for laminated safety glass meant that the whole screen instantaneously became opaque if struck by a flying stone, a shattering experience that had happened to the Surgical Registrar and the Otologist. The Psychiatrist gave a moving description of the frustration he had experienced while touring abroad, particularly in mountainous countries, now that sunshine roofs had virtually disappeared.

The Surgeon summed up as he rose to go to his theatre: "I think we have got to admit that Old Stuffy is right, but this is the first time I have agreed with him for twenty years."

* * *

The National Health Service had not concerned him. A bachelor, he lived alone quietly, worked industriously, and had no occasion to consult his doctor until this week. An appointment was offered him as an outpatient at a time to suit his work, but he did not arrive. Later he was found, obviously lost, wandering through the nurses' quarters. He might have known better and probably wondered at the changes that had taken place in the last few years; but his only concern was to be examined by a specialist, and he faithfully followed the many signposts apparently placed to guide him on his way about the spreading hospital grounds. He did not know that the hospital was an examination centre for the nurses of this area and that the signs "To State Examinations" were not for him. We hope they never will be.

* * *

Father (murmuring over his advertisements at breakfast): "Urolucosil."

Peter (aged 3, indignantly): "No, I'm not."

Letters to the Editor

REVIEW OF MEDICAL ESTABLISHMENTS

SIR,—A letter from the Ministry of Health to boards of governors of teaching hospitals on medical establishments has come to the notice of the Joint Consultants Committee. This letter recommends in many cases reductions in the establishment of consultants, S.H.M.O.s, and registrars, though in some instances additional consultant posts are proposed. Although the committee knew of the inspections upon which these letters have been based, it had no opportunity of discussing with the Ministry the very important implications of the actions proposed.

These include the security of tenure of consultants threatened with displacement, the obligation upon boards to find them alternative work imposed by paragraph 16 of the Terms and Conditions of Service, and the effects of these measures upon the registrar problem.

A typical letter includes the following sentence: "When the Board's proposals have been examined and the establishment approved by the Ministry, the Board will be expected to take action to achieve any necessary reduction as soon as practicable so far as such action has not already been taken; it will be permissible for the Board to increase the number of medical establishments in any grade in any specialty only with the Minister's consent in each case." It is unquestionable that some control must be exercised over the total consultant establishment, but many will doubt whether this is best achieved by referring the decision in every individual case to Savile Row.

The Ministry's letter provides yet further evidence that the Health Service can be steered safely between the Scylla of planlessness and the Charybdis of excessive central control only by utilising the guidance of appropriate medical advisory committees at all levels, from the hospital management group up to the Ministry itself. I hope that boards of governors and their medical committees when considering these matters will bear in mind that the Joint Consultants Committee has still to discuss them with the Ministry.

W. RUSSELL BRAIN

Royal College of Physicians,
London, S.W.1.

Chairman,
Joint Consultants Committee.

FIBROCYSTIC DISEASE OF THE PANCREAS

SIR,—We are very pleased that Dr. J. C. W. MacFarlane (Aug. 16, p. 311) has been able to confirm the potential value of the antithrombin test in the condition of fibrocystic disease of the pancreas. It is gratifying that he has found it possible to simplify the test and the method of obtaining blood specimens. We are particularly impressed with the large series of cystic fibrosis cases studied and the number and selection of controls.

We agree that the most valuable information is obtained from the fifteen-minute and twenty-minute samples and that the shorter-time samples may be unnecessary. Expressing results as percentage of the mean of the normals tested on the same day certainly makes more accurate any comparisons of cases tested at different times.

The variance between Dr. MacFarlane's findings of uniformly lowered antithrombin titre in 60 of 67 cases, with near normal levels in 7 cases, and our determination of low titre in 1, elevated titre in 3, and normal titre in 9 cases seems to require further study or some reasonable explanation.

In our view the assumption that serum-antithrombin titre and plasma-antithrombin titre are so identical is *not fully established*, although our experience of many thousands of antithrombin determinations indicates that the curve resulting from plotting antithrombin action against time of incubation in the case of serum antithrombin is low and relatively flat, whereas that from antithrombin in defibrinated plasma rises in relation to the time of incubation of the mixture. Thus it is difficult for us to reconcile the finding of low antithrombin titres obtained from serum with unequivocal diagnosis of cystic fibrosis of the pancreas regardless of the extent of involvement.

In our data only *extreme* cases of cystic fibrosis of the pancreas, with minimal or absent external pancreatic secretions, show very low antithrombin titres. Further, in our experience there is no constant relation between absent pancreatic secretions in the duodenum and the antithrombin level in the blood.

Since it is apparent that serum-antithrombin determinations result in low flat curves, the stage of pancreatitis characterised by markedly increased antithrombin and trypsin levels in the blood would necessarily be missed in serum determinations.

It would indeed be most helpful in clarifying the differences in results obtained if plasma-antithrombin determinations could be made on the 67 cases so well presented and discussed by Dr. MacFarlane.

Department of Physiology
and Pharmacology,
New York Medical College,
New York.

IRVING INNERFIELD
ALFRED ANGRIST
JAMES W. BENJAMIN.

CONGENITAL DEFECTS FROM MATERNAL RUBELLA

SIR,—As an otologist and a member of the committee of the Deaf Children's Society, I have been very perturbed to learn that some general practitioners are questioning the diagnosis of rubella in the first three months of pregnancy when associated with fœtal abnormalities. In 1940 and subsequently, Gregg, Swan, and others in Australia pointed out the very definite danger of rubella early in pregnancy leading to congenital deafness, blindness, and sometimes a cardiac lesion. It is thought by some that the infection was not true rubella and that other cases have not occurred since.

This is a very dangerous, as well as an erroneous, supposition. There is no doubt whatever that children are still being seen with these tragic defects as the result of infection in their mothers by a "simple" illness indistinguishable from typical rubella; often this has been very mild. Pregnant women should still be extremely careful to avoid contact with rubella: in fact there seems every justification to recommend that all girls should be exposed to rubella before leaving school.

London, W.1. IAN G. ROBIN.

DENTAL TREATMENT FOR CHILDREN

SIR,—Your leading article of Oct. 25 contains the following statement concerning children's dentistry: "The work is mainly routine and holds little interest for the highly trained dental surgeon." May I encroach on your space to challenge as briefly as possible the correctness of this statement.

The public dental officer in treating the priority classes performs the same range of operations as is performed in the general dental service. In the case of school-children, who form the bulk of his patients, he must perform these same operations in a much smaller oral cavity and on a patient who is emotionally less stable than an adult, requiring from the operator a greater skill and more tact and patience than is necessary in other spheres of dentistry. As the school dentist is dealing with patients in their developmental stage, his knowledge and understanding of developmental irregularities, and their prevention and treatment, must be of a high order. By contrast the treatment of mature mouths, subject only to the processes of decay, is flat and insipid. The more frequent use of general anæsthetics, with increased difficulties of administration, is a further feature of children's dentistry.

I trust that this letter will go some way towards removing your implied slur on those dental surgeons who for vocational reasons remained faithful to the children, and resisted the financial attractions of the easier, though less satisfying, work of general service.

T. H. LIPTROT
Hon. Secretary, Public Dental Officers' Group,
British Dental Association.

THE CORRECT SPELLING OF MEDICAL TERMS

SIR,—Dr. L. E. Napier (Nov. 1) is fighting a battle for many of us in defence of etymologically correct spelling. Nowadays, editors refuse to accept *empyemata* and one journal recently removed *sinus* into the second declension.

Camberwell, London, S.E.5. KENNETH MARSH.

SKIING ACCIDENTS

SIR,—In 1950 a committee was set up by the Ski Club of Great Britain to inquire into ways of reducing the number of skiing accidents. A simple safety device was introduced consisting of a strap passing from the heel-spring of the ski binding to a ring attached to the ski 2 in. behind the heel. The object of this device was to cause the foot to come adrift from the ski in the event of a severe forward fall. Other and more elaborate safety bindings prevent rotation strains, but they have not yet been widely used in the Alps.

In order to obtain information on (*a*) the incidence of skiing injuries, and (*b*) the effectiveness of this simple safety device, a card was circulated in 1951 to 12,750 members of the Ski Club of Great Britain, asking for the following information:

Age; sex; number of seasons' experience; safety device used, if any; description of injury from any accident in previous season; causes of accident (fall, collision, snow conditions); days on ski before accident; feet downhill per day (average).

254 replies were received; the results of analysis were as follows:

	Accident	*No accident*	*Total*
S.C.G.B. safety device	20	95	115
No safety device	38	101	139
Total	58	196	254

$X^2 = 3{\cdot}80 \quad P < 0{\cdot}05$

Incidence of accidents:

Over-all	22·9%
With safety device	17·4%
Without safety device	27·3%

The injuries were as follows: *sprains* 46 (ankle 22, knee 20, shoulder 4); *fractures* 7 (ankle 3, patella 1, thumb 1, ribs 2); *muscle lesions* 2 (calf 1, thigh 1); *lacerations* 2 (thigh 1, wrist 1); *unspecified* 1.

Under causes of the accident the replies were as follows: *snow conditions* 40 (powder snow 15; wet soft snow 9; ice 7; icy ruts 5; breakable crust 4); *obstructions* 4 (tree, rock, or ice block); *collisions* nil. Snow conditions were not reported in 3 cases; 11 accidents happened *in good snow conditions* on the piste.

There are obvious statistical objections to this type of inquiry. The findings would not necessarily be the same in a random sample of the members of the Ski Club of Great Britain; they may apply only to the type of person who takes the trouble to reply, and people who have had accidents may be more likely to reply than those who have not. On the other hand, those who have worn a safety device and escaped injury may be more likely to reply than those who have had no injury and worn no safety device.

Despite these objections, the results confirm the impression gained from empirical observation that injuries to skiers are extremely common, though most of them are not serious. The evidence also suggests that the Ski Club of Great Britain safety device significantly reduces the incidence of accidents. This device clearly cannot influence the incidence of injuries to parts of the body other than the lower limbs. The number of such ther injuries is, however, distributed evenly between he two groups and does not affect the statistical result.

It is of interest that of 58 accidents only 11 happened n the piste in good snow conditions. Soft snow and icy onditions were important predisposing factors.

The replies indicated that 10–21 days is the usual uration of the post-war winter-sports holiday. There vas no evidence that the amount of downhill running ach day has increased since the war, despite the greater umber of ski lifts and funiculars.

Detailed analysis of the influence of factors such as ge, sex, experience, &c., will be deferred until more naterial has been collected.

Division of Human Physiology,
National Institute for Medical Research,
London, N.W.3.
G. PUGH.

MALE-TOAD TEST FOR PREGNANCY

SIR,—In connection with the letter last week from aptain Farrant and myself, my attention has been called o a letter from Dr. Jayewardene,[1] of the Medical Research nstitute, Colombo, which I had unfortunately missed eeing. I am very glad to see that our findings are in greement, and that *Bufo melanostictus* has served us oth so well.

Porton, near Salisbury,
Wiltshire.
F. E. BUCKLAND.

CAUSE AND TREATMENT OF LEG ULCERS

SIR,—Dr. Anning's excellent article (Oct. 25) leads me o record views gained from personal observation:

1. The application of compression-bandages must be arefully supervised. Attention to details of bandage tension, ize of pressure-pads, adequate stirrup-pieces, &c., makes the lifference between success and failure in gaining the patient's oöperation. Dr. Anning must have seen patients initially ntagonistic to the method because of bad technique in other places. There are even practitioners who expect satisfactory elf-application by the patient. I have used an 'Ichthopaste' bandage between the skin and adhesive-plaster layer, to protect from and minimise irritation. Reversal of the adhesive surface further helps. Application of pressure-pads over ichthopaste, and not directly to the skin surface, also lessens damage to the skin surface.

2. I agree that ulcer bacteriology counts for little except for the "foul, putrescent type." Of three recent cases one grew proteus and hæmolytic streptococci, and compression-bandaging had to be abandoned. Of the other two, one grew proteus and *Staphylococcus albus*, and the other hæmolytic streptococci, *Staph. albus*, and *Bacterium coli*. The ulcers healed with continuation of compression-bandaging and the application of 'Vioform' cream to the ulcer at the same time.

3. The most difficult type of ulcer seems to be associated with the hidebound, thinned leg and a long history of ulceration. General compression-bandaging of the leg seems of little value since there is nothing to compress. The ulcer is no less indolent and painful than the arteriosclerotic type.

A large pressure-pad supported by an ichthopaste bandage is helpful; but I have often found the local application of vioform cream more useful. Cream is put on the ulcer only—usually twice daily—and the leg supported by a crêpe bandage. The patient remains up, and the ulcer is not cleaned during treatment. Healing is slow, but pain is relieved at an early stage. Granulation tends to be profuse and heaped above the skin surface. A tenacious membrane forms over the ulcer surface and this seems peculiar to the mode of healing. The stimulus to granulation and epithelial growth is pronounced and apparently quite distinct from any bactericidal effect. The effect is greater than that of scarlet-red ointment or the balsam of peru preparation of the Mayo Clinic.

4. Unless the tissues have become excessively indurated and fibrosed, the long-standing ulcer is not necessarily the most difficult to heal. One can quite easily confirm Heller's observation that the larger the ulcer the more rapid the initial rate of healing. The most dramatic response to compression-bandaging may be seen in the large ulcer of long duration.

Dermatological Clinic,
Nottingham.
H. LEE.

FULL-TIME AND PART-TIME CONSULTANTS

SIR,—We note in the Supplement of the *British Medical Journal* of Nov. 8 that the Staff Side of Whitley Committee "B" accepted the new mileage rates under protest as these benefited part-time consultants at the expense of their full-time colleagues. Why, in these circumstances, was the matter not submitted to arbitration?

A considerable time ago we were informed that the Central Consultants and Specialists Committee was negotiating on behalf of full-time consultants for the implementation of the terms proposed in the Spens report (which was accepted by the Government of the day), and the only result so far is that full-time consultants are now worse off than they were before. The Central Consultants and Specialists Committee has refused to allow consultants holding full-time contracts with regional boards any representation on the Staff Side of Whitley "B" Medical Council, and has also refused to sponsor negotiations for the payment of full-time consultants for domiciliary visits.

If this partisan attitude continues unchecked it will provide an absolutely unanswerable case for any Minister of Health seeking to introduce a whole-time salaried National Health Service.

W. S. L. GILCHRIST
L. L. GRIFFITHS
K. J. RANDALL
I. G. WILLIAMS.
Farnborough Hospital,
Kent

TREATMENT OF VITILIGO

SIR,—With reference to your annotation[1] on this subject, I wish to draw your attention to the fact that ammoidin and ammidin have been found to be identical with the well-known substances xanthotoxin and imperatorin.[2] I suggest that the names ammoidin and ammidin should be replaced by xanthotoxin and imperatorin respectively.

Faculty of Science,
Fouad I University, Cairo, Egypt.
A. SCHÖNBERG.

PREMATURITY AND THE OBSTETRICIAN

SIR,—I was interested in the leading article on this subject in your issue of Nov. 8. You cite the successful prevention of eclampsia at the Women's Hospital, Sydney, and say that "This success has been achieved by an elaborate check of all antenatal patients to ensure regular attendance."

I feel that in this country it is most important that there should be a similar elaborate check. In reviewing maternal deaths due to toxæmia of pregnancy I have been struck by the lack of personal responsibility on the part of the patient to keep her antenatal appointments. I do not believe that, in the National Health Service, this should be the patient's responsibility. I feel that if the general practitioner and midwife are working on the case together, it should be the midwife's responsibility to see that the patient keeps her appointments at the antenatal clinic. If she does not, the midwife should visit her and communicate the reason for non-attendance to the patient's doctor. Only if the two of them work together shall we prevent the unpleasant results from patients' failure to attend. In rural areas the doctor is in daily contact with his district nurse and midwife, but in cities this is not so.

Close coöperation between midwife and doctor would reduce, not only maternal mortality from toxæmia of pregnancy, but also premature labours at home and the incidence of prematurity. The best "flying squad" container for the premature baby is the mother's uterus. The mother in premature labour, therefore, should be admitted to hospital.

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[1] Jayewardene, L. G. *Lancet*, 1950, i, 184.

[1] *Lancet*, 1952, i, 1059.

[2] Schönberg, A., Sina, A. *Nature, Lond.* 1948, 161, 481; *J. Amer. chem. Soc.* 1950, 72, 4826.

There is also an urgent need for doctors and midwives to regard toxæmia of pregnancy as an obstetrical emergency and to refer such cases to hospital, not when the condition has become well established, but when the early signs, particularly a rise in blood-pressure, have become evident. An intense campaign to this end will undoubtedly pay dividends.

Department of Obstetrics and Gynæcology, University of Bristol. G. GORDON LENNON.

CONFUSIONAL PSYCHOSIS FOLLOWING ISONIAZID THERAPY

SIR,—I was greatly interested in Dr. Hunter's paper last week on confusional psychosis following isoniazid therapy, leading ultimately to an organic cerebral impairment of the Korsakow type.

The description of symptoms and signs is reminiscent of the encephalopathic syndrome first described in 1939 by Jolliffe[1] and by Sydenstricker's group.[2] They observed the condition by itself, and also in association with the dermatological and mucous membrane lesions of pellagra; nicotinic acid quickly reversed the confusional state. Whilst pellagrous, dermatological signs were apparently not noticed by Dr. Hunter, his patient's "mouth was very dry and she developed sores at the corners." Considering the many reports on the relation of confusional states to vitamin deficiencies,[3] it might be worth giving suitable vitamin treatment in further cases of this sort, in the hope of preventing organic cerebral impairment.

London, W.1. Z. A. LEITNER.

CERTIFICATION OF INSANITY

SIR,—There are two articles in your issue last week which, though they seem to have nothing in common, are connected in a very significant manner.

Dr. W. Rees Thomas ended his Maudsley lecture on the Unwilling Patient with an account of the increased use of voluntary admission to mental hospitals under the Act of 1930, and, according to your annotation, "looked forward to the time when admissions for mental illness will be regarded no differently from those for other causes." He expressed the hope "that certification will fall altogether into disuse."

I am sure that all (or nearly all) psychiatrists would agree, and look forward with him to the day when this can come to pass. But present progress in this direction, though all to the good, has brought about some strange repercussions in unexpected quarters. I would refer to the account in your "Medicine and the Law" section of a case in which a voluntary patient who became a "chronic" inmate of a mental hospital has given the Law Lords cause for much legal argument in settling divorce proceedings.

The difficulty was made painfully clear to me in a recent case in which I was consulted.

The patient, now a middle-aged man, has been in a mental hospital many years. He passed through the acute stages of his illness (in the hospital) without certification, though he was clearly certifiable at the time. Presumably it had been possible to get him to hospital and to keep him there as a voluntary patient, and so the need for certification had not arisen. But after the acute phase he steadily deteriorated, and when I saw him there was nothing to distinguish him from the ordinary run of incurable chronic cases in mental hospitals. Now that his wife wants a divorce, the "mental" clauses of the Herbert Act are inapplicable as he is not and never has been under certificate. On the other hand his mental incapacity, with lack of initiative, &c., is such that a petition for divorce on the grounds of desertion is pretty certain to fail on account of the absence of *animus deserendi* on his part. Yet were he to leave the hospital and return home it is generally agreed that he would break down again. (Of course he could then be certified; but apart from the objectionable nature of the procedure, there would be another wait of several years.)

A situation like this clearly defeats the object of the "mental" clauses of the Matrimonial Causes Act, and it is one that must become more common as more and more patients are treated in mental hospitals on a voluntary basis. The failure in the above case is, of course, due to the absence of certification—a purely sociolegal procedure which had hitherto been found unnecessary. Now, the introduction of a petition for divorce or desertion has introduced a new sociolegal factor, calling for certification before the required sociolegal remedy can be applied.

The danger is that, with examples like this in mind, there may be an understandable, but none the less regressive, tendency to hold on to certification *just in* case, or even to put a patient under certificate where there is a premonition of chronicity. (I believe this has happened already.) It is a matter that the legal experts would do well to look into; one day they may have to find some other and more appropriate way of defining "incurable insanity."

Leeds. H. EDELSTON.

A NEW ANTISEPTIC

SIR,—Your annotation of Nov. 15 states that the quaternary ammonium salts have no appreciable effect on the pseudomonas group. Although this is true for cetrimide, it is not a valid criticism of all quaternary ammonium salts. At least one of them, 'Roccal,' has appreciable activity against *Pseudomonas pyocyanea*. Furthermore, it should be appreciated that this criticism is one that can be levelled at all disinfectants.

Although the effectiveness of quaternary ammonium compounds against *Ps. pyocyanea* is very much less than it is against streptococci and staphylococci, *nevertheless* it is better than that of many disinfectants widely used in hospital practice. For instance, the killing power of roccal (containing 1% benzalkonium chloride) against *Ps. pyocyanea* is about three times greater than solution of chloroxylenol *B.P.* (containing 5% of active ingredient). Similarly, the same quaternary ammonium salt is about thirty times more potent than phenoxyethanol ('Phenoxetol') which was specifically developed as a disinfectant against gram-negative organisms.

As yet there is no disinfectant available which has a high killing power against the pseudomonas group. In the meantime, this should not prevent the use of those quaternary ammonium salts which are as effective against this group as most other disinfectants, and which have other advantages which are *leading to* their more widespread adoption.

London, W.4. L. M. SPALTON.

TUBERCULIN SENSITIVITY

SIR,—In his paper on tuberculin sensitivity of children (Nov. 8) Dr. Coles gave as the criterion of a positive Mantoux test the appearance of an area of erythema or erythematous infiltration at the injection site. It is, however, surely agreed that in the Mantoux test an area of erythema by itself, without infiltration, should be disregarded.

In the Prophit survey the standard laid down for a positive interpretation was œdema *with* surrounding erythema (the italics are mine); and in the World Health Organisation report on tuberculin testing[1] Ustvedt says that redness alone does not constitute a positive reaction.

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[1] Jolliffe, N. *Ass. Res. nerv. ment. Dis. Proc.* 1939, 19, 111.

[2] Cleckley, H. M., Sydenstricker, V. P., Geeslin, L. E. *J. Amer. med. Ass.* 1939, 112, 2107.

[3] Hardwick, S. W. *Recent Progr. in Psychiat.* 1950, 2, 111.

[1] *Bull. World Hlth Org.* 1950, 2, 359.

Dr. Coles's comparison of the two jelly tests with the Mantoux test is of great interest, for it shows that when the modified jelly test is the only preliminary test in selecting candidates for B.C.G. vaccination a considerable number may wrongly be rejected as reactors. In a recent paper a comparison of the patch and 10 and 100 tuberculin unit Mantoux tests led the authors to conclude that the patch and the 100 tuberculin unit tests may give between 8 and 10% false positive reactions, and that the 10-unit test is the most specific.

H. G. CALWELL
Medical Director,
B.C.G. Vaccination Service,
Belfast. Northern Ireland Tuberculosis Authority.

FIFTY YEARS OF MIDWIFERY

SIR,—In referring (Nov. 1) to the recent golden jubilee celebration at the Royal College of Midwives of the passing of the Midwives Act, 1902, you have given a timely reminder of the many improvements in the training and status of midwives in the past half-century, and you have rightly emphasised the important place the midwife now holds in the health team. When, however, you relate these changes as closely as you do to the decline in maternal mortality your ground is less sure, and your statement that the midwives "may fairly take *much* (my italics) credit for the fall" may give a wrong impression to some of your readers. Most of the credit for this belongs to the medical profession, as the evidence clearly shows.

At the turn of the century, and for a few years after, the maternal mortality-rate was showing a downward trend. But this did not continue, and during the quarter-century 1910–35 the rate remained more or less constant at about 4 per 1000 total births. This was most disquieting, and in 1928 and subsequent years various committees were formed to examine this subject. Their reports, together with the confidential reports on the causes of maternal death by the chief medical officer to the Ministry of Health, brought many matters to light. Most important, perhaps, was the clear demonstration that maternal mortality was closely related to the availability and quality of antenatal and intrapartum treatment. About the same time, as a result of much research,[1] it became clear that in puerperal sepsis the responsible organism had often been introduced from the nose and throat of an attendant at the labour. This most important advance in knowledge led to much prevention and a better control of puerperal sepsis, which at that time was the first cause of maternal death. The throat-swabbing of those about to work in labour wards, the use of efficient face masks, and the isolation of septic cases were the main new methods introduced as a result of these observations. Also, there was the discovery, isolation, and testing of the new alkaloid of ergot, ergometrine.[2] Not long after came the sulphonamides, and later penicillin and the other antibiotics. The obstetrical flying squads in the charge of doctors and equipped to transfuse and give other emergency treatment to the woman too ill to move to hospital, were also started. The demonstration of the rhesus antigen and rhesus antibodies in human blood and the developments following the introduction of a National Blood Transfusion Service also led to a measurable lowering of the maternal-mortality rate.

The reduction in maternal mortality from a rate of about 4 per 1000 total births to the low figure of 0·65 per 1000 total births in 1951 has been the result of new discoveries and improved techniques. The midwife's main contribution has been her careful and conscientious attention to the normal case, her timely recognition of the abnormal pregnancy or labour, and her wil ness to act as a maternity nurse when a docto present.

Department of Obstetrics and Gynæcology,
University of Sheffield. C. S. RUSSEL

EFFECTS OF HEXAMETHONIUM

SIR,—We were most interested in the report Professor McMichael and his co-workers (Nov. 8) on effect of hexamethonium on the pulmonary circulat as these experimental observations provide a theore basis for our clinical experience with this drug emphysema.

We were first prompted to use hexamethonium in a wo aged 66, who had hypertension and emphysema, cyanosis and dyspnœa at rest which had failed to imp with the usual treatment. There was no evidence of ventricular failure and no response to mersalyl and dig She improved distinctly after 30 mg. of hexamethonium cutaneously; since being discharged 2 months ago she continued to take 30 mg. thrice daily, and has rema well.

We were not satisfied that this improvement due to relief of left ventricular failure and decide try the drug in further cases of emphysema and hy tension and of emphysema alone. The improven was equally good in both groups.

A man, aged 57, had been under our care for 4 years bronchitis and very gross emphysema. He had faile respond to breathing exercises, Christie's abdominal bin pneumoperitoneum, antispasmodics, and repeated course antibiotics. His heart was small, and blood-pressure aver 145/90 mm. Hg; and his cyanosis and dyspnœa rest could only be attributed to pulmonary disease. condition was immediately relieved after 20 mg. h methonium subcutaneously, and 30 mg. thrice daily conti to control his symptoms.

So far we have tried this treatment in too few ca of pulmonary disease to judge the likelihood of resp and of complications. We have found, however, t smaller doses are effective than those usually requ by hypertensives.

It seems probable that the improvement in t cases of emphysema is due to increased pulmonary bl volume, allowing a more efficient respiratory intercha of gases. If this is so, hexamethonium should ben many other types of pulmonary disease.

St. Richard's Hospital,
Chichester, Sussex.
J. D. WHITESID
M. H. COIGLEY.

SIR,—In their important paper Dr. Gilmore his colleagues interpret the increase in circulati time on tilting after administration of hexamethoni to the effect of gravity on pulmonary vessels to wl vasoconstrictor impulses have been reduced. But d this accord with the anatomy of the lung-vessels? pulmonary arteries and veins radiate in all directions, radiograms of these vessels after opacification sug that in some adults their total volume may be gre above than below their cardiac orifices, and roug equal on the dorsal and ventral sides of their orifices. this is so the centre of gravity of the whole mass of bl in the two lungs is within the heart, and tilting the b would alter the effect of gravity on the pulmonary bl no more than rotating it about its centre of gravit that is, not at all.

The figures given for cardiopulmonary blood volu indicate that in the tilted position after hexamethoni it may be double that in the horizontal position be hexamethonium. If so radiograms should show difference in pulmonary vascularity under the conditions. Lastly it would be interesting to know if change in respiration was noted when the

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1. Colebrook, D. C. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 205. H.M. Stationery Office, 1935.

Public Health

Unification of the Health Services

Dr. Hugh Paul, medical officer of health for Smethwick, suggests, in his annual report for 1951, that "the splitting of the health and medical services of this country into three sections is almost universally admitted to have been a mistake, and most observers would agree that unification is the most pressing medical problem before us at the present time."

Dr. Paul considers how such a unified service might be operated. A corporation of the B.B.C. type would, he says, be too vast and too impersonal; while a board such as the Midland Electricity Board would be unsuitable because its efficiency could not be measured at the end of each year in pounds, shillings, and pence. The new body, says Dr. Paul, must be elected; and he suggests a two-tier system of control.

The country, he proposes, should be divided into 40 "counties," each with an average population of just over a million, though in more sparsely populated parts the total would be smaller and around the conurbations it would be about two million. (London, with its special problems, is not included in this scheme.) Each of the "counties" would be divided into four or five "county boroughs." The county council would consist of all the councillors of each of the county-borough councils; and to secure liaison between the county boroughs, each might appoint one member to serve on the other three or four in the county. The county council would be the supreme health authority in its area; and the special interests of the various professions would be cared for by coöption at county and county-borough level.

The health authorities "would have constantly before them the knowledge that their foremost function was to reduce the number of beds in hospitals by reducing the need for their occupation." The medical officer of health should be closely associated with the hospitals as well as with the district. All professional workers in the hospital should spend only part of their time there and the remainder on the district: "The hospital consultant would be expected to spend more time in the homes of the people and in the workshops and factories." The health visitor should go round the hospital with the consultant, study the home problems of patients, and visit them on the district. She should be able to bring to the physician or surgeon in charge, when the patient first goes to hospital, a picture of the background of his disability; and when he is discharged she should be in a position to arrange for him to have such assistance as would help to prevent recurrence of his illness.

"The service in this country can never be completely satisfactory until the controlling body, whatever its name, views its duties and responsibilities as a whole."

Housing in Sheffield

In his report on the year 1951, Dr. Llywelyn Roberts, medical officer of health for Sheffield, remarks that in the late war the flow of new houses was completely stopped. In the city houses condemned but still occupied total 10,597, made up as follows: houses included in clearance areas confirmed by the Minister of Health and tenants not yet rehoused, 4506; houses for which demolition orders have been made and tenants are awaiting rehousing, 57; houses where schemes have been accepted under section 11 of the Housing Act, 1936, and tenants are still awaiting rehousing, 28; houses where public inquiries have been held by the Minister of Health in regard to clearance areas but no decision has yet been reached, 1529; houses in clearance areas represented by the medical officer of health but no public inquiries have been held, 4477. In addition, 138 houses have no piped water-supply from the corporation mains, and 277 houses have no access to a water-closet.

There is still, says Dr. Roberts, a great deal of overcrowding, and he cites the following instances:

A tenant and three subtenant families (total of 13 people, all related) live and sleep in a three-room house of poor type; two of the families (8 people) sleep in one room.

A tenant and four families related by marriage (total of 20 people) live in a four-bedroom-type house.

A man, his wife, and 4 children of both sexes and of ages ranging from 11 to 18 years, are sleeping in one bedroom.

Dr. Roberts observes that the provision of new houses by itself will not cure the many ills associated with poor accommodation: "A policy of education in responsibility *and in the proper enjoyment and improvement* of amenities must be part of housing policy."

Domestic Help at Night

At a meeting last Tuesday, London County Council approved a proposal by its health committee that a night service of domestic help should be provided for the chronic sick in their homes. Such a service, the committee suggested, "would give relief to the relatives and friends by enabling them to obtain some undisturbed sleep each week." This extension of the home-help service will have to be approved by the Ministry of Health.

Poliomyelitis in England and Wales

In England and Wales uncorrected notifications of poliomyelitis in the week ended Nov. 8 were as follows: paralytic 81 (65), non-paralytic 36 (21); total 117 (86). This is an increase of 31 on the previous week, the figures for which are shown in parentheses.

Appointments

Fletcher, G. C., M.B. Manc.: appointed factory doctor, Middleton district, Lancashire.
Frankland, A. W., M.A., B.M. Oxfd: M.O. to the allergy clinics, St. Mary's Hospital, London.
Grainger, C. N., M.D. Lond., D.C.H.: appointed factory doctor, Totnes district, Devon.
Greer, James, L.R.C.P.I.: asst. school M.O., Sheffield.
[illegible], M.B.: house-physician, The Hospital for [illegible] at Ormond Street, London.
[illegible] B. Aberd., F.R.C.S.E.: part-time registrar, [illegible] ment, The Hospital for Sick Children, Great [illegible] ondon.
[illegible] M.B. Lond., M.R.C.P.: asst. physician (con- [illegible] Garrett Anderson Hospital, London.
[illegible] Lond., D.P.H.: deputy M.O.H., Tottenham.

Colonial Service:

Boardman, H. M. S., L.R.C.P.E.: senior M.O., Sierra Leone.
Bruvels, N. R., M.D. Latvia: M.O., Federation of Malaya.
Eckhart, G., M.D., D.T.M. & H.: M.O., Tanganyika.
Leitch, Neil, B.M. Oxfd, D.P.H., D.T.M. & H.: senior M.O., Nigeria.
McCreery, W. C. C., M.B. Dubl.: M.O., Federation of Malaya.
MacFarlane, A. L., M.B. Lond., F.R.C.S.E.: senior M.O., Kingston Public Hospital, Jamaica.
O'Brien, J. J., M.B. Belf.: M.O., Federation of Malaya.
Purcell, Bridget, L.R.C.P.E.: M.O., Federation of Malaya.
Richardson, Alison, M.B. Camb.: M.O., Federation of Malaya.
Wells, A. V., M.B. Edin., D.T.M. & H.: M.O., St. Lucia, Windward Islands.

South Western Regional Hospital Board:

Bussell, L. J., B.A., D.M. Oxfd, M.R.C.P., D.C.H.: senior medical registrar, Plymouth clinical area.
McGwinn, P. L., M.B. N.U.I., D.A.: anæsthetic registrar, Frenchay Hospital, Bristol.
Ray, R. L., M.B. Lond.: asst. chest physician, West Cornwall clinical area.

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Williams.—On Nov. 12, to Anne (*née* Boddington), wife of Dr. Ivor Williams, of 59, Gainsborough Road, Ipswich—a son.

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Cummins—Heneker.—On Nov. 15, Arthur Dillon Croker Cummins, M.R.C.P.I., surgeon-commander, R.N. retd, of Worthing, Sussex, to Dorothy Alice Heneker, formerly of Montreal, Canada.

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Stacey.—On Nov. 9, at Critters, Curbar, near Sheffield, John Eric Stacey, M.D. Sheff., F.R.C.S.E., F.R.C.O.G.

*Amended Notice.

Obituary

DAVID MUNRO

K.C.B., C.I.E., M.A., LL.D. St. And., M.B. Edin., F.R.C.S.E.

Air Vice-Marshal Sir David Munro was an expert in occupational health, and as director of the R.A.F. Medical Service, as secretary to the Industrial Health Research Board, and as chief medical officer to the Ministry of Supply he had gathered his experience among Servicemen and civilians, and in war and peace. He died at Halton on Nov. 8.

The twelfth child of his parents, he was born in 1878 at Boreham Wood, near Elstree, where his father owned a not too successful preparatory school. Consequently he had somewhat of a financial struggle to get educated, first at St. Andrews University, which he entered at the age of 14, and later at Edinburgh, where he was able to study medicine only because he was awarded a scholarship by the Skinners' Company.

Elliott & Fry

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In India he served two years on the military side, mainly on the Waziristan front, and from then till 1914 in Bengal on the civil side. He took the F.R.C.S.E. in 1911.

At the outbreak of the first world war he was recalled to military service, first with the Indian troops in France, and later in Mesopotamia where he was appointed C.I.E. for distinguished service at Basra. It was there he met Colonel Matthew Fell, a meeting which was completely to alter his later life. In 1918 he was transferred from Mesopotamia to Egypt, at his own request, as surgical specialist to the 23rd Indian General Hospital which was stationed at Masaid near El Arish on the borders of Palestine. There had been trouble in France in March, 1918: the war was not going well, and twenty-four British battalions had been withdrawn from Palestine, sent to the Western front, and replaced by Indian troops. This created problems of hospital administration to which the British medical officers in Palestine were unaccustomed—problems of religion and race, food, sanitation, touchable and untouchable. In consequence Munro was pulled out of his post as surgeon at Masaid, rather against his will, and appointed D.A.D.M.S. Indian troops under Lieut.-Colonel J. Johnston Abraham, who was A.D.M.S., Lines of Communication. He held this appointment until the end of the war.

Back in England in 1919, he again met Colonel Fell, who had been given the task of creating the medical service of the Royal Air Force. Fell offered him the post of first principal medical officer in India, and after considerable difficulty he was able to transfer from the I.M.S. to the new service. Two years later, when Sir Matthew Fell became director-general of Army Medical Services, Munro succeeded him in the R.A.F. Nine years of fine administrative work followed during which he built well on the foundations laid by Fell. He retired in 1930 from the R.A.F. with a K.C.B. at the age of 52, only to take up another job. The same year he became secretary of the Industrial Health Research Board of the Medical Research Council, a post which he held for twelve years. The students of St. Andrews University elected him rector in 1938. During the late war he was chief medical officer of the Ministry of Supply from 1940 to 1943. One of his greatest moments was in 1942 when he was elected master of the Skinners' Company, to which he owed his chance to become a doctor. Two years later he was elected vice-chairman of the board of management of the London School of Hygiene and Tropical Medicine.

A friend writes: "David was a good mixer. He played an excellent game of golf. He learnt to fly. He played polo for the R.A.F. He rode to hounds. He picked the right men for his service, and when he put them into posts he let them prove themselves. He was in fact a great success as an administrator. It was uphill work fighting for his service, but he held his own against the Treasury with a disarming grin that got him just where he wanted. He had charm. He loved music, pictures, good literature, good food. He used to contribute occasionally to *Blackwoods*, traditionally the Indian officer's magazine, and in 1941 he published his charming nostalgic autobiography. In *It Passed Too Quickly*, with characteristic sly humour, he described life in his beloved St. Andrews, the final years of the British Raj in India, life in the Air Force, and the last years in Buckinghamshire."

Recalling the early days of the R.A.F. Medical Service, T. C. M. says: "When Munro succeeded Fell as Director-General he promptly entered the arena to serve as a member of the Cabinet committee to decide whether there should be a separate R.A.F. medical branch, or whether it should be taken over by either the Army or Navy medical services. Subordination no, coördination certainly. The battle was soon over, for David Munro was a 'bonny fechter' with a silver tongue. 'If I had one ideal for my new medical service,' he later wrote, 'it was that the officers should be doctors first and not become too military, and I believe it was attained.' This was what he strove for during his nine years as Director-General and in this he was strongly supported by Lord Trenchard, and so the R.A.F. Medical Branch came into being and the camaraderie between the flying and medical branch was cemented for all time.

"David Munro, the man himself, was one who warmed both hands before the fire of life. Fear was a stranger to him; blessed with excellent hands and a good eye, all games came easily to him: a scratch golfer, he represented the R.A.F. on many occasions. A keen rider to hounds with the Old Berkeley and Whaddon Chase, an enthusiastic polo player, he believed that the best view of the world was between the ears of a horse. At 55 he rode his first of many point-to-points, but if the truth be told, with many falls, for he was a thruster. He preached the dogma and who will gainsay him that 'guts count as high as brains,' and he was the fortunate possessor of both in ample measure. At 75, as commanding officer of the local A.T.C., he plunged with enthusiasm into the art of gliding, piloting his glider over the countryside in his beloved Bucks and gazing nostalgically from 300 feet over the scene of his past athletic triumphs."

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Public Health

Unification of the Health Services

Dr. Hugh Paul, medical officer of health for Smethwick, suggests, in his annual report for 1951, that "the splitting of the health and medical services of this country into three sections is almost universally admitted to have been a mistake, and most observers would agree that unification is the most pressing medical problem before us at the present time."

Dr. Paul considers how such a unified service might be operated. A corporation of the B.B.C. type would, he says, be too vast and too impersonal; while a board such as the Midland Electricity Board would be unsuitable because its efficiency could not be measured at the end of each year in pounds, shillings, and pence. The new body, says Dr. Paul, must be elected; and he suggests a two-tier system of control.

The country, he proposes, should be divided into 40 "counties," each with an average population of just over a million, though in more sparsely populated parts the total would be smaller and around the conurbations it would be about two million. (London, with its special problems, is not included in this scheme.) Each of the "counties" would be divided into four or five "county boroughs." The county council would consist of all the councillors of each of the county-borough councils; and to secure liaison between the county boroughs, each might appoint one member to serve on the other three or four in the county. The county council would be the supreme health authority in its area; and the special interests of the various professions would be cared for by coöption at county and county-borough level.

The health authorities "would have constantly before them the knowledge that their foremost function was to reduce the number of beds in hospitals by reducing the need for their occupation." The medical officer of health should be closely associated with the hospitals as well as with the district. All professional workers in the hospital should spend only part of their time there and the remainder on the district: "The hospital consultant would be expected to spend more time in the homes of the people and in the workshops and factories." The health visitor should go round the hospital with the consultant, study the home problems of patients, and visit them on the district. She should be able to bring to the physician or surgeon in charge, when the patient first goes to hospital, a picture of the background of his disability; and when he is discharged she should be in a position to arrange for him to have such assistance as would help to prevent recurrence of his illness.

"The service in this country can never be completely satisfactory until the controlling body, whatever its name, views its duties and responsibilities as a whole."

Housing in Sheffield

In his report on the year 1951, Dr. Llywelyn Roberts, medical officer of health for Sheffield, remarks that in the late war the flow of new houses was completely stopped. In the city houses condemned but still occupied total 10,597, made up as follows: houses included in clearance areas confirmed by the Minister of Health and tenants not yet rehoused, 4506; houses for which demolition orders have been made and tenants are awaiting rehousing, 57; houses where schemes have been accepted under section 11 of the Housing Act, 1936, and tenants are still awaiting rehousing, 28; houses where public inquiries have been held by the Minister of Health in regard to clearance areas but no decision has yet been reached, 1529; houses in clearance areas represented by the medical officer of health but no public inquiries have been held, 4477. In addition, 138 houses have no piped water-supply from the corporation mains, and 277 houses have no access to a water-closet.

There is still, says Dr. Roberts, a great deal of overcrowding, and he cites the following instances:

A tenant and three subtenant families (total of 13 people, all related) live and sleep in a three-room house of poor type; two of the families (8 people) sleep in one room.

A tenant and four families related by marriage (total of 20 people) live in a four-bedroom-type house.

A man, his wife, and 4 children of both sexes and of ages ranging from 11 to 18 years, are sleeping in one bedroom.

Dr. Roberts observes that the provision of new houses by itself will not cure the many ills associated with poor accommodation: "A policy of education in responsibility and in the proper enjoyment and improvement of amenities must be part of housing policy."

Domestic Help at Night

At a meeting last Tuesday, London County Council approved a proposal by its health committee that a night service of domestic help should be provided for the chronic sick in their homes. Such a service, the committee suggested, "would give relief to the relatives and friends by enabling them to obtain some undisturbed sleep each week." This extension of the home-help service will have to be approved by the Ministry of Health.

Poliomyelitis in England and Wales

In England and Wales uncorrected notifications of poliomyelitis in the week ended Nov. 8 were as follows: paralytic 81 (65), non-paralytic 36 (21); total 117 (86). This is an increase of 31 on the previous week, the figures for which are shown in parentheses.

Appointments

FLETCHER, G. C., M.B. Manc.: appointed factory doctor, Middleton district, Lancashire.
FRANKLAND, A. W., M.A., B.M. Oxfd: M.O. to the allergy clinics, St. Mary's Hospital, London.
GRAINGER, C. N., M.D. Lond., D.C.H.: appointed factory doctor, Totnes district, Devon.
GREER, JAMES, L.R.C.P.I.: asst. school M.O., Sheffield.
HIMMELHOCH, ALBERT, M.B.: house-physician, The Hospital for Sick Children, Great Ormond Street, London.
HUNTER, THOMAS, M.B. Aberd., F.R.C.S.E.: part-time registrar, orthopædic department, The Hospital for Sick Children, Great Ormond Street, London.
MORGANS, MARGARET, M.B. Lond., M.R.C.P.: asst. physician (consultant), Elizabeth Garrett Anderson Hospital, London.
SUMMERS, FRANK, M.B. Lond., D.P.H.: deputy M.O.H., Tottenham.

Colonial Service:

BOARDMAN, H. M. S., L.R.C.P.E.: senior M.O., Sierra Leone.
BRUVELS, N. R., M.D. Latvia: M.O., Federation of Malaya.
ECKHART, G., M.D., D.T.M. & H.: M.O., Tanganyika.
LEITCH, NEIL, B.M. Oxfd, D.P.H., D.T.M. & H.: senior M.O., Nigeria.
McCREERY, W. C. C., M.B. Dubl.: M.O., Federation of Malaya.
MACFARLANE, A. L., M.B. Lond., F.R.C.S.E.: senior M.O., Kingston Public Hospital, Jamaica.
O'BRIEN, J. J., M.B. Belf.: M.O., Federation of Malaya.
PURCELL, BRIDGET, L.R.C.P.E.: M.O., Federation of Malaya.
RICHARDSON, ALISON, M.B. Camb.: M.O., Federation of Malaya.
WELLS, A. V., M.B. Edin., D.T.M. & H.: M.O., St. Lucia, Windward Islands.

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BUSSELL, L. J., B.A., D.M. Oxfd, M.R.C.P., D.C.H.: senior medical registrar, Plymouth clinical area.
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"It is fitting that he should rest in the quiet churchyard of Wendover Church, near to his house high in the Chilterns; near to the Royal Air Force Hospital he had seen built; and in the county he loved so well and in which he had spent so many happy years."

Sir David Munro married in 1905 Isabel Cunningham, who had been a fellow student at St. Andrews. She survives him with a son and a daughter.

JOHN ERIC STACEY

M.D. Lond., M.B. Sheff., F.R.C.S.E., F.R.C.O.G.

THE death of John Eric Stacey, on Nov. 9, at Curbar, Derbyshire, has taken from Sheffield and the North of England one of its most distinguished obstetricians and gynæcologists.

He was born in Sheffield just over sixty years ago, and he entered the University of Sheffield from Christ's Hospital with an open medical scholarship in 1908. He had a brilliant undergraduate record, graduating M.B. at the age of twenty-one, and carrying off the gold medal in clinical medicine and surgery. The same year he became house-surgeon at the Jessop Hospital for Women, Sheffield, and his service to the hospital was only interrupted by his service abroad with the R.A.M.C. during the first world war as regimental medical officer with the Royal Berkshire Regiment. At the battle of Loos he sustained a severe wound in his back, which caused a complete paraplegia lasting for eight months. When signs of recovering function appeared, his determination to recover overrode all obstacles, and it was not long before he was playing his part again, operating at the 3rd Northern Hospital in Sheffield for long hours with the aid of surgical supports. His fortitude in circumstances that would have crushed a lesser spirit was a source of wonder to his friends and an inspiration to his patients.

At the end of the war he turned again to obstetrics and gynæcology as a career; he was appointed registrar to the Jessop Hospital in 1920. The same year he took the F.R.C.S.E., in 1921 the M.B. Lond., and the following year the M.D. Lond. in diseases of women. In 1924 he was elected assistant surgeon to the Jessop Hospital.

In his specialty he had wide contacts, and as a consultant he was popular with the general practitioners of South Yorkshire. He held appointments as surgeon to the Beckett Hospital, Barnsley, and Retford Cottage Hospital, and he was for many years lecturer in obstetrics and gynæcology to the University of Sheffield.

L. B. P. recalls his delight in teaching and the popularity of his lectures. "Mr. Stacey," he continues, "did not write much. His great energy was devoted to the practice of gynæcology—he was a deft and rapid operator—and his writings were based on his experience. A fair fighter, he was ever ready to champion those in trouble with authority, if he believed in their case. His opinions were forthright, and he did not hesitate to express them. He had many and varied interests and entered into social activities with zest. He was a lively and entertaining host, delighting his friends by his ability as a raconteur."

As a founder member Stacey took a great interest in the Royal College of Obstetricians and Gynæcologists. In 1937 he was elected F.R.C.O.G., and he served as a member of council for ten years, and as vice-president from 1949 to 1952. He acted as examiner for its membership for many years and last year visited Canada and the United States as its representative. He examined, too, for the Universities of Sheffield and London, for the Conjoint Board, and the Central Midwives Board. A week before his death, although he did not know it, he was elected an honorary fellow of the Royal College of Obstetricians and Gynæcologists of Athens.

C. G. P. writes: "Stacey was a man brimming over with vitality and cheerfulness. Whatever the problem that faced him, he tackled it with a single-minded sincerity and determination, coming to decisions rapidly, and acting upon them resolutely. He enjoyed opposition, but when he could be convinced that his views were wrong, he gave way with a charming grace. His manner could be at times aggressive, but this was born of his convictions, and he never bore ill will to his opponents. His surgical work was a reflection of his character; he was a neat, speedy, and intrepid operator and his kindness, skill, and impish good humour endeared him to his patients.

"As a teacher he spared no pains to explain any problems, drawing rather from his experience than the textbook to emphasise his points. His clinics were always crowded with students and every lesson was illustrated by shafts of wit. It is perhaps the long succession of residents, many coming from the Dominions, who have the greatest cause to be grateful to him as a teacher. He took great trouble to make them a credit to his hospital, encouraged them to take responsibility, and supported them wholeheartedly in all their actions.

"He made relatively few contributions to the literature of his specialty, but those he made were outstanding. His influence was felt perhaps more in his contributions to the North of England Obstetrical and Gynæcological Society, where his vast experience, shrewd judgment, and salty phrase always provided an expectant and never disappointed audience. It is hard to feel that John Eric, a man who seemed to be imbued with perennial youth, is no longer with us."

His wife, Dr. Margaret Stacey, herself a former resident at the Jessop Hospital, survives him with their son and daughter.

HENRY SORDS MEADE

M.Ch. N.U.I., F.R.C.S.I.

BY the death of Prof. Henry Meade, Ireland has lost one of her great surgical figures. He was one of the last of the general surgeons, who could turn their hands successfully to widely different tasks.

He qualified in 1909 from the Catholic University of Dublin, now part of the National University of Ireland, and he took the F.R.C.S.I. the following year. Soon afterwards he was appointed visiting surgeon to St. Vincent's Hospital, Dublin, and he shared in the work of this large teaching hospital for over forty years. In the first World War he served both in the R.A.M.C. and in the French Army, and in recognition of his work the French government conferred on him the decoration of chevalier in the Legion of Honour.

In 1928 he was appointed to the chair of systemic surgery at University College, Dublin. His many hospital appointments included that of surgeon to the National Maternity Hospital. In 1934 the National University of Ireland conferred on him the honorary degree of M.CH. He served a term of office as president of the Royal College of Surgeons in Ireland, and he also presided over the Association of Surgeons of Great Britain and Ireland when they met in Dublin in 1949. Most of his holidays abroad were spent searching for new techniques, and observing the work of the leaders of surgery in European centres, and he was a well-known figure at surgical conferences throughout Europe. He had a competent knowledge of many languages, and one of his greatest delights was riding around Paris beside a taxi-driver, discussing the affairs of the day. Besides these informal contacts he had many academic links with the Continent. He was a member of the council of the International Society of Surgery, and he represented Ireland in this society for many years. He was also a member of the French Association of Surgery, an associate of the French Académie de Chirurgie, a member of the Société Internationale d'Urologie, of the German Society of Surgery, and during his last illness he received notice of his election as an honorary member of the Belgian Society of Surgery.

"To his colleagues in St. Vincent's," writes T. C. J. O'C., "Harry Meade was more than a leader. He was, in the true sense, a colleague, and perhaps his greatest attribute was his lack of envy or jealousy at the success of his juniors or assistants. Many a time he appeared at clinical meetings in the Academy of Medicine and elsewhere in the rôle of an assistant to one of his juniors. He fostered amongst his colleagues the development of specialist lines in surgery and helped them in their work, but he himself remained a general surgeon to the end.

"In the university and at the bedside his teaching was essentially personal. His students will remember the wagging finger, the dogmatic pronouncements, and the practical nature of his instruction. One of his favourite questions to a candidate in the final medical examination was: 'What would you do with this patient on the side of a mountain, twenty miles from the nearest hospital, on a wet Saturday night?' He never neglected, however, also to impart the knowledge of recent advances in surgery, and he was a pioneer in Ireland of many modern techniques. He was one of the first in these islands to introduce, after the first world war, Böhler's treatment of fractures.

"Meade was a hard worker. He spent long hours in the operating-theatre and demanded from his assistants and house-surgeons a devotion to duty never less than exacting. His relaxations were stamp-collecting and the cultivation of flowers, in which he was expert. He was a staunch supporter of the university rugby football and athletic clubs. He never wore an overcoat, and his old students, scattered throughout Ireland and the British Commonwealth, will remember the familiar figure, with his hands in his trousers pockets, standing on the touch-line on a sleety afternoon watching an inter-hospital battle. His real hobby, however, was surgery, and often he would leave a social gathering to come to the hospital to operate upon a patient in his wards. He entertained in his home in the old style, and at his table, presided over by his beautiful and gracious wife, one met the leaders of the cultural life of the country."

He leaves his wife with a daughter and two sons.

JAMES THOMAS EDWARDS

D.Sc. Lond., M.R.C.V.S.

Dr. Edwards, whose death we announced last week, had had a distinguished career as a veterinary research-worker in this country and in India.

Soon after graduating in 1911, he came under the influence of Sir John McFadyean, who drew him into the research work which was being undertaken in the department of pathology at the Royal Veterinary College, London. Here Edwards was closely concerned with investigations covering such diverse subjects as joint-ill in foals, contagious abortion in cattle, and Johne's disease. He also shared in the teaching of the department. When war broke out in 1914 he at once joined the Royal Army Veterinary Corps, and he saw service in France, including the battle of Mons, but he was soon recalled to his research work at the Royal Veterinary College.

In the years immediately after the war, despite a heavy burden of teaching and research, he undertook the editorship not only of the *Tropical Veterinary Bulletin*, but also of the *Veterinary Record*, which, having passed through evil times, was being built up as the official organ of the National Veterinary Medical Association. He was singularly fitted for this task, for he combined a sound knowledge of scientific literature with a fine command of the English language. His literary ideals were high, and he strove, often far into the night, to bring out journals which would be a credit to the veterinary profession.

His talents did not go unmarked, and in 1923 he was appointed director of the Imperial Institute at Muktesar, India. Here he found ample scope for his genius for original research. He had always shown a great interest in, and a profound knowledge of, tropical diseases. He immediately plunged into extensive researches, the most important of which was the attempt to improve the methods of combating rinderpest. It is no exaggeration to say that the adaptation of rinderpest virus to the goat, an investigation which required great intuition coupled with painstaking and, at times, most discouraging experiments, revolutionised the whole problem of rinderpest control in all parts of the world, and laid the foundations of a progressive programme for the conservation of livestock, the full benefits of which have yet to be reaped.

On his return to England Edwards joined a group of workers who were investigating foot-and-mouth disease. He made the important observation that variations in diet could alter the susceptibility of experimental animals to infection. He also pointed out that not only is the hedgehog highly susceptible to this virus, but the agent persists in a latent form in the species during hibernation: in addition, the hedgehog is capable of disseminating infection from the lungs by the dispersal of air-borne particles. He was also engaged in various projects for improving vaccines for the control of the disease. His death has removed a scientist of outstanding ability.

ROBERT MILNE DICKSON

O.B.E., M.D. St. And., D.O.M.S.

Colonel Dickson, director of the Ross Foundation for the Study of the Prevention of Blindness, Edinburgh, died on Nov. 8.

After graduating M.B. from the University of St. Andrews in 1906 he joined the R.A.M.C. While he was on service in India with the King's Dragoon Guards the first world war broke out, and he was recalled to serve in France. He was mentioned in despatches for attending wounded under fire. During the retreat from the advancing Germans he was severely wounded at Hooge. He spent his convalescence preparing his M.D. thesis and in postgraduate studies of ophthalmology. He took the D.O.M.S. in 1921, and later was appointed ophthalmic specialist at the Queen Alexandra Hospital at Millbank. In London he had opportunities to work at Moorfields with Sir William Lister and Sir John Parsons, but he had to interrupt this work when he was transferred to Ceylon as senior medical officer. His power of administration made a permanent mark on Army medical organisation there.

On his retirement from the Army in 1937 Colonel Dickson was appointed the first director of the Ross Foundation for the Study of the Prevention of Blindness in Scotland. On the outbreak of the second world war he was recalled to the Army and he was appointed A.D.M.S. Edinburgh area. He filled this post with distinction until, for reasons of health, he had to retire in 1941, when he resumed his work at the Ross Foundation.

A colleague writes: "No better appointment as director of the Ross Foundation could have been made. Dickson's zeal and energy have already produced far-reaching results. He visited factories and mines to study conditions of work. He made contact with research-workers, coördinated their efforts, and in every way encouraged them by his recognition of the importance of their investigations. He had a happy knack of getting on with all kinds and conditions of men, and his humour and friendliness made him a most acceptable companion everywhere. Underneath it all was a basic seriousness that recognised that 'here we have no continuing city.'"

HELEN MARGARET WOOD

M.B., B.Sc. Birm., D.A.

Dr. Wood, who died at the Queen Elizabeth Hospital, Birmingham, on Nov. 8, was consultant anæsthetist to the Midland regional thoracic unit, to Yardley Green Sanatorium, and to the Birmingham Children's Hospital. By her skill she had contributed greatly to the successful development of thoracic surgery in the Midlands.

She was a student of Birmingham University and she graduated B.SC. there in 1931 and M.B. in 1936. After holding some general hospital appointments, she decided to become an anæsthetist, and she received her specialist training in the Birmingham United Hospitals and in the Nuffield Department of Anæsthetics at the Radcliffe Infirmary, Oxford. She obtained the D.A. in 1943.

F. B. writes: "Helen Wood was a fine happy healthy-looking young woman who seemed able to work hard, to play hard, and to enjoy life to the full. Indeed it was because she found that in her favourite game of golf she was not quite up to standard that she came to realise that something was amiss. She slipped quietly away to see what could be done—so quietly that weeks passed before many of her friends knew that she was seriously ill. Her placid temperament, her quiet humour, and her imperturbability made her peculiarly well suited for her work, and she quickly won a place in the first rank of her specialty."

Her father, Dr. J. Arthur Wood, of Ludlow, survives her.

Notes and News

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Azamethonium Bromide	3-Methyl-3-azapentane-1:5-bis(ethyl-dimethyl-ammonium) dibromide. Pendiomide.
Benzylalkonium Chloride	Alkylbenzyldimethylammonium chloride. Zephiran Chloride.
Caramiphen	2-Diethylaminoethyl 1-phenyl*cyclo*pentane-1-carboxylic acid. Parpanit is the hydrochloride.
Chloropyrilene	*N*-5-Chloro-2-thienylmethyl-*N'N'*-dimethyl-*N*-2-pyridylethylenediamine.
Chloroquine	7-Chloro-4-(4-diethylamino-1-methylbutyl-amino)quinoline. Aralen.
Co-carboxylase	Pyrophosphoric ester of aneurine.
Dextran	
Dichlorophenarsine	3-Amino-4-hydroxyphenyldichloroarsine.
Disulfiram	Tetraethylthiuram disulphide. Antabuse.
Doxylamine	2-(α-2-Dimethylaminoethoxy-α methylbenzyl)-pyridine. *Decapryn.*
Eucatropine	4-Mandeloyloxy-1 : 2 : 2 : 6-tetramethylpiperidine. Euphthalmine.
Gentisic Acid	2 : 5-Dihydroxybenzoic acid.
Glutamic Acid	1-Aminopropane-1:3-dicarboxylic acid.
Hydralazine	1-Hydrazinophthalazine. Apresoline is the hydrochloride.
Hydroxamethocaine	[illegible]
Meralluride	[illegible] Mercuhydrin.
Mercaptomerin Sodium	Disodium salt of *N*-(3-carboxymethyl-thiomercuri-2-methoxypropyl)camphoramic acid. Thiomerin Sodium.
Mercurophylline Sodium	Mixture of the Sodium salt of *N*-(3-hydroxymercuri-2-methoxypropyl) camphoramic acid and Theophylline. Mercuzanthin.
Methanthelinium Bromide	2-Diethylaminoethyl xanthen-9-carboxylate methobromide. Banthine Bromide.
Methaphenilene	*N'N'*-Dimethyl-*N*-phenyl-*N*-(2-thienylmethyl)-ethylenediamine. Diatrin is the hydrochloride.
Methiodal Sodium	Sodium iodomethanesulphonate. Skiodan Sodium.
Methœstrol	*αβ-Diethyl-4 : 4'-dihydroxy-3 : 3'-di*methyl-stilbene.
Methylergometrine	(+)-1-Hydroxy-2-butylamide of (+)-lysergic acid. Methergine is the tartrate.
Neocinchophen	Ethyl 6-methyl-2-phenylquinoline-4-carboxylate.
Oxyphenonium Bromide	2-Diethylaminoethyl α-*cyclo*hexyl-α-phenyl-glycollate methobromide. Antrenyl.
Pentaquine	6-Methoxy-8-(5-*iso*propylaminoamyl-amino)-quinoline.
Phentolamine	2-*N*-*m*-Hydroxyphenyl-*p*-toluidinomethyliminazoline. Regitine is the hydrochloride.
Phenylbutazone	4-*n*-Butyl-1 : 2-diphenylpyrazolidine-3 : 5-dione. Butazolidine.
Piperocaine	3-(2-Methylpiperidino)propyl benzoate. Metycaine is the hydrochloride.
Polyvidone	Polyvinylpyrrolidone.
Pregnenolone	3-Hydroxy-5-pregnen-20-one.
Propyliodone	*n*-Propyl 3 : 5-di-iodo-4-pyridone-*N*-acetate.
Sodium Cyclamate	Sodium *cyclo*hexysulphamate. Sucaryl.
Sulphamethizole	2-*p*-Aminobenzenesulphonamido-5-methyl-1 : 3 : 4-thiadiazole. Urolucosil.
Suxamethonium Chloride	[illegible] succinate [illegible] Scoline.
Suxethonium Chloride	[illegible] succinate bisetho-chloride.
Thonzylamine	*N*-*p*-Methoxybenzyl-*N'N'*-dimethyl-*N*-2-pyrimidylethylenediamine. Neohetramine.
Vinbarbitone	5-Ethyl-5-(1-methylbut-1-enyl) barbituric acid. Delvinal.

The approved names amidone and isoamidone are withdrawn, and replaced as follows:

Approved name	*Other names*
Methadone	6-Dimethylamino-4 : 4-diphenylheptan-3-one. Amidone. Physeptone is the hydrochloride.
Isomethadone	6-Dimethylamino-5-methyl-4 : 4-diphenylhexan-3-one. Isoamidone.

THERAPEUTIC SUBSTANCES REGULATIONS, 1952

THESE regulations,[1] which have just been published, consolidate the various regulations issued between 1931 and 1950, and make certain new provisions. Streptomycin, in forms intended for parenteral injection, and dimercaprol (BAL) and its derivatives will be added to the Schedule to the *Therapeutic Substances Act, 1925*, as substances the purity or potency of which cannot be adequately assessed by chemical means. Detailed regulations are now made for the preparation, testing, and labelling of certain substances which already come within the schedule to the Act, but which are at present covered only by general provisions. These substances are B.C.G. vaccine, tuberculin P.P.D., oxophenarsine salts, globin insulin, and protamine zinc insulin. The regulations will take effect from Jan. 1, 1953.

MEDICAL LIBRARIES

ON Oct. 31 the medical section of the Library Association met at the Royal College of Surgeons of England, when Mr. W. R. Le Fanu, librarian of the college, described an American report on Scope and Coverage in Medical Libraries. The committee which drew up the report, as a guide to the future development of the Army Medical Library (or, as it is now called, the Armed Forces Medical Library) in Washington, took "scope" to mean the range of subjects considered pertinent to the main field of the library, and "coverage" the extent to which these subjects are covered by the literature in the library. They laid down four degrees of coverage—skeletal, reference, research, and exhaustive—into which they arranged the subjects included in the library. Thus, they suggested that purely medical subjects should be treated exhaustively—that is to say all relevant literature would be collected—whereas borderline scientific subjects should only be covered by a skeletal collection. Mr. Le Fanu believed that the report offered a new approach to book-selection.

The following officers and committee of the section were elected for 1953:

Chairman, Mr. W. A. Lee (Liverpool Medical Institution); hon. secretary, Mr. G. J. Hipkins (British [illegible]; exchange manager, Mr. F. N. L. Poynter [illegible] Medical Library); members of committee, [illegible] dcliffe Science Library), Mr. W. J. Bishop [illegible] Medical Library), Mr. W. R. Le Fanu (R[illegible] ons of England), Mr. F. A. Tubbs (St. Thom[illegible] chool), and Mr. G. Wilson (Manchester Univ[illegible]

ITALIAN HOSPITALS

IN May and June this year the International Hospital Federation made a study tour of Italy. Mr. John Dodd took part in this tour and has written an account of his impressions.[2]

THE PRIVATE LIFE OF A UNIVERSITY

EMBARRASSED by the need to explain the essential Oxford—to utter, in fact, to three American senators, and at short notice, the secret none can utter—members of a senior common room in one of the ancient colleges sat down to compose an Oxford guide-book. The result, as presented by J. C. Masterman,[3] is necessarily partial and incomplete (for who are dons to think they know their Oxford ?), providing very inadequate exponents of science and religion, showing an imperfect knowledge of contemporary undergraduate mood, and entirely omitting—as the senators when they arrive, are the first to point out—the women's colleges. But for one side of Oxford life—the masculine club-life of the colleges, in which many find the inspiration to do their best work—it is as disarming an apologia as could be written. Here are the beautiful surroundings, the matchless service, the long tradition, the courtesy, the gentle malice, the precise use of language, the loyalty to one college before all other colleges, and one university before its only peer, and the subtly flavoured stories of past dons—all those things which are enjoyed perennially by the few and remembered appreciatively by the many. Whether readers who catch the siren song of the place for the first time through these pages will feel impelled to jump in and swim for it is rather hard to say. Certainly Mr. Masterman's dons had in mind that one of the senators might think of sending his sons to Oxford, and so were at pains to deliver the air truly and keep good time; and considering their average age they made a very pretty concert of it. It is, as others have hinted, a difficult song to sing.

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[1] Therapeutic Substances Regulations, 1952. S.I. no. 1937. H.M. Stationery Office. Pp. 55. 1s. 6d.

[2] Italian Hospitals and Health Services: Notes and Impressions. By JOHN DODD, B.COM., A.C.I.I. Obtainable from the British Hospitals Contributory Schemes Association (1948), Royal London House, Bristol, 1. 7s. 6d.

[3] To Teach the Senators Wisdom. London: Hodder & Stoughton. 1952. Pp. 283. 15s.

University of Cambridge

On Nov. 8 the degrees of M.B., B.CHIR. were conferred on Nora L. Blackwell.

Royal College of Surgeons of England

At a meeting of the council on Nov. 13, with Sir Cecil Wakeley, the president, in the chair, Mr. Hedley Atkins and Prof. Victor Dix were re-elected, and Mr. A. Dickson Wright was elected, members of the court of examiners. A Hunterian lectureship was awarded to Prof. Milroy Paul (Ceylon) for a lecture on the Surgery of the Congenital Anomalies of the Mid-line Ventral Abdominal Wall. Sir James Paterson Ross was appointed Bradshaw lecturer for 1952 in place of the late Mr. Mitchiner, and Sir Reginald Watson-Jones was appointed Bradshaw lecturer for 1953.

The John Tomes prize was presented to Prof. E. B. Manley (Birmingham); the James Berry prize to Mr. R. H. C. Robins (Newcastle and Exeter); the Hallett prize to Dr. J. K. Ross (Middlesex Hospital); the Begley prize to Mr. J. H. Breed (Westminster Hospital). Mr. R. Sprinz, F.D.S., was appointed assistant lecturer in the department of anatomy.

Diplomas of membership and diplomas in medical radiodiagnosis and medical radiotherapy were conferred on the candidates named in our report of the comitia of the Royal College of Physicians (*Lancet*, Nov. 8, 1952, p. 943). A diploma in child health was also conferred on K. M. Pearce, and diplomas in tropical medicine and hygiene on T. G. Behan, D. E. W. Knight, and M. J. J. T. Becker.

Royal College of Obstetricians and Gynæcologists

At a recent examination for the D.OBST. the following were successful:

J. F. Adam, Anne Alexander, Maryan G. Anderson, Eileen Atkinson, Margaret A. Austin, Pamela M. Bacon, G. F. Barnes, Edith M. Beecher-Bryant, J. D. Belt, J. S. G. Blair, W. W. Bowie, J. D. Brackenridge, Gladys V. Bradshaw, J. M. Brown, Janet C. Bryce, A. E. R. Buckle, M. G. Budden, D. W. Bull, Sheila G. Burnie, A. F. Bushby, Mary Campbell-Mackie, I. T. Carrie, Carmelo Cassar, D. J. Cawthorne, J. S. W. Chambers, Vera Choithramani, Sheila R. Clarke, P. W. Clements, June P. Cooper, K. V. Cooper, J. H. Cowie, Ann C. Coyle, O. J. Curl, J. W. B. Dalgleish, J. K. Davidson, H. F. Davies, Elizabeth Dennys, J. C. Dilley, Prabhavati Ravindranath Dixit, F. B. Dobbs, D. J. Dobson, Margaret K. Douglas, Diana F. J. Duncan, W. A. W. Dutton, G. F. E. Edmondson-Jones, Mary G. Eldridge, Wilfred Ellenbogen, J. M. Elliott, Luba Epsztejn, Jack Eyton-Jones, Margaret D. Findlay, G. R. C. Fisher, Mary L. Fraser, G. C. Galea, Barbara E. Gibbs, Alan Gillespie, D. L. Golightly, J. L. Goodger, Anne L. M. Graham, D. A. H. Grieve, Stanley Hacking, A. B. Haigh, Ethna J. Halpin, Ikbal Abd El-Walid Hamdy, Marion Hanson, H. A. Harding, Elizabeth M. Harpur, D. T. G. Harris, Helen J. Harthoorn, Robert Hewitt, J. M. Hiddleston, Margaret I. Hill, J. A. Holmes, J. L. Honig, J. M. Hood, R. A. St. C. Hoyte, Anne L. Hunter, Anne E. Jameson, M. H. Jameson, Helen Jessler, J. M. Jewitt, G. A. H. Jones, W. T. Joseph, Margaret Kassab, J. A. N. Keane, G. E. Kelly, Sybil V. Kinley, Frances E. W. Kinnaird, Frances E. Kirk, A. L. Kirkland, Chung Yue Lai, E. C. Lewis, Isabel J. Lim, M. D. W. Low, Helen M. M. McCallum, J. M. S. McCoy, Yvette McCoy, J. A. McCraith, Sarah C. McEwan, Anne M. McKechnie, J. G. McKenny, Edith M. McLean, Margaret E. Maclean, B. N. McQuade, D. H. McVie, A. R. Magarey, Maureen A. F. Malcolm, M. D. Manion, J. G. Markus, G. F. G. Marshall, G. G. M. Miles, J. L. Miller, R. C. Molk, Elisabeth Monkhouse, D. J. R. Morgan, June Morgan, K. D. Mullen, B. J. Murphy, Salvino Muscat, J. P. Norris, K. R. Norton, K. F. O'Callaghan, D. W. Orton, T. G. Osmond, R. B. Ottley, H. J. G. Palmer, [illegible] Perry, R. J. Pett, Mary P. Phelan, [illegible] S. J. S. Polwin, Joan M. Ponsford, [illegible] Hilary R. Pullon, D. W. Quantrill, D. J. H. Rogers, Annapurna Sabhesan, Prem Sarin, Rachel D. R. Sasieni, M. K. Sawday, G. C. W. Sharpe, R. W. Simpson, S. L. Skoll, Henry Stabile, A. J. H. Stephens, J. E. L. Sutcliffe, C. G. W. Sykes, P. K. Sylvester, Derek Tacchi, Aly Dawood El-Tannir, A. R. Taylor, Joseph Taylor, J. G. A. Troup, P. W. Tucker, J. B. Turtle, I. S. Waller, Daphne M. L. Walters, Paula M. Watkin, Joyce M. Watson, W. L. Whitehouse, Kathleen M. Whitham, L. M. Wolf, Elizabeth J. A. Yool.

Royal College of Surgeons of Edinburgh

On Nov. 5 Sir Cecil Wakeley, P.R.C.S., and Sir Reginald Watson-Jones were admitted to the honorary fellowship of the college. Prof. Walter Mercer, the president, said that it had been the custom of the college through many generations to grant the honorary fellowship to distinguished members of the medical profession and others who had deserved well of the nation. Mr. W. Quarry Wood, the vice-president, referred to Sir Cecil's achievements as surgeon, author, and as president of the Royal College of Surgeons of England; and Mr. R. I. Stirling spoke of Sir Reginald's appointments as extra orthopædic surgeon to the Queen and as president of the British Orthopædic Association.

Royal College of Physicians of Ireland

On Nov. 7 the following were admitted to the membership:

D. F. Cantwell, J. A. C. de Silva, J. C. McGoldrick, K. M. Hickey, R. J. Marshall, E. M. A. McElligott, G. E. Peters, A. L. Wells.

Chadwick Trust

Mr. J. Rawlinson, chief engineer of the London County Council, will deliver a Bossom lecture at 2.30 P.M. on Tuesday, Nov. 25, at the Royal Sanitary Institute, 90, Buckingham Palace Road, London, S.W.1. His subject will be the History of the Main Drainage of London.

Royal Society

A Royal medal of the society has been awarded to Sir Frederic Bartlett, F.R.S., for "his creation of an experimental school of psychology which has established under his leadership an outstanding position recognized internationally as without superior."

Institute of Psychiatry, London

Prof. J. Elkes will deliver a lecture at the Maudsley Hospital, Denmark Hill, S.E.5, on Thursday, Nov. 27, on Uses and Limitations of Pharmacological Method in Psychiatric Research. Dr. Graham Weddell will give a lecture on Thursday, Dec. 4, on the Mechanisms of Cutaneous Sensibility. Both lectures are at 3 P.M.

British Psycho-Analytical Society

Prof. Roger W. Russell, PH.D., will deliver the Ernest Jones lecture at a meeting of this society to be held at 1, Wimpole Street, London, W.1, on Monday, Dec. 1, at 8.15 P.M. The lecture is entitled Behaviour under Stress.

Institute of Laryngology and Otology, London

Dr. Ettore Bocca, of the otolaryngology clinic of the University of Milan, will deliver a lecture at the institute, 330, Gray's Inn Road, W.C.1, on Wednesday, Dec. 3, at 5.30 P.M. The title of the lecture, which will be illustrated by a cinematograph film, is Laryngectomy with Block Dissection of the Neck—Unilateral and Bilateral.

Helicopters for Evacuating Wounded

Helicopter ambulance units are to be formed as an integral part of the U.S. Army Medical Service. Helicopters have been used in the Korean war to rush severely injured soldiers to mobile army surgical hospitals and evacuation hospitals, but hitherto they have not been formally incorporated in field units. Each of the new units will include five two-rotor helicopters capable of carrying three stretcher or four walking patients, together with a medical attendant and a pilot.

Food and the Future

The nutrition panel of the food group of the Society of Chemical Industry is to hold four meetings on this subject. The first will take place on Wednesday, Dec. 10, at 6.15 P.M., in the rooms of the Chemical Society, Burlington House, London, W.1, when Mr. F. Le Gros Clark and Dr. E. W. Russell will speak on the Problem of Future World Food Supply. Other speakers in the series will include: Dr. G. A. C. Herklots and Prof. John Yudkin (Present Methods of Attack on the Problem); Mr. N. W. Pirie, F.R.S., and Dr. A. C. Thaysen (New Natural Sources of Foodstuffs); Dr. W. F. J. Cuthbertson, Mr. P. N. Williams, and Mr. Norman Wright, D.SC. (Synthetic Food Potentialities).

Volunteers for Common Cold Research Unit

About 600 volunteers between 18 and 45 years of age are wanted to take part in experiments next year at the Medical Research Unit at Harvard Hospital, Salisbury. They are needed to test experimental materials for the presence of cold germs. Since the unit began its work six years ago 2989 volunteers have taken part in the trials; 248 volunteers have paid two visits and 140 have taken part in three or more trials. The method of testing for the cold virus in experimental materials is by means of nasal drops given to volunteers after a preliminary period of observation to make sure that they are free from a "natural" cold. The procedure gives little or no discomfort at the time, and any colds that result are usually mild. Volunteers are isolated in pairs for periods of ten days, and full medical and nursing facilities are available at all times. Fares to and from Salisbury up to a maximum of £3 are paid, and volunteers are given 3*s*. a day pocket-money. Anyone who wishes to volunteer should write to the medical officer, Harvard Hospital, Salisbury.

British Medical Association

For 1953 the council of the association has chosen for the essay prizes for medical students the topic that a Good General Education is a Necessary Preliminary to a Medical Career. Further particulars may be had from the secretary of the association, B.M.A. House, Tavistock Square, London, W.C.1.

Competition for Medical Films

The *Presse Médicale* is again offering a prize of 100,000 francs and other awards for the best medical and surgical films submitted by amateurs. The films (16 mm.) may not be subsidised by a commercial laboratory or firm. Further particulars may be had from the secretariat of the journal, 120, Boulevard Saint-Germain, Paris. Films should reach the secretariat not later than March 10, 1953.

Manchester Mental Nursing Survey

The University of Manchester and the Manchester Regional Hospital Board have arranged for a survey of mental nursing to be made at Lancaster Moor Mental Hospital, the Royal Albert Mental Deficiency Hospital, Lancaster, and the Calderstones Mental Deficiency Hospital, Whalley. The investigation was suggested by the survey of nursing in general hospitals on which the Nuffield Provincial Hospitals Trust is shortly to report. Mr. H. A. Goddard, who directed the Nuffield survey and who is now an independent management consultant specialising in health service problems, is also to direct the Manchester survey, and he and his team of four graduates have already studied the routine nursing duties at one of the selected hospitals.

Society of Medical Officers of Health

The child health group of the Scottish branch of this society will meet at Ayrshire Central Hospital, Irvine, on Saturday, Nov. 29.

Medical Honour

Major James Stuart Hitsman, M.D. Queen's University, Ontario, R.C.A.M.C., has been appointed M.B.E. (military division) in recognition of gallant and distinguished services in Korea.

Plea for a New Hospital

In the report for 1951–52 of Charing Cross Hospital, London, Lord Inman, chairman of the board of governors, remarks on the continued delay in starting construction of the new hospital at Northwick Park. "No new hospital," he says, "has been erected in this country for over a decade. It would be a tremendous fillip throughout the entire health services of the country if a new hospital could be established incorporating the latest and most modern developments. It would draw as visitors to this land medical men and hospital administrators from all over the world and restore the country to its traditional place in the forefront of medical and surgical science."

EMERGENCY BED SERVICE.—In the week ended last Monday, acute cases numbered 1069. The proportion

Prof. B. S. Platt and Prof. A. A. Moncrieff are attending a conference on kwashiorkor, at Fajara in the Gambia, British West Africa. The conference, which opened last Wednesday, is being held under the auspices of the *Commission for Technical Coöperation in Africa, south of the Sahara.*

Diary of the Week

NOV. 23 TO 29

Monday, 24th

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Prof. R. V. Christie, Dr. Neville Oswald: Bronchitis.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5.30 P.M. Prof. Thomas Nicol: Applied Anatomy of the Orbit.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Prof. W. I. B. Beveridge, D.V.SC.: Resistance and Susceptibility to Viruses.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
4.30 P.M. Dr. E. Stengel: Lecture-demonstration.

MANCHESTER MEDICAL SOCIETY
9 P.M. (University of Manchester.) *Section of General Practice.* Dr. M. C. Tod: Carcinoma of the Cervix.

Tuesday, 25th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine) Prof. Adrien Albert, D.SC.: Selective Toxicity. (First of two lectures.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Section of Medicine.* Dr. Stanley Banks, Dr. J. C. Broom, Mr. J. V. Crawford: Treatment of Non-tuberculous Meningitis.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Prof. Henry Barcroft: Peripheral Circulation.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Sir Stanford Cade: Scope and Limitations of Surgery after Pelvic Irradiation.

WEST END HOSPITAL FOR NERVOUS DISEASES, 73, Welbeck Street, W.1
5.30 P.M. Dr. Douglas Gordon: Radiological Methods in Neurology.

PADDINGTON MEDICAL SOCIETY
8.45 P.M. (St. Mary's Hospital, Paddington, W.2.) Discussion on Recommendations of the Working Party.

Wednesday, 26th

ROYAL EYE HOSPITAL
5.30 P.M. Mr. A. J. Cameron, Miss Iris Kane, Mr. R. A. Burn: Methonium. (Symposium.)

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. A. Austin Eagger: Health in the Factory—Slough Industrial Health Service.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Haber: Benign Epithelial Tumours.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. H. P. Winsbury-White: Frequency and other Disturbances of Micturition.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St. Vincent Street, Glasgow, C.2
5 P.M. Mr. T. Holmes Sellors: Cancer of the Lung. (Weild lecture.)

Thursday, 27th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Professor Albert: Selective Toxicity. (Second of two lectures.)

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Major-General Sir Heneage Ogilvie: A Eulogy of the Yes-man.

ROYAL EYE HOSPITAL
5.30 P.M. Miss M. Savory: Newer Therapeutic Measures.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. Desmond Curran: Psychiatry lecture-demonstration.

INSTITUTE OF PSYCHIATRY
3 P.M. Prof. J. Elkes: Uses and Limitations of Pharmacological Method in Psychiatric Research.

UNIVERSITY OF OXFORD
8.30 P.M. (Wingfield-Morris Orthopædic Hospital.) Mr. R. G. Pulvertaft: Problems of the Injured Hand and its Repair.

MANCHESTER MEDICAL SOCIETY
8.15 P.M. *Section of Anæsthetics.* Dr. A. H. Galley: Kidney in Relation to Anæsthesia and Analgesia.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Dr. Robert Hughes: Treatment of Coronary Thrombosis with Anti-coagulants. Dr. B. J. Bickford: Treatment of Angina Pectoris by Sympathectomy.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, *Edinburgh.*) Dr. J. A. Fraser Roberts: Inheritance *of* Sex-linked Abnormalities in Man.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. G. A. G. Mitchell: Innervation of the Thoracic Viscera.

Friday, 28th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Pædiatrics.* Mr. James Robertson: A Two-year old Goes to Hospital. (Film.)
8.15 P.M. *Section of Obstetrics and Gynæcology.* Mr. A. L. Gunn,
[illegible] and Recording of
Dr. Mic[illegible] Fœtal Distress in
Fœtal H[illegible] A. B. Clemetson:
Relation [illegible] Artery and Vein
Oxygen [illegible] o Cord Obstruction.
Blood at [illegible]

ROYAL EYE HOSPITAL
4.30 P.M. Mr. A. J. Cameron: Medical Ophthalmology.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. P. F. Borrie: Vascular Disorders.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
4.30 P.M. Mr. A. R. Dingley: Sulphonamides in Otitis Media.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. A. N. Ashworth: Cortisone in Treatment of Syphilis of Eye.

Saturday, 29th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11 A.M. (Hammersmith Hospital, Ducane Road, W.12.) Dr. C. L. Cope: Anæmia and Pregnancy.
NOON. Dr. Mary Barber: Investigation of Sepsis in a Maternity Ward.

THE SURGICAL TREATMENT OF ULCERATIVE COLITIS

P. BRIAN COUNSELL
F.R.C.S.
SENIOR SURGICAL REGISTRAR, GUY'S HOSPITAL, LONDON; FORMERLY SURGICAL REGISTRAR, ST. MARK'S HOSPITAL, LONDON

J. C. GOLIGHER
Ch.M. Edin., F.R.C.S.
ASSISTANT SURGEON, ST. MARY'S HOSPITAL, AND SURGEON, ST. MARK'S HOSPITAL, LONDON

THE modern radical surgical treatment of ulcerative colitis, which has been developed mainly as a result of the work of Bargen (1928), Bargen et al. (1932), Lahey (1949), Cattell (1939, 1948), Cave (1945), and McKittrick and Moore (1949) in America, consists of ileostomy, usually followed by colectomy and excision of the rectum. At first physicians were reluctant to advise such a drastic step as a permanent ileostomy to their patients before the issue had clearly become one of life or death, and as a consequence patients were only referred to the surgeon when they had become virtually moribund. This led to a very high operative mortality, which in turn confirmed the physician in his cautious approach to surgery. Recent improvements in the design of ileostomy appliances, however, have robbed ileostomy of several of its objectionable features; so these patients can now lead full and active lives with remarkably little inconvenience. As a result more patients with ulcerative colitis are now coming for surgical treatment and at an earlier stage, and surgery has a growing part to play in the management of this disabling and lethal disease.

At St. Mark's Hospital some 120 patients are seen each year with various forms of chronic non-specific proctocolitis, and about 15–20 of the more severe cases are operated on. We report here the collective experience of the hospital in the management of the first 90 cases of ulcerative colitis submitted to the modern surgical régime; 6 of these patients had already undergone ileostomy elsewhere and were referred for completion of their treatment.

INDICATIONS FOR SURGERY

Chronic Invalidism

This was by far the commonest indication and led to operation in 71 of the cases. Though these patients had usually been admitted to hospital many times before during exacerbations of their colitis and had eventually recovered from these, they were seldom restored to normal health. On discharge they still usually had troublesome diarrhœa confining them to the house, passed blood and mucus, were well below their normal weight, and were capable at best of only light duties. After a time with periodic aggravations of their condition they entered a chronic invalid state, becoming extremely emaciated and looking like the semi-cadaverous inmates of the notorious Belsen and Auschwitz concentration camps. The duration of the disease in about half the cases was more than four years, and retrospectively it seems that a decision in favour of surgical management could in many instances have been made earlier and the patients thus spared much unnecessary disability and suffering. However, we appreciate the point made by McKittrick and Moore (1949) that patients must have suffered severely from ulcerative colitis if they are to be convinced that an ileostomy had become essential for their recovery. Too early a resort to surgery might have led to the patients being less well adjusted psychologically to their ileostomies.

When these patients were admitted to St. Mark's Hospital they were usually in a phase of remission of symptoms, but in a few, where the disease seemed active, further medical treatment was adopted for a time to allow them to reach a quiescent period before resort was made to surgery. 4 patients, however, looked as if they were going to die unless something more than medical measures (transfusions, vitamin therapy, protein concentrates, and intestinal antiseptics) were adopted, and with considerable reluctance ileostomy was done while they were virtually in extremis, with 3 deaths.

Perforation

1 patient was operated on for perforation of the colon. At laparotomy the cæcum was found ruptured and, owing to the friable condition of its wall, was sutured with difficulty; an ileostomy was also done. The patient died sixteen hours after operation, apparently of shock. In a fitter patient we think it might have been better to have attempted exteriorisation of the perforated bowel instead of suture, or to have done an immediate subtotal colectomy and ileostomy.

Hæmorrhage

In 1 case severe hæmorrhage was the indication for operation. The bleeding took place a week or so after an ileostomy and was eventually stopped only by an emergency subtotal colectomy. In our view severe bleeding in ulcerative colitis is an indication not for ileostomy but for combined ileostomy and colectomy, as recommended by Ferguson and Stevens (1948) and by Lahey (1949), as soon as the patient's general condition can be sufficiently improved by massive blood-transfusion.

Abscesses and Fistulæ

In 12 patients anal fistulæ or perianal or ischiorectal abscesses were present and were the immediate indications for ileostomy. These were long-standing severe cases which would probably have come to surgery in any event. We know from experience that these complications of colitis never clear up unless an ileostomy is established to render the diseased colon and rectum inactive. Usually some local surgical treatment was necessary, the abscesses and fistulæ being laid open. Some of the patients later underwent colectomy with excision of the rectum.

Metastatic Complications

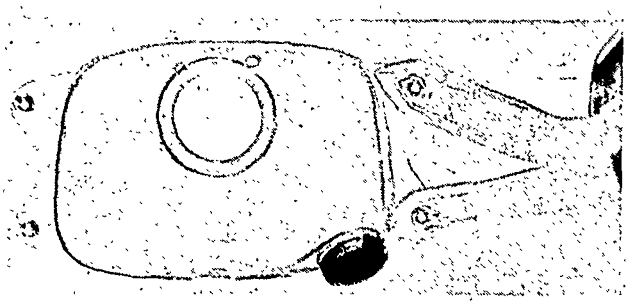
Arthritis developed in 4 cases. Of these 4 patients 1 already had an ileostomy when the arthritis first appeared, and in another it persisted after subtotal colectomy till the rectal stump was excised. These experiences indicate the necessity for complete removal of the colon and rectum in patients with a complicating arthritis, and this was done in all 4 cases in this group.

One patient with severe ulcerative colitis had *erythema multiforme*, which cleared up completely after ileostomy and excision of the colon and rectum.

PREOPERATIVE CARE

Most of the patients requiring surgical treatment were anæmic and had some hypoproteinæmia and vitamin deficiency. For nearly all of them blood-transfusion was necessary, and this was the most important single factor in restoring them to a reasonable condition. Usually several slow drip transfusions of one or two pints were given at intervals of twenty-four to forty-eight hours until the hæmoglobin level was raised to 70–80%. In addition a high-protein diet was prescribed and supplemented by the addition of the casein preparation 'Casilan,' 5 or 6 oz. daily. Vitamins were also given in suitable doses, vitamin-B complex and vitamin C being the most important. Intestinal antiseptics—e.g., phthalylsulphathiazole, succinylsulphathiazole, and oral streptomycin and other antibiotics—were not usually given in preparing patients for ileostomy. They were used, however, in the preparation for colectomy because,

Fig. 1—Original pattern of Donald Rose ileostomy appliances as seen from the front: (a) ileostomy box; (b) ileostomy bag with plastic upper part. Note raised edge showing as a ring surrounding opening in appliance which fits against ileostomy, and ventilating holes present on upper part of box or bag.



(a)

(b)

no matter how carefully this operation is done, occasionally the friable bowel is opened. An emulsion of phthalylsulphathiazole 5 g. and streptomycin 1 g. in 5 oz. of water was instilled daily for five or six days into the rectum and distal ileostomy opening, when present.

ILEOSTOMY APPLIANCES

In this country there are at present available two main types of ileostomy appliance:

(1) *The plastic box or rubber bag with plastic upper part* manufactured by Donald Rose Ltd. to the specification of Mr. R. S. Corbett of St. Bartholomew's Hospital (fig. 1). The essential feature of this appliance is the raised rim immediately round the opening, which when firmly pressed against the skin by a rubber belt ensures a fairly watertight apposition. A small ventilating hole is provided; obviously some sort of vent is essential in the box type at least because nothing can enter unless the contained air is displaced. Unfortunately during the night, if the patient is lying flat, the ileal contents gravitate into the upper part of the appliance and tend to leak through the ventilating aperture. Rose has recently modified his appliance by fitting it with a ventilating snout, and leakage is less common with it.

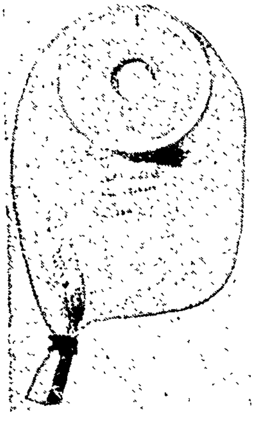


Fig. 2—Posterior aspect of Salt ileostomy bag. Note opening into which ileostomy fits and slightly convex disc of metal covered with rubber which surrounds this opening and which is cemented to skin of abdominal wall.

(2) *The stick-on type of bag.*—Unfortunately the original Koenig-Rutzen pattern of adhesive bag, which is manufactured in America, is not available to patients in this country unless they have dollars. Recently similar bags have been made by British firms:

(*a*) Salt & Son Ltd. make an appliance (fig. 2) which closely resembles the original Koenig-Rutzen apparatus. It consists of a rubber bag with a hole in the upper part of its posterior surface which fits over the ileostomy opening. Surrounding this hole is a slightly convex disc of metal covered with rubber, or a flat disc of firm rubber, with a central perforation corresponding to the aperture in the bag. This disc is stuck to the skin with special cement. As an additional precaution, an elastic belt is also worn to hold the appliance to the body. The bag is emptied through an opening at its lower end which is normally kept clipped off. The usual procedure is to empty the bag every four hours or so as required, usually every time the patient micturates. Complete removal of the appliance, by dissolving the cement with benzene, is necessary every twenty-four to forty-eight hours for washing and changing; otherwise the rubber is apt to smell.

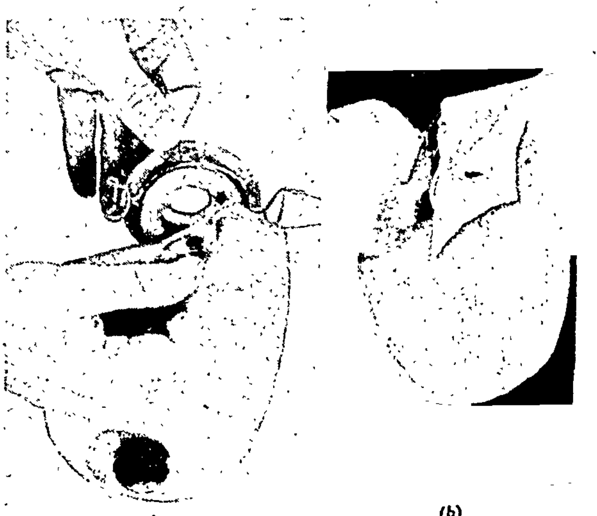
(*b*) Down Brothers also make a stick-on bag (fig. 3). It comprises a rubber disc with a projecting grooved neck to which a detachable rubber bag is fitted. Fixation to the skin is achieved with a square of double-sided adhesive plaster with a central perforation, one side of which sticks to the disc and the other to the skin. For washing, the bag may be detached from the rigid rubber upper part without having to unstick the adhesive disc, which may therefore be left undisturbed for five or six days at a time. A further modification of Down Brothers' appliance is the light rectangular bag made of plastic material. It has the advantage of being free from the smell associated with rubber bags. It is worn for two or three days, being emptied at its lower end as required, and is finally discarded.

In our experience, when they work, the adhesive types of bag are the more satisfactory, but some of our patients have had so much irritation of the skin from the adhesive cement or plaster that they have had to discontinue using this form of appliance. In several such cases it has been found convenient to prescribe both an adhesive bag and a Donald Rose appliance so that the patient may use them alternately according to the amount of skin irritation produced. We feel that there is still considerable scope for improvement in the design of stick-on bags as regards both the material and the cement.

SITE OF ILEOSTOMY

American writers usually recommend a site in the right iliac region, at or a little below McBurney's point, sufficiently far away from both the umbilicus and the anterior superior iliac spine to allow the easy application of the disc of an adhesive ileostomy bag to the intervening skin without overlapping either of these landmarks (fig. 4B).

Most of the ileostomies done at St. Mark's Hospital, however, have been placed at a higher level, in the wais



(a) (b)

Fig. 3—Down Brothers rubber ileostomy bag: (a) bag being fitted to rubber disc which is applied to ileostomy; (b) posterior view showing square of adhesive plaster with central perforation stuck to back of rubber disc (in actual practice the adhesive is first fixed to the skin, and the bag is then applied to the adhesive).

line about $1^1/_2$ in. to the right of the midline (fig. 4A). We believe that ileostomy appliances can be more firmly pressed against the abdominal wall if they are worn in the belt line rather than lower down, where a belt if tightened is liable to slip up, pulling the bag with it, and preferably near the midline, where the taut rectus muscle makes the abdominal wall more rigid. It must be borne in mind, moreover, that, though one may hope to prescribe a stick-on type of bag the patient's skin reaction to the adhesive may compel her to rely entirely on pressure to prevent leakage, and the ileostomy should therefore be sited so that this may be exerted most advantageously. More recently, as an alternative to a belt, we have been using a roll-on type of corset with a perforation (fig. 5), which holds either the Donald Rose or the adhesive bag much more securely than does any belt.

OPERATIVE TECHNIQUE

Loop Ileostomy

In 13 of the earlier cases the ileostomy established was of the loop variety, but the difficulty of fitting a satisfactory appliance and the increased tendency to prolapse led to the abandonment of this procedure in favour of a terminal ileostomy.

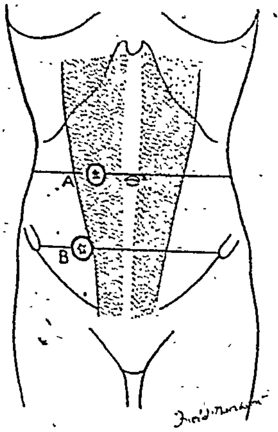


Fig. 4—Ileostomy sites : A, site generally used at St. Mark's Hospital ; B, site recommended by many American workers.

Terminal Ileostomy

In this operation the lowest loop of ileum and its mesentery are divided 6 in. or less from the ileocæcal junction, care being taken to ensure that the distal ileum itself is not involved in the disease, as it was in 3 of our cases, when a more proximal section was required. The proximal end is brought to the surface as the functioning ileostomy. The distal end can either be exteriorised 3 or 4 in. from the ileostomy (fig. 6) or closed like a duodenal stump in a gastrectomy and dropped back—Rankin's method (Bargen et al. 1932). Though the latter method is open to the theoretical objection that in these debilitated patients the blind ileal stump might rupture, nearly half the terminal ileostomies in this series were of the Rankin type, the ileum being divided within 1 in. of the ileocæcal valve (fig. 7), and in none of these cases was there leakage or other complication referable to this blind end.

In about half the operations a right rectus-splitting incision was used, the proximal ileum being brought out through this main incision on a level with the umbilicus, and the distal ileum, if exteriorised, drawn through a separate stab incision in the right iliac region. In the other half a gridiron incision centred on McBurney's point or slightly medial to it was chosen, and in these cases the proximal ileum was implanted in a separate stab wound $1^1/_2$ in. to the right of the umbilicus, and the distal ileum placed in the gridiron wound itself.

In securing the terminal ileum direct suture of the bowel to the parietes has been avoided because of the danger of producing subcutaneous ileal fistulæ at the site of the stitches. To hold the terminal $1^1/_2$–2 in. of ileum out of the abdomen reliance has been placed on the support given by several layers of wool to a Paul's tube tied into the end of the projecting bowel. In many instances also the cut edge of the ileal mesentery has been sutured to the anterior parietal peritoneum (fig. 6), as recommended originally by Cattell (1939). In some of the cases with a double ileal opening the lateral peritoneal space on the outer side of the distal ileal opening has been closed, as recommended by Hardy et al. (1949), to prevent small gut from passing through this lateral space and becoming obstructed. Technically it has not always been easy to do this, particularly in cases with only one ileal opening near the midline in which this space has been very large. The parietal incision was usually sutured with non-absorbable material, such as fine silk and stainless-steel wire, and the skin wound was finally sealed off round the projecting ileum with gauze soaked in Whitehead's varnish (Sumatra benzoin in coarse powder 100 g., prepared storax 75 g., balsam of tolu 50 g., iodoform 100 g., solvent ether to 1000 ml.). Finally a Paul's glass tube was tied into the extreme end of the proximal ileum and connected with a wide-bore thin rubber tube to a urinal in the bed alongside the patient. The inactive ileal end was left closed with a Zachary Cope's clamp.

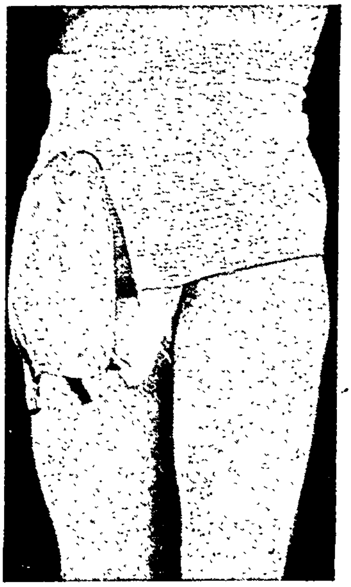


Fig. 5—Method of holding Koenig-Rutzen bag by roll-on corset with perforation which fits between bag and its metal flange.

The projecting ileum can be covered with skin to produce a penile type of ileostomy. This is done by applying Thiersch grafts, as recommended by Dragstedt et al. (1941), or pedicle grafts of abdominal skin, as proposed by Monroe and Olwin (1949). We used the former method on two occasions but found that, with the ordinary type of ileostomy bag, the skin covering the ileum, which protruded into the appliance, was liable

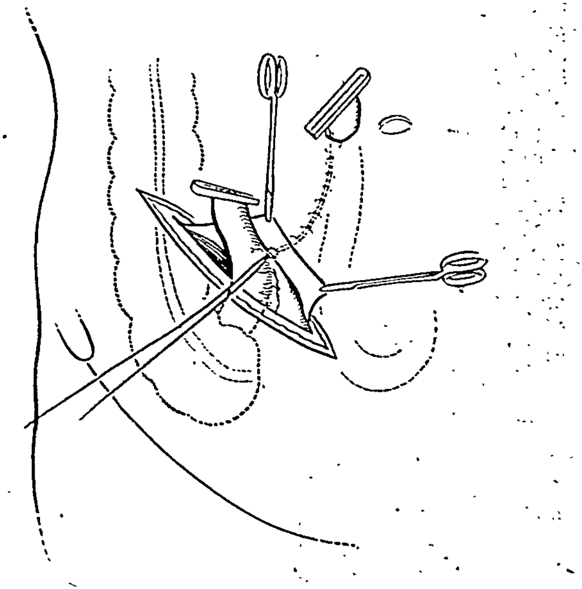


Fig. 6—Technique of ileostomy : proximal end of ileum has been drawn through separate stab incision traversing right rectus muscle at or just above level of umbilicus, and distal end has been implanted in the gridiron wound ; suture of cut in ileal mesentery to anterior parietal peritoneum has just been completed.

to become digested and sore, and we are not convinced that the method presents any real advantages.

POSTOPERATIVE CARE

Two special considerations dominate the postoperative management of ileostomy cases: the maintenance of fluid and electrolyte balance, and the care of the ileostomy opening.

Maintenance of Fluid and Electrolyte Balance

In the average case, though there may be some small ileostomy actions on the first day after operation, it is usually not until 24–48 hours after operation that the ileostomy starts to act properly, and then the discharge is often profuse and watery. This usually continues for several days, during which time it is very easy for the patient to become dehydrated and depleted of sodium and potassium. It is therefore especially important for the surgeon to bear in mind the severe losses of fluid and electrolytes that may be sustained in these circumstances and to allow for them in calculating the intake required.

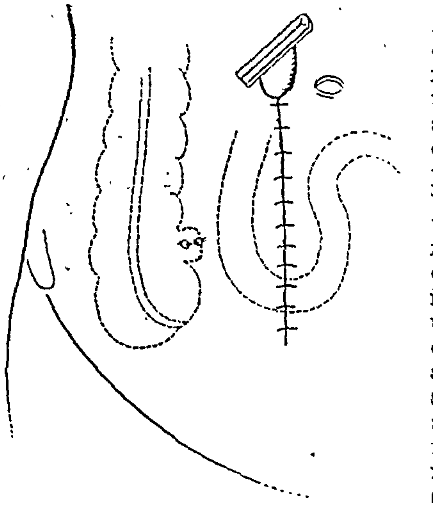


Fig. 7—Alternative ileostomy technique: suture of distal piece of ileum close to ileocæcal junction; ileostomy established at usual site to right of umbilicus at upper end of right paramedian wound used for this operation.

Many ileostomy patients do not require intravenous fluids as a routine but rely in the first instance on oral administration. Only if the fluid balance cannot be maintained in the face of profuse ileostomy actions, or of obstructive symptoms with perhaps vomiting, is an intravenous infusion instituted. In such patients prolonged intravenous administration may be required and may have to be supplemented by blood-transfusions and administration of vitamin and protein concentrates.

Management of Ileostomy Opening

(1) The patient returns to the ward with a Paul's tube tied in the active ileostomy opening. This provides a safe conduit for ileal contents to the receiving bottle in the bed for the first few days.

(2) After five to seven days the silk ligature holding the Paul's tube in situ cuts through, and the bowel contents are liable to soil the wound. We have relied at this stage on fitting a temporary or first-stage ileostomy bag of Donald Rose pattern, leakage being minimised by the application of soft-paraffin gauze immediately round the ileostomy. Occasionally, to guard against digestion of the abdominal skin if there is any leakage of ileal contents, we have painted it with "Baltimore paste" (powdered aluminium, zinc oxide cream, paraffin as required).

TABLE I—POSTOPERATIVE COMPLICATIONS IN 60 CASES TREATED BY ILEOSTOMY

Complication	No. of cases
Early:	
Intestinal obstructive episodes	26
Subphrenic abscess	2
Wound disruption	1
Severe wound sepsis	1
Subcutaneous fistula	1
Late:	
Ileostomy prolapse	9
„ retraction	3
„ stenosis	3

(3) By the end of three or four weeks the ileostomy has shrunk to its permanent size and shape, projecting about 1 in. above the skin surface and being covered on its outer surface with mucosa. The patient may now be fitted with the final ileostomy appliance.

POSTOPERATIVE COMPLICATIONS

The complications encountered in this series are listed in table I, from which it will be seen that the most important immediate trouble in these ileostomy cases was the occurrence of *obstructive episodes*, which were a feature in nearly half the cases. These usually began about a week after operation, the patient complaining of abdominal pains, distension, and vomiting, and the ileostomy ceasing to act. Their symptoms and signs suggested a mechanical obstruction rather than a paralytic ileus, but if treated conservatively with gastric suction and administration of fluids they often recovered satisfactorily, though such a régime may have had to be continued intermittently for more than two weeks. Five patients were submitted to laparotomy because the surgeon believed that a true mechanical obstruction must be present, but in none was a "surgical" obstructive lesion found. Usually the ileum was dilated right down to the ileostomy opening in the abdominal wall.

These experiences have convinced us that in the management of these obstructive episodes it is usually best to avoid re-exploration and to persist with conservative measures. An important part of these is the insertion of a soft rectal catheter for a distance of 6–12 in. into the terminal ileum. This is often followed by the escape of some 200–300 ml. of ileal contents apparently under pressure. This may require to be repeated two or three times a day for several days, or the catheter may be left in situ, especially during the night.

TABLE II—CAUSES OF HOSPITAL DEATHS IN 60 CASES TREATED BY ILEOSTOMY

Cause of death	No. of cases
Subacute intestinal obstruction	4
Toxæmia and electrolyte imbalance	4
Bronchopneumonia	1
Perforation of cæcum and peritonitis	1
Terminal ileitis, perforation, and peritonitis ..	1
No cause found at necropsy	2
Total	13

By far the most troublesome late complication of ileostomy has been *ileostomy prolapse*, which has already occurred in about a fifth of our cases and may, of course, yet develop in other patients in this series. The prolapse involves the full thickness of the ileal wall and may project as far as 5 or 6 in. We have discovered no certain means of avoiding this complication, and in particular have not found that the technique described by Cattell (1939) of stitching the cut edge of ileal mesentery to the anterior parietes is a reliable preventive. Once prolapse has developed, we have sometimes reoperated and tried to tighten the opening in the abdominal parietes and also stitched the ileum to the anterior parietal peritoneum, but this has only rarely been successful. We have also experimented with anti-prolapse discs which fit over the opening on the ileostomy box or bag, but it is difficult to strike the right size for the disc perforations which will at the same time allow easy escape of ileal contents but not permit the ileum to prolapse.

Ileostomy stenosis and retraction have been dealt with by the same sort of simple reconstruction operation used for these complications developing in connection with colostomies. To prevent the development of an ileostomy

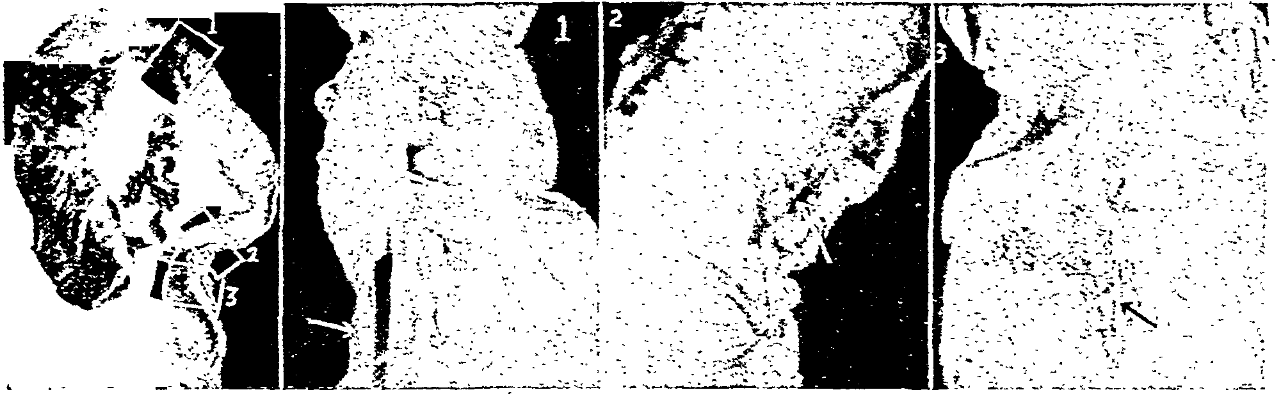


Fig. 8—Specimen of colon and rectum, removed by immediate ileostomy and panproctocolectomy from case of ulcerative colitis, with three separate carcinomata of plastic non-ulcerating type simulating simple fibrous thickenings of bowel wall ; histologically two of these (growths 1 and 2) were anaplastic colloid carcinomata.

stenosis the occasional passage of a finger into the opening may be useful.

OPERATIVE MORTALITY

Of the 60 patients submitted to ileostomy 13 died, giving an operative mortality of 21·6%. If, however, the 4 cases of emergency ileostomy and the 1 case of cæcal perforation, for which ileostomy and suture of the perforation were done, are excluded, the series is reduced to 55 patients with 9 deaths, a mortality of 16·4%. The causes of death are shown in table II, from which it will be seen that intestinal " obstruction " was often the lethal factor.

COLECTOMY AND EXCISION OF THE RECTUM

Indications

Recently our views at St. Mark's Hospital on the indications for colectomy in ulcerative colitis have undergone a sharp change. This has been brought about by the experience we have had in the last two years of observing carcinoma develop in some part of the diseased large bowel in no less than 11 of the 90 patients on whom this report is based. In 4 of the cases the growth arose in the rectum and was detected on clinical examination. In 1 other case an unsuspected rectal carcinoma was discovered at necropsy, and in 1 other case an apparently benign stricture of the splenic flexure was treated by colectomy and found on microscopy to be a carcinoma. In 4 cases, after routine colectomy and excision of the rectum, several carcinomata were discovered in the large bowel (fig. 8). In the 11th case an inoperable growth of the transverse colon was revealed at laparotomy done with a view to colectomy. As Dukes has emphasised a striking feature of these growths was that they were often multiple, often atypical in their gross appearance, in that they presented not as ulcerating lesions but as a slight " fibrous " thickening of the bowel wall, and on histological examination were usually found to be highly active and invasive (Counsell and Dukes 1952).

The precise incidence of neoplastic change in ulcerative colitis is difficult to estimate. Cattell (1948), reporting on the experience of the Lahey Clinic, states that no less than 1 in 3 of their cases of colitis of more than nine years' duration have developed carcinoma in the large bowel. In view of the fact that the symptoms and signs produced by a growth in these patients may easily be attributed to an exacerbation of the colitis and the presence of the neoplasm overlooked, we consider that the only safe course is prophylactic colectomy and removal of the rectum in all cases of ulcerative colitis sufficiently severe to require ileostomy. We do not know enough about the incidence of carcinoma in the milder forms of colitis, which would not usually be deemed severe enough to warrant surgical treatment, to say whether the danger of malignant degeneration justifies advising ileostomy and colectomy more often at this stage of the disease.

The policy in the earlier part of this series therefore was to advise colectomy and excision of the rectum only to patients who did not make a complete recovery in general health after ileostomy, or had complicating fistulæ, arthritis, or skin lesions. But now all cases are proceeding to this operation as a routine, and patients who have had ileostomy some years ago are being recalled for colectomy and excision of the rectum.

Interval between Ileostomy and Colectomy

Generally an interval of three to six months has been allowed to elapse after the ileostomy to give time for improvement in the general condition of the patient before proceeding to colectomy. More recently the tendency has been to shorten this interval and to do colectomy within three to six weeks of ileostomy, whilst latterly most of us have adopted as a routine the proposal of Miller et al. (1949) and of Bacon and Trimpi (1950) to do colectomy and ileostomy simultaneously. We hope that this will avoid the rare instances where the patient has not responded after ileostomy alone, and will also be associated with a more rapid restoration of general health than would occur after simple ileostomy. Colectomy may seem a serious addition to ileostomy in the sort of patient who presents for this operation, but it is not technically difficult ; and, if the distal end of the divided sigmoid colon is

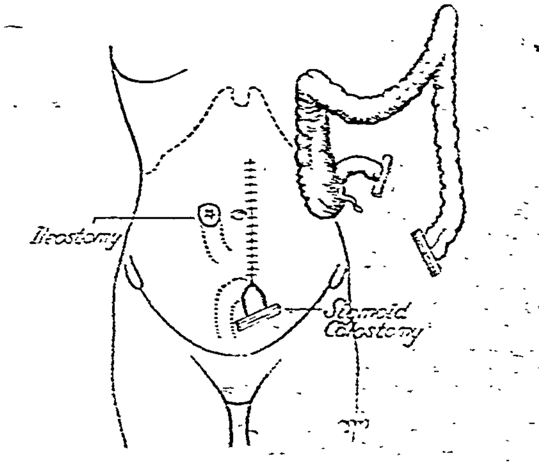


Fig. 9—Incision used for second-stage of subtotal colectomy, or for one-stage ileostomy and subtotal colectomy, and the amount of bowel removed at this operation. Note that distal sigmoid colon is brought to surface as colostomy at lower end of left paramedian incision.

brought out as a colostomy, no suture lines are created in the alimentary tract which might leak because of the patient's poor general condition. In fact the more gravely ill the patient the stronger is the argument for immediate colectomy, and the best results obtained to date in the treatment of acute fulminating ulcerative colitis, which is nearly always fatal if treated medically or by ileostomy alone, have been secured by immediate ileostomy and colectomy combined (Crile and Thomas 1951). We have treated 14 patients by simultaneous ileostomy and colectomy followed by excision of the rectum, and 4 by one-stage ileostomy and panproctocolectomy; all made speedy and successful recoveries.

Technique of Colectomy and Excision of Rectum

Some of the earlier colectomies were done as staged procedures, consisting of right hemicolectomy as the first stage, left hemicolectomy down to an iliac colostomy as the second, and excision of the rectum as the third, the intervals between stages being about three months. More recently, however, these have been reduced to two stages, the first comprising subtotal colectomy, and the second excision of the rectum. This is the technique described below.

First stage—subtotal colectomy.—A long left paramedian incision usually gives adequate access (fig. 9). If the distal ileum has been exteriorised, a circular incision is made round this and deepened into the peritoneal cavity. Through the main wound the peritoneum on the outer side of the cæcum and ascending colon is next divided as in a right hemicolectomy for cancer and the right colon mobilised, care being exercised at this stage to avoid damaging the ileostomy by too vigorous retraction. The greater omentum is next divided between forceps and the splenic flexure, and the descending and iliac colon fully mobilised. It merely remains now to tie and divide the ileocolic and right, middle, and left colic vessels and the medial leaves of peritoneum still attached to the colon. Finally the lower end of the iliac colon is brought out through the lower end of the main paramedian wound as an iliac colostomy. Since the sigmoid colon is thickened and friable, the usual type of crushing clamp, such as de Martel's or Parker-Kerr's, tends to cut right through the bowel and is therefore unsatisfactory. A very good clamp for this purpose is an enterotome fixed transversely across the bowel and tightened just sufficiently to grip the colon and to prevent it from falling back. We have preferred exteriorisation of the iliac colon in this way to the technique advocated by Brooke (1951) of dividing the bowel at a lower level and closing the rectal stump by intraperitoneal suture. We have been afraid that the unhealthy bowel wall would not lend itself well to suturing and might leak. We have not attempted to peritonealise the raw surface on the posterior-abdominal wall created by the excision of the colon. Of the 30 patients submitted to subtotal colectomy to date 2 have died, one of peritonitis and the other of paralytic ileus.

Second stage—excision of rectum.—28 cases have proceeded to excision of the rectum as a second stage. This has usually been done three to six months after subtotal colectomy but is perhaps better done rather sooner. The operation has followed the lines of a combined excision of the rectum, each surgeon using his normal technique for this procedure, either synchronous combined or perineo-abdominal excision. Owing to the perirectal fibrosis often present in these cases the excision has often been difficult. One patient died after removal of the rectum, death probably being due to a perforated peptic ulcer.

Colectomy with preservation of sphincter action.—This may take the form of a colectomy with ileosigmoid anastomosis, often done by the modification of the Mikulicz-Paul extraperitoneal colectomy technique described by Devine and Devine (1948), or may follow Ravitch's (1948) plan and consist of removal of all the colon and the proximal part of the rectum, "coring out" of the mucosa from the anorectal stump, and the establishment of a "pull-through" ileo-anal anastomosis. The former operation is really only suitable for cases in which the rectum and lower colon are unaffected by the disease, a state of affairs which, though apparently not uncommon in America (Cave 1945, Sloan et al 1950), is exceedingly rare in this country. In our experience the rectum is the part of the large bowel most consistently and usually most severely affected in ulcerative colitis; and, though the proximal extent of the disease may vary considerably from a point on the descending colon to as far as the cæcum or even the lower ileum, distally it practically invariably reaches to the mucocutaneous junction in the anal canal. Our opportunities for using this operation therefore have been limited, but in 4 cases, in which the rectum was only very mildly implicated, colectomy with ileosigmoid or ileorectal anastomosis was done. All 4 patients did well at first; owing to the loss of the greater part of the colon they had frequent motions but were perfectly continent. However, eventually one of the patients developed an anal abscess and fistula, and another, after remaining fairly fit for over a year, started to discharge a great deal of blood and mucus per rectum and suffered some loss of weight and failure of general health; both patients had their ileostomies re-established and the colorectal remnants removed. The other 2 patients are satisfied with their condition though they pass some mucus and blood with the motions and sigmoidoscopy shows that the rectal mucosa is still inflamed and therefore presumably liable to septic complications or to malignant degeneration. Having now accepted the possibility of carcinoma arising in the diseased large bowel as one of the dominating considerations in the management of ulcerative colitis we doubt if there can be much place for incomplete operations of this sort.

Proctocolectomy with ileo-anal anastomosis has the merit of removing all the diseased mucosa down to the mucocutaneous junction in the anal canal. Unfortunately this step also impairs rectal sensation with the result that the retained sphincters cannot act efficiently. We have only submitted 2 patients to this operation, but, as previously reported (Goligher 1951), they were both incontinent.

CONCLUSION

From this survey one fact emerges very clearly: ileostomy is but part of the surgical management of ulcerative colitis. Ileostomy alone often fails to secure the greatest improvement in general health or to prevent complications such as malignant degeneration, severe hæmorrhage, arthritis, and other metastatic manifestations of the disease. To achieve a complete cure the colon and rectum must be removed, and this should be the ultimate aim of the surgeon who undertakes to treat severe cases of ulcerative colitis. The present trend is towards earlier colectomy, which is perhaps best done simultaneously with the ileostomy.

We are greatly indebted to the surgeons of St. Mark's Hospital for permission to undertake this review of their cases; to Dr. Cuthbert Dukes and the Research Department, St. Mark's Hospital, for the photographs and pathological report on the case illustrated in fig. 8; and to Dr. P. N. Cardew and the photographic department, St. Mary's Hospital Medical School, for the photographs of ileostomy appliances in figs. 1, 2, 3, and 5.

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EFFECT OF WEIGHT-REDUCTION ON NORMAL AND RAISED BLOOD-PRESSURES IN OBESITY

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THERE is abundant evidence from life-assurance statistics and other sources (Hartman and Ghrist 1929, Levy et al. 1947, Boynton and Todd 1948, Green and Beckman 1948, Master et al. 1950) that people who are overweight have higher average blood-pressures than those whose weight is normal. Clinical experience also shows that obese hypertensive patients are subjectively improved by weight-reduction, which forms part of orthodox treatment. What is not so clear, however, is whether reduction in weight is likely to be followed by a significant fall in blood-pressure in cases of obesity with hypertension.

The relevant literature is by no means explicit on this matter, either because reports are founded on average figures for blood-pressure before and after weight-reduction in large series of cases, or because they only describe spectacular falls in blood-pressure in selected cases of obesity after treatment.

Master and Oppenheimer (1929) recorded their results in 99 obese patients of whom 65 had a systolic blood-pressure exceeding 150 mm. Hg. In 53 of the latter, whose average loss of weight was 25–30 lb., the average reduction of systolic pressure was 25–30 mm. Hg and of diastolic pressure 15–20 mm. Hg.

Terry (1923) observed in 24 obese hypertensive patients an average drop in blood-pressure from 196/103 mm. Hg before treatment to 170/95 afterwards, and in his patient with the greatest individual loss of weight (60 lb.) a fall in blood-pressure from 190/90 to 148/95.

Moreover it is not apparent in various similar reports that the common fallacies inherent in serial blood-pressure records have always been taken into account, and in general the clinician who wishes to know the likely effect of weight-reduction on the blood-pressure in any individual case will receive little help.

It therefore seemed worth investigating this question in obese patients with normal blood-pressures and in others with hypertension. By using a standard sphygmomanometric technique suitable for the clinic or the consulting-room, and by making proper allowances for variability in the expression of the results, it was hoped to reach conclusions of clinical value.

GENERAL CONSIDERATIONS

All blood-pressure readings obtained with a sphygmomanometer have inevitable and well-known sources of error which can be reduced or standardised to some extent by using a constant technique. In any investigation such as the present one, however, which entailed serial readings over several months, it was also desirable to allow for the well-known observation that the first reading is not uncommonly higher than any other (Diehl and Lees 1929). Neglect of this pitfall may clearly vitiate the results of a study involving the effect of any treatment on blood-pressure.

For example, if the widely cited paper of Rose (1922) be examined, in which presumably selected obese patients with hypertension were treated by diet and other measures, it is clear that in many cases very high initial readings had given a false impression of the efficacy of the treatment. Thus, in the first case the initial blood-pressure at a weight of 180·5 lb. was 204/110 mm. Hg, but seven days later, after only 2·5 lb. of weight had been lost, the blood-pressure was 178/100, and eleven months later still, when a further 20 lb. had been lost, 156/90.

Results of other series in which the effect of weight-reduction was measured solely by the first and last blood-pressure readings must be similarly suspect.

There is also the difficult problem of the circumference of the arm to which the sphygmomanometer cuff is applied. Ragan and Bordley (1941) made observations by arterial manometer and sphygmomanometer on 51 adult males (but avoiding "excessively obese individuals") and concluded that in those with an arm circumference of 30·0–42·5 cm. there was a positive error of 3 mm. Hg in the sphygmomanometric diastolic pressure for each 1 cm. increase in circumference. The same trend was followed by the systolic pressure, and an error of 30 mm. Hg might be attained. Wendkos and Rossman (1943), who estimated the blood-pressure in the thighs and arms of 500 people, found a higher average reading of 154·8/91·9 mm. Hg in the thighs compared with 118·3/70·6 in the arms. This they attributed to the greater thickness of the thighs, and it is reasonable to suppose that the greater the thickness of soft tissues surrounding an artery the greater will be the pressure needed in the sphygmomanometer cuff to secure compression. Nevertheless, when the arm readings of Wendkos and Rossman are examined, it is seen that they only rose by an average of 6·6 mm. Hg systolic, and 3·3 mm. diastolic through a range of body-weights of 100–220 lb. These differences are small and unlikely to be of clinical importance but, with the findings of Ragan and Bordley, they show that the matter should be borne in mind when establishing criteria for significant falls in blood-pressure after reduction of weight in the obese.

MATERIALS AND METHODS

The present series consisted of 37 obese patients of whom 18 had normal blood-pressures and 19 had hypertension. None had chronic nephritis, malignant hypertension, or valvular heart-disease. They were unselected apart from fulfilling the criteria of having kept to Marriott's (1949) reducing diet and thereby lost at least 14 lb. in weight during a period of observation of at least six months. The only other treatment given was 'Dexedrine' 5 mg. twice daily to 17 patients to assist them to keep to the diet. It was considered that such dosage would not influence the blood-pressure, because published reports do not show any constant effect of *d*-amphetamine in doses of less than 20 mg. by mouth. Thus Dyer (1939) reported a rise of systolic blood-pressure of 10 mm. Hg in only 2 of 10 people given amphetamine sulphate 10 mg. by mouth.

Patients were seen monthly, and one blood-pressure estimation was made on each occasion from the right arm with the patient recumbent after a few minutes' rest. All the readings were taken personally in the outpatient clinic or consulting-room with which the patients were familiar, the same sphygmomanometer being used with the technique recommended by the Cardiac Society of Great Britain and Ireland (1939). Readings were recorded to the nearest 5 mm. interval above the observed level unless coincidence with a 10 mm. marking was obtained.

To reduce the errors of day-to-day variation and the possibility that the first reading might be the highest of a series, the average of the first three monthly readings was taken as the initial level of each patient. On this average figure each patient was classified as normal or hypertensive, and the arbitrary level of 160/90 mm. Hg

TABLE I—LOSS OF WEIGHT

Blood-pressure	No. of cases	Male	Female	Average age (yr.)	Average initial weight (lb.)	Average loss of weight (lb.)
Normal	18	5	13	46·0	218·8	42·3 (*19%*)
Hypertensive	19	6	13	48·8	212·6	35·7 (*16%*)

TABLE II—EFFECT OF WEIGHT-REDUCTION ON BLOOD-PRESSURE OF 18 OBESE PATIENTS WITH NORMAL BLOOD-PRESSURE

Case no.	Age (yr.)	Sex	Height (in.)	Period of observation (mos.)	Initial weight (lb.)	Weight lost (lb.)	Average blood-pressure (mm. Hg)		Result
							Initial	Final	
1	57	M	64·5	19	303	83 (*27·3%*)	147/83	123/78	Systolic lower, diastolic unchanged
2	61	M	65·5	9	215	49 (*22·8%*)	147/73	127/72	Systolic lower, diastolic unchanged
3	55	F	61·5	12	200	44 (*22·0%*)	138/82	137/83	Unchanged
4	41	F	67·5	6	202	31 (*15·4%*)	128/72	112/68	Unchanged
5	45	F	63·0	12	191	31 (*16·2%*)	128/80	125/78	Unchanged
6	27	F	62·0	16	198	15 (*7·6%*)	132/70	128/73	Unchanged
7	15	M	69·0	7	215	53 (*24·6%*)	120/60	112/57	Unchanged
8	48	M	69·0	8	301	79 (*26·2%*)	137/72	117/60	Systolic lower, diastolic unchanged
9	65	F	62·0	6	168	23 (*13·6%*)	158/82	165/77	Unchanged
10	34	F	59·5	8	204	53 (*25·9%*)	148/77	132/77	Unchanged
11	49	F	65·0	6	194	37 (*18·5%*)	155/82	140/78	Unchanged
12	17	F	64·0	6	217	57 (*26·2%*)	125/62	117/68	Unchanged
13	47	F	68·0	6	285	75 (*26·3%*)	157/83	145/78	Unchanged
14	54	F	61·0	6	196	36 (*18·4%*)	138/87	133/83	Unchanged
15	65	M	67·0	8	198	24 (*12·1%*)	132/73	153/82	Systolic higher, diastolic unchanged
16	66	F	60·5	7	177	22 (*12·4%*)	142/83	143/83	Unchanged
17	61	F	60·5	7	234	21 (*8·9%*)	133/83	138/78	Unchanged
18	23	F	68·5	6	241	29 (*12·0%*)	139/80	114/60	Systolic lower, diastolic lower

was taken as the dividing line between normality and hypertension.

Similarly, an average of the last three monthly readings was taken as the final level of blood-pressure after treatment. Under these conditions it was considered that a significant fall of blood-pressure could be claimed if the final average systolic or diastolic pressure showed a fall of, or exceeding, 20 mm. Hg or 15 mm. Hg respectively, compared with the initial average level.

RESULTS

Table I shows average values for age, initial weight, and loss of weight which are similar for the patients with normal blood-pressure and the patients with hypertension.

The effect of weight-reduction on each group was:

Normal Blood-pressure (18 cases, table II).—Systolic and diastolic levels were unchanged in 13, both were lowered in 1, and systolic pressure alone was lowered in 3 and raised in 1.

Hypertension (19 cases, table III).—Systolic and diastolic levels were unchanged in 12, both were lowered in 2, and systolic pressure was lowered alone in 5.

Statistical Analysis

Examination of the protocols of each case led to the following conclusions:

(1) There was an over-all significant regression of systolic blood-pressure on weight having a value of + 0·35 ± 0·08, meaning that, on average, the blood-pressure was reduced by *3·5 mm. Hg for every 10 lb. of weight lost.* There were considerable individual variations, but it was clear that weight-reduction in the series as a whole did have some slight effect on blood-pressure.

(2) No significant differences were found between the two groups or between males and females, and there was no particular correlation with the patient's age or initial weight.

(3) More information might have been obtained from more extensive data, but on the present material there is no suggestion of any striking relation between weight-reduction and changes in systolic or diastolic blood-pressure.

DISCUSSION

Although statistical analysis has shown a significant regression of systolic blood-pressure amounting to about 3·5 mm. Hg for each 10 lb. of weight lost, this finding is insufficient to be of clinical importance. Admittedly there were individuals in the present series who did show clinically significant falls of blood-pressure in response to dieting. But unfortunately they did not provide any evidence or characteristics upon which such a response could be predicted in future cases. Thus it must be concluded from the present series, in accord with the opinion of Green and Beckman (1948), that the effect of weight-reduction on blood-pressure in obesity with hypertension is both inconstant and unpredictable. Nevertheless the chance of an occasional success, coupled with subjective improvement in the great majority of cases, appears to justify the continuation of weight-reduction as a routine measure in obese hypertensive patients. Moreover the loss of a substantial weight of fat must reduce the demands made on the heart during ordinary daily life, quite apart from strenuous exertion.

SUMMARY

37 obese patients, of whom 18 had normal blood-pressures and 19 hypertension, were treated by weight-reduction.

According to the criteria specified, a clinically significant fall in systolic blood-pressure, alone or with the

TABLE III—EFFECT OF WEIGHT-REDUCTION ON BLOOD-PRESSURE OF 19 OBESE PATIENTS WITH HYPERTENSION

Case no.	Age (yr.)	Sex	Height (in.)	Period of observation (mos.)	Initial weight (lb.)	Weight lost (lb.)	Average blood-pressure (mm. Hg)		Result
							Initial	*Final*	
1	57	F	63·5	7	177	22 (*12·4%*)	177/97	138/92	Systolic lower, diastolic unchanged
2	32	M	75·5	7	343	58 (*16·9%*)	158/95	128/77	Systolic lower, diastolic lower
3	38	M	60·0	14	234	46 (*19·9%*)	198/107	193/102	Unchanged
4	55	F	62·5	12	202	37 (*18·3%*)	160/90	157/100	Unchanged
5	42	F	66·0	7	292	58 (*19·8%*)	155/97	153/95	Unchanged
6	53	M	69·5	14	233	30 (*12·8%*)	177/100	165/97	Unchanged
7	42	F	60·0	14	137	14 (*10·2%*)	183/102	195/100	Unchanged
8	45	M	70·5	6	225	29 (*12·8%*)	185/122	158/102	Systolic lower, diastolic lower
9	48	F	68·5	11	183	19 (*10·3%*)	176/92	140/80	Systolic lower, diastolic unchanged
10	51	F	60·0	10	266	45 (*16·9%*)	163/73	152/75	Unchanged
11	47	F	64·0	8	223	43 (*19·2%*)	167/88	133/82	Systolic lower, diastolic unchanged
12	34	F	64·0	6	186	44 (*23·6%*)	165/75	150/82	Unchanged
13	35	F	61·0	6	234	57 (*24·3%*)	162/87	123/72	Systolic lower, diastolic unchanged
14	56	M	65·0	15	186	22 (*10·7%*)	200/112	183/107	Unchanged
15	59	M	64·5	16	199	35 (*17·5%*)	153/105	142/92	Unchanged
16	58	F	65·0	12	192	23 (*11·9%*)	225/108	200/105	Systolic lower, diastolic unchanged
17	51	F	63·5	9	172	32 (*18·5%*)	210/105	208/103	Unchanged
18	68	F	62·0	6	157	21 (*13·3%*)	180/97	190/110	Unchanged
19	58	F	65·0	7	199	44 (*22·1%*)	197/127	182/115	Unchanged

diastolic blood-pressure, was observed in 4 cases with normal blood-pressures, and in 7 cases of hypertension.

No clinical or statistical evidence could be adduced to distinguish the cases in which the blood-pressure fell with weight-reduction from those in which it did not.

Statistical analysis revealed that, on average, the systolic blood-pressure was reduced by 3·5 mm. Hg for every 10 lb. of weight lost.

I am indebted to Mr. Norman T. J. Bailey, statistician to the medical school in the University of Cambridge, for making and interpreting the statistical analysis of the data.

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JEJUNAL DIVERTICULOSIS WITH HÆMORRHAGE

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MASSIVE gastro-intestinal hæmorrhage presents a diagnostic as well as a therapeutic problem. Estimates of the proportion of cases attributable to peptic ulceration of the stomach or duodenum vary from 59 to 90% (Ivy et al. 1950), and œsophageal varices are also a common cause. But there are many other possibilities, one of which is illustrated by the following case.

CASE-RECORD

A Civil Service clerk, aged 59, was admitted to the London Hospital shortly after midday on June 15, 1948, in coma.

History.—For about five months he had complained of increasing lassitude and of central abdominal discomfort, which he later described as "a pulling on the navel." Three months before admission a hydrocele on the right side had been tapped. Ten days before admission he vomited once (there was apparently no obvious blood in the vomit) and soon after this he passed a copious black tarry stool. Next day he passed some bright-red blood, with clots, and his stools on subsequent days were tarry. He was sigmoidoscoped four days before admission, but without much success, because of a rather loaded bowel. He was not seriously ill until ten hours before admission (2 A.M. on June 15), when he began to lose bright-red blood per rectum; this hæmorrhage continued. His bowels were normally regular; he had had no abdominal injury, recent acute infection, or dietary indiscretion; and he rarely took aspirin, because it always gave him acute abdominal discomfort. He had not had any recent acute emotional disturbance. He had been gaining weight in the past few years. There was no significant family history.

Condition on Admission.—He was an obese elderly man in coma, with gross pallor of the skin and mucosæ, a weak pulse, and a blood-pressure of 100/65 mm. Hg.

Treatment and Progress.—He was given an immediate transfusion of 1 pint of plasma followed by five pints of blood. Next day he spoke on being roused but was rather confused; his blood-pressure had risen to 170/100 mm. Hg. Three days after admission he was much better, with Hb 10·5 g. per 100 ml. Eight days after admission sigmoidoscopy to a distance of 22 cm. revealed no abnormality. He was well at this time, but two days later, on getting up, he felt faint and passed two tarry stools; that evening he became pale and shocked, with sighing respiration, and his blood-pressure fell to 90/60. He was given a further transfusion of 3 pints of blood. Next morning, about 8 A.M., he passed about 3 pints of bright-red blood, including some clots, into the bed. A third transfusion, of 5 pints of blood, was started. That afternoon he vomited 10 fluid oz. of dark-brown "coffee-ground" material; however, by midnight he was conscious and rational. Two days later (June 28) he had another transfusion, this time of 3 pints of blood, and two days after that (June 30) his Hb was 7·6 g. per 100 ml. At about 3 P.M. on that day he suddenly complained of a feeling of impending death, became pale, and sweated profusely; his pulse became weak and rapid, while his blood-pressure fell to 80/60. He was given another 4 pints of blood and his condition improved; he passed a small black stool (about 1½ fluid oz.) that evening. Next day his general condition was fairly good, and his blood-pressure had risen to 160/95 mm. Hg; but it was decided to perform an exploratory laparotomy, with a view possibly to emergency partial gastrectomy. Penicillin 100,000 units twice daily was started. The bleeding-time and clotting-time were both normal.

Operation (Mr. E. C. B. Butler).—The abdomen was opened through a right upper paramedian incision under thiopentone and cyclopropane anæsthesia with curare. No abnormality was found in the stomach or duodenum. There were numerous saccular diverticula, 1·0–5·0 cm. in diameter, in the first 3 or 4 ft. of the small intestine below the duodenojejunal flexure, on the mesenteric border, with evidence of recent fibrinous peritonitis over many of them. The part most severely affected was that immediately below the duodenojejunal flexure, and here one diverticulum contained a concretion which could be extruded easily into the lumen of the bowel and was small enough to be passed without difficulty. The small intestine contained no blood except in the lowest 1 or 2 ft. of the ileum; the cæcum and colon contained much dark-red blood but were otherwise apparently normal. The liver and spleen both appeared normal. It was considered that the source of the bleeding was the diverticulum containing the enterolith. Resection of the affected segment of bowel would have been the treatment of choice, but it was thought inadvisable to embark on this in a fat elderly man debilitated by severe hæmorrhage. The abdomen was closed without drainage.

Postoperative Course.—The patient was given 3 pints of blood during and after the operation, making a total of 23 pints since admission. There was no recurrence of the bleeding. On July 19 his Hb was 11·6 g. per 100 ml. On July 22 (three weeks after laparotomy) he was discharged from hospital free from abdominal pain. He has since been seen regularly and has had no more intestinal hæmorrhage; and four years after operation he was in good health. However, because resection was impracticable, he may possibly have a recurrence.

COMMENT

Diverticulosis of the jejunum has been reviewed fully, with a report of 13 cases, by Orr and Russell (1951). It may be diagnosed during life radiologically after an opaque meal, or it may be found as an associated abnormality at necropsy, or it may draw attention to itself by causing intestinal obstruction (Gordinier and Sampson 1906), perforation (Butler 1937, Scholefield 1946), or severe bleeding (Braithwaite 1923, Tengwall 1931, Klidjian 1946, Kozoll et al. 1950). Berger et al. (1951) have reported 2 further cases of hæmorrhage, but it is impossible to be certain in one of their cases that the jejunal diverticulosis was the only or the primary cause of the hæmorrhage. Of Orr and Russell's (1951) patients, 4 had had hæmorrhage, never so severe as to threaten life. Klebs (1869) described the association of diverticula of the small intestine with the point of entry of arteries, and Fischer (1900) pointed out the very close anatomical relation of blood-vessels to even the smallest diverticula in a case of diverticulosis of the ileum; it is not difficult to see why serious hæmorrhage may occur.

The formation of enteroliths in the diverticula is a source of further trouble; in Klidjian's (1946) case it was apparently the diverticulum containing a concretion from which the bleeding had come, and Armitage et al. (1950) attribute the recurrent attacks of abdominal pain in their patient to intestinal obstruction caused by an enterolith becoming alternately impacted in the ileum and released. In the present case the bleeding probably came from the diverticulum in which the enterolith was; certainly, after this had been dislodged at operation, there was no more hæmorrhage.

Jejunal diverticulosis, though rare, should be borne in mind as a cause of massive intestinal hæmorrhage. Kozoll et al. (1950) describe how failure to recognise it cost their patient a second laparotomy. Gastro-intestinal hæmorrhage is a clinical event, not an ultimate diagnosis.

I am indebted to Mr. E. C. B. Butler for permission to publish this case.

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CEREBRAL DISEASE DUE TO FUNCTIONING ISLET-CELL TUMOURS

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The interest of the following six cases lies in the similarity of the clinical course. Relations used identical phrases to describe the onset; house-physicians made similar notes about the appearance of the patients on admission; and consultants seem to have gone through similar mental processes and reached the same conclusion. It is odd that such a constant syndrome should be so little appreciated; but islet-cell adenomas are usually small and must often have been overlooked at necropsy.

These six cases are the only ones recognised in the London Hospital in the last five years. Each presented as a neurological problem. Patients attending a teaching hospital are a selected sample. The first four cases were recognised as unusual and thus referred to the large neurological and neurosurgical clinics under Sir Russell Brain and Mr. D. W. C. Northfield; the fifth patient attended a hospital for nervous diseases. Possibly other patients in the region with islet-cell adenomas presented with psychological disturbances and were referred to mental hospitals (Fraser et al. 1938). The symptoms of the disease must largely be determined by the constitutional susceptibility exposed to the stress of the functioning tumour.

CASE-RECORDS

Case 1 (L.H. record no. 21051. 48).—*A married woman,* aged 43, was transferred to the London Hospital neurosurgical unit on April 14, 1948, from Queen Mary's Hospital, Stratford, with a provisional diagnosis of "hypothalamic tumour." An accompanying letter from Dr. H. J. Goldsmith, the house-physician, stated that she was originally thought to be suffering from the after-effects of a hypoglycæmic attack, but that this diagnosis had been reversed by the consultants who had seen her.

Background.—Her husband, a bus conductor, said that they had been married for 23 years. Their only son was grown up, and his wife had gone out to work again in a wholesale grocery. She was a sensitive person but, apart from a left Bell's palsy at the age of 23, her health had always been good. Menstruation was normal and there had been no recent change in weight. In October, 1947, she began to get peculiar sensations in her right leg. She would sit down and grasp her right foot, which was inverted. There were several of these attacks, mostly in the mornings. Each attack lasted several minutes. At the same time she seemed excited. She spoke of having morbid thoughts "of things that would not happen." During November, nearly every Sunday morning, there were attacks in which her arms and legs shook for several minutes. The day before Christmas she could "hear, think, and see" but could not move or speak. On Christmas morning her speech was thick and unintelligible. She was sweating but not trembling. She permitted passive movements of her limbs but was incapable of active ones. After about 15 minutes she said "I can move my arms now." On the morning of Dec. 26, 1947, she complained of stiffness of her legs, with inversion of the right foot. There were also occasional spontaneous arm and foot movements. On Dec. 29 she was seen in the London Hospital neurological outpatient department, but no evidence of any anatomical lesion was found, and her husband seems to have got the impression that the attacks were considered to be hysterical. She continued to be drowsy in the mornings. On March 26, 1948, she was particularly drowsy. When asked "*What are you doing in bed?*" she gave a hysterical laugh, and for the next three hours her hands trembled. This was followed by loss of consciousness until 4 o'clock next morning, when she woke up, had a meal, and said: "I musn't have another turn like this, Mum." On March 28, 1948, she spoke to her husband on waking and decided to stay in bed as it was a holiday. At 10.30 A.M. she was found unconscious, and on March 30, without having regained consciousness, she was admitted to Queen Mary's Hospital, Stratford.

On admission her temperature was 97·8°F, pulse-rate 92 per min., and blood-pressure 160/100 mm. Hg. Her limbs were hypotonic, and there were feeble withdrawal movements to painful stimuli. There was no response to speech. The eyes made occasional roving conjugate movements, and there was sluggish lid closure on corneal irritation. The pressure and contents of the cerebrospinal fluid (C.S.F.) were normal on lumbar puncture.

Treatment and Progress.—Initial treatment was based on the supposition of barbiturate poisoning, but chemical tests did not confirm this. On April 6, 1948, the fasting blood-sugar level was 38 mg. per 100 ml. During the next week the patient passed gradually into a state of decerebrate rigidity. There were attacks of generalised sweating in which her skin went very red. There was constant slight variable pyrexia. The blood-pressure fluctuated between 150 and 240 mm. Hg systolic and 120 and 160 mm. Hg diastolic; the pulse-rate remained about 80. A revised provisional diagnosis of irreversible damage due to hypoglycæmia was made; but, since various consultants considered this unlikely, the patient was transferred to the London Hospital neurosurgical unit. From April 13 to 23 her temperature fluctuated from 99° to 101°F and her pulse-rate from 94 to 132. Ventriculograms were substantially normal. The lesion was thought to be an infiltrating glioma situated high in the brain-stem and probably involving the hypothalamus. On April 24, the patient was transferred back to Queen Mary's Hospital.

Readmission.—On May 16, 1948, Dr. Goldsmith wrote suggesting readmission to the London Hospital for a further encephalogram. The patient was said to be slightly more attentive, less drowsy, and able to recognise people and single words. The similarity to the picture described by Cairns et al. (1941) as akinetic mutism was emphasised. The fasting blood-sugar level on May 5 was 72 mg. per 100 ml. Feeding by gastric tube during this time included two pints of milk plus 110 g. of glucose a day. From June 8 to 19 the patient was again observed in the London Hospital; little change was found. The look in her eye was described as intelligent and observant, but there was no response to voice or to painful stimuli. At times she made meaningless noises when disturbed. There was extreme decerebrate rigidity with generalised sweating. The blood-pressure was 200/130 mm. Hg, the pulse-rate usually 100–130, and the temperature about 100°F. A ventriculogram showed little abnormal. Vascular degeneration secondary to chronic nephritis was suggested but was excluded by renal-function tests. On June 19, 1948, the patient was transferred back to Queen Mary's and on June 26, she died. The body was sent to the London Hospital for necropsy. Dr. Goldsmith, who had never abandoned the original diagnosis of an islet-cell adenoma, asked that the pancreas should be specially examined.

Necropsy (P.M. 221. 48).—The necropsy was made 48 hours after death. The body, which had been in the cool chamber for only part of this time, was that of a moderately nourished woman with two ulcerating bed-sores on the dorsum of either foot. The chief findings were degeneration of the central nervous system from hypoglycæmia, and an islet-adenoma of the pancreas. A trephine opening was present in each parietal bone. There was a slight excess of fluid in the subarachnoid spaces. There was slight grey thickening of the leptomeninges in the cisterna interpeduncularis. The main cerebral arteries were normal, and the spinal cord was of normal external appearance. A well-defined soft pinkish-red nodule, measuring 1·0 × 0·8 cm., was found near the inferior border of the body of the pancreas, which was small and soft. Two thrombotic vegetations were present on the free margins of the anterior and posterior cusps of the mitral valve, together with slight, microscopically inactive, chronic rheumatic endocarditis of this valve. There was slight general atheroma. The lungs, liver, spleen, and kidneys were slightly congested. Two small adenomas were found in the thyroid gland. The other endocrine glands appeared normal. The stomach showed congestion and post-mortem digestion. Scattered submucous hæmorrhages, up to 1 cm. in diameter, were present in the lower ileum. The trigone of the bladder was extremely congested. In the upper 28 cm. of 41 cm. of the right femur the red marrow was hyperplastic.

Examination of brain and spinal cord after fixation showed that the brain had remained unusually soft in spite of prolonged fixation in formaldehyde. The cerebral hemispheres were symmetrical, the convolutions being uniformly slightly atrophied. Descending degeneration of the pyramidal tracts was found in the basal parts of the pons, shrinkage of the pyramids in the upper medulla, and creamy opacity of both lateral columns of the spinal cord, corresponding to the crossed pyramidal tracts, and of the direct tract on the right side. Both lenticular nuclei were shrunken and reddish-brown. In other respects the central nervous system appeared normal.

Histology.—The *brain* showed massive loss of neurones in the cerebral cortex, confined to the hippocampal gyri, where in Ammon's horn there was extensive laminar necrosis accompanied by an active microglial reaction shown by impregnation with silver. These cells were laden with sudanophil droplets. There was also here a moderate proliferation of astrocytes. In other parts of the cerebral cortex there was no massive loss of neurones, though individual cells had been destroyed and were replaced by small groups of reacting microglial cells. Gross post-mortem degeneration precluded further estimates of stages of significant neuronal degeneration; in the subcortical white matter diffuse areas of partial demyelination were associated with disseminated droplets of sudanophil lipoid and small aggregates of fat-laden phagocytes in adjacent perivascular spaces. The degree of demyelination varied in different parts of the cerebrum. A patch of complete necrosis beneath the right area striata was occupied by numerous compound granular corpuscles, and in one focus these had taken the place of the overlying cortex. There was great loss of neurones in the lenticular nuclei, especially in the globus pallidus; the large cells of the latter had completely disappeared apart from a few "ghosts." In silver preparations there was intense microglial proliferation, diminishing in the putamen. Slight gliosis was present. In the hypothalamus the supra-optic nucleus (one side only was examined) was intact, though the cells were in stages of chromatolysis (probably a post-mortem change). The paraventricular nucleus could not be recognised; but, since the ventricular wall had been lost through softening, it was by no means certain that this nucleus had been completely destroyed. No further observations could be made on this region, because of gross softening. Short stretches of the cerebellar cortex were devoid of Purkinje cells, but most had survived. Apart from this there were no noteworthy changes in the cerebellum. The descending pyramidal degeneration throughout the brain-stem and spinal cord was incomplete; many microglial cells with swollen bodies infiltrated the tract and were, in places, so closely aggregated that they resembled multinucleate foreign-body giant cells. There did not appear, however, to be complete fusion of their cytoplasm. The *adenoma of the pancreas* was composed of a solid mass of small polygonal cells. Although post-mortem degeneration was fairly advanced, the resemblance to islet-cells was obvious. The cells were supported by an anastomosing framework of connective tissue and blood-vessels, which was not so prominent as usual in tumours of this class. Elsewhere the islets were numerous and conspicuous.

Comment.—It is regrettable that post-mortem degeneration was so advanced in case 1. Death took place during a spell of hot weather, and there was delay in transferring the body to the cold chamber. The changes in the central nervous system, however, corresponded closely to those recognised in death following a hypoglycæmic crisis (Lawrence et al. 1942). In the series cited the length of coma did not exceed 17 days and subcortical demyelination was not observed. But Hsü and Ch'eng (1938) found this change in three cases when the patients survived carbon monoxide poisoning for 1–4 months; and O'Brien and Steegman (1938) found advanced demyelination of the cerebrum and partial demyelination of the pyramidal tracts in a woman who died 16 months after nitrous oxide anæsthesia, during which time she had gross impairment of cerebral function progressing to a state of decerebrate rigidity. In case 1 it is concluded that repeated hypoglycæmic attacks led to a final phase in which irreversible changes in the neurones were responsible for the clinical picture observed during the last 3 months of life.

Case 2 (L.H. record no. 36469. 50).—A married woman, aged 35, was admitted in coma to Whipps Cross Hospital on Aug. 31, 1950. Next day, still in coma, she was transferred to the London Hospital with a provisional diagnosis of a tumour of the third ventricle. She was under the care of Dr. A. E. Clark-Kennedy.

Background—According to her husband's story, they had been married 10 years. His wife had always been a healthy happy woman. She had never had fits, and he knew of no head injury. There were three children, aged 9, 6, and 4 years. The first time he noticed anything wrong was about three months before admission. He had left his wife asleep when he went to work, and when he got home at 4 P.M. she was still half asleep and sweating profusely. At first he was unable to rouse her. Later she recovered enough to eat an ice-cream, and after this she seemed normal again except that she could not remember what had happened during the day. During the next 2 months she made no complaints and behaved normally; then, about a month before admission, she had two similar attacks within 4 days. He found it impossible to wake her up until about 2 P.M., and each time he noticed that she was sweating profusely. In the next 3 weeks she had two further attacks. The attack which brought her into hospital was the fifth; it began on the morning of Aug. 31. This time he was unable to rouse her and sent for the doctor. At 9 P.M. she was admitted to Whipps Cross Hospital. According to the letter from Whipps Cross Hospital she made a partial recovery soon after admission but relapsed.

On admission to the London Hospital she was comatose and breathing stertorously. There was some sweating. Her face was flushed but not cyanosed. Her temperature was 103·4°F, pulse-rate 100, and blood-pressure 135/80 mm. Hg; no masses were felt in the abdomen; the heart and lungs appeared healthy. In so far as they could be tested the cranial nerves were normal. The limbs were held in extension and adduction, and passive movements were resisted. All the tendon-jerks were brisk, and there was an extensor plantar reflex on both sides. The C.S.F. pressure was normal and the C.S.F.-protein level was less than 20 mg. per 100 ml. There was no increase in the number of cells.

Treatment and Progress.—On Sept. 1, 1950, an intravenous injection of 100 ml. of 25% dextrose was given in the belief that this was a hypoglycæmic attack. There was no response; if anything, the coma deepened. Next morning the blood-sugar level was 100 mg. per 100 ml. and the blood-urea level 30 mg. per 100 ml. At 2 P.M. burr holes were drilled in both parietal bones. The C.S.F. pressure in the left ventricle was normal; the right ventricle was not found. After this the patient was put on nasal feeds. At 9 P.M. her blood-sugar level was 64 mg. per 100 ml. On Sept. 3 it was 180 mg. per 100 ml., and on Sept. 5, it was 118 mg. per 100 ml. The coma persisted. On Sept. 6, her temperature rose to 104·5°F and on Sept. 7 to over 105°F. Her pulse-rate and respirations increased, and on the 7th day after admission she died.

Necropsy (P.M. 324. 50.)—The necropsy was made 3 days after death. The body was that of an obese woman. The chief findings were purulent bronchitis, irreversible hypoglycæmic coma, and islet-cell adenoma of the pancreas. A dark-red nodule, measuring 1·3 × 0·7 c.m, was found on the anterior surface of the pancreas 2 cm. from the end of the tail and containing a pale creamy area, 0·3 cm. in diameter, in its substance. The rest of the pancreas had undergone post-mortem autolysis. The suprarenals, especially the left, showed central softening. The other endocrine glands appeared normal. The thymus was adipose and contained islands of glandular tissue visible microscopically. The myocardium, liver, spleen, and kidneys showed post-mortem degeneration. There was a splenunculus 1 cm. in diameter near the tail of the pancreas. There was slight general atheroma. No abnormality was visible in the brain (cut after fixation). Congestion, œdema, and purulent bronchitis were present throughout the lungs; microscopically there was early purulent bronchopneumonia in the left lower lobe.

Histology.—The *islet-cell tumour of the pancreas* lay in the border of the pancreas, being separated from the gland proper by a zone of fibro-adipose tissue. It was a solid mass, subdivided into two lobules of unequal size, of homogeneous character. Acini of compact polyhedral cells were separated by a highly vascular reticular stroma of connective tissue. The tumour cells were of even size, with eosinophil cytoplasm and oval or round nuclei with a rather coarse chromatin network and nuclear membrane. Because of the long interval between death and necropsy, specific staining of cytoplasmic granules was unsatisfactory. The islets in the adjacent pancreas were not remarkable; the remainder of the tissue showed moderate post-mortem degeneration. The *liver* showed moderate diffuse fatty change in the parenchymal cells, and many Kupffer cells were slightly distended by sudanophil droplets. A few groups of parenchymal cells contained granules of glycogen. The anterior lobe of the *pituitary gland* was conspicuously engorged; the glandular elements appeared to be normal, but post-mortem degeneration was considerable. The *brain*, in a coronal section through the right basal ganglia, crus cerebri, and hippocampal gyrus, showed diffuse congestion. In Ammon's horn there was advanced laminar necrosis of the neurones. These had either completely disappeared or were in stages of advanced degeneration and necrosis. There was no cellular reaction to the necrosis. In the optic thalamus a further area of necrosis, adjacent to the upper part of the internal capsule, was well defined and contained loosely grouped compound granular corpuscles. In the right lobe of the cerebellum there was a patchy loss of Purkinje cells; many of those present were in advanced stages of degeneration, with chromatolysis and karyolysis. The granule cells were well preserved.

Comment.—The islet-cell tumour of the pancreas had the characteristic appearances of the benign type, in situation, size, and microscopical appearances. That it was a functioning tumour cannot be doubted both from the clinical history and from the changes of anoxic type found in the brain. The special vulnerability of Ammon's horn is generally recognised in this connection, and the pattern of damage in case 2 conforms closely to those reported by Lawrence et al. (1942) in their series with hypoglycæmic manifestations. The focus in the optic thalamus must have been slightly older than that in Ammon's horn, in view of the phagocytic cells in the area, though these were scanty. The Purkinje cells of the cerebellum are recognised as being especially sensitive in anoxic and allied states; the patchy loss found in case 2 is therefore in conformity with the other changes found.

Case 3 (L.H. record no. 42178. 50).—A married woman, aged 36, was admitted to the London Hospital in coma on Oct. 26, 1950. Her history had been taken 12 days before in the neurosurgical outpatient department, and she was already on the waiting-list for admission under the provisional diagnosis of "hypothalamic tumour or paroxysmal hyperinsulinæmia."

Background.—According to her outpatient record she was happily married and had three children. Her general health was good and her appetite excellent. Menstruation had ceased abruptly in December, 1949, and since then she had gained about 3 st. in weight. Her husband described her attacks. The first one took place on the day before Christmas, 1949. She sat down in a chair after breakfast with a fixed stare and took no notice of what was said to her. From time to time she shut her eyes. After about 20 minutes she "came to" quite suddenly and carried on with her work as if nothing had happened. Three months later (March, 1950) there was a similar attack. In May, 1950, there were nine further attacks all within the space of 3 weeks. Each time the patient was described as sitting in a chair in a dreamy state with her eyes opening and shutting. From time to time she would jerk her legs in and out and throw her arms about. She would keep muttering over and over again: "What is the matter with me?" If her husband bathed her head in cold water the movements would stop, but she would not regain consciousness fully. An attack usually lasted about 5 hours. At that time she never fell down, bit her tongue, or hurt herself. She was incontinent of urine once, and once she was seen to be sweating. In August, 1950, she was admitted to another regional hospital, but no evidence of anatomical disease was found. Her electro-encephalogram (E.E.G.) was said to be grossly abnormal and compatible with epilepsy. A psychiatrist thought that her behaviour suggested rather hysteria than schizophrenic withdrawal. In the week after the patient had attended the London Hospital outpatient department the attacks became more frequent. Her husband complained that he had to get up at 5 A.M. to make her wake by 8 A.M. For 4 days before admission she was in a continuous dreamy state, muttering and talking about her activities of the week before. On the day before admission she had three more violent fits. Her arms and legs made clonic movements, her face and right eye twitched, she bit her tongue, and she frothed at the mouth. Between these fits she remained comatose.

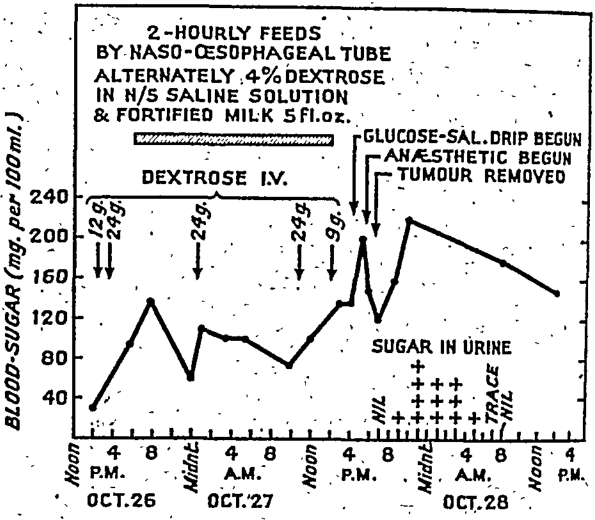

Fig. 1—Preoperative and postoperative blood-sugar levels in case 3.

On admission she was flushed but not sweating, her temperature was 100°F, her pulse-rate 110, and her blood-pressure 130/85 mm. Hg. No mass was felt in the abdomen, and her heart and lungs were normal. The specific gravity of her urine was 1·030; there was neither albumin nor sugar, but the Rothera test was positive. Her eyes were described as "roving." The pupils were dilated and equal; they reacted to light and accommodation. There was no facial weakness. The limbs were hypertonic, the tendon-jerks exaggerated, the plantar reflexes extensor, and the abdominal reflexes absent.

Treatment and Progress.—An islet-cell adenoma of the pancreas was diagnosed and confirmed by a blood-sugar level of 33 mg. per 100 ml. Intravenous dextrose was given, and within an hour there was a partial recovery of consciousness. The patient knew her name and address and her husband's name and age.

Operation.—The day after admission she was transferred to the surgical unit, and an adenoma of the pancreas, situated at the junction of the head and neck on the main duct, was excised. No other tumour was felt in the pancreas. The immediate preoperative and postoperative blood-sugar levels are shown in fig. 1.

Operation Specimen (S.D. 4880. 50).—This was a solid mass of tissue, 1·3 cm. in diameter and weighing 1 g., surrounded by tags of adipose tissue, and with a brown granular fairly homogeneous cut surface. Microscopically the adenoma, which measured 0·7 × 0·5 cm., was almost entirely enclosed by a fringe of normal pancreatic tissue from which it was well demarcated. The tumour was composed of trabeculæ and solid acini of small polygonal cells, closely resembling islet cells, and supported by an abundant vascularised stroma.

Convalescence and Follow-up.—During the next 3–4 days the patient slowly regained full consciousness, and 12 days after operation she was discharged to convalescence. She has attended the follow-up clinic at intervals. On Feb. 26, 1951, her E.E.G. still suggested epilepsy. She was last seen on March 20, 1952. Her weight seems to be keeping fairly constant at about 11 st. 2 lb. She describes herself as "very well indeed," and there have been no further dreamy states or fits.

Case 4 (L.H. record no. 36140. 50).—A married woman, aged 55, was seen in the London Hospital neurological outpatient department on Feb. 21, 1951. A cerebral tumour was provisionally diagnosed, and she was admitted at once under the care of Dr. Kenneth Perry.

Background.—According to the house-physician's notes, she was well built, well covered, and healthy-looking, with average intelligence. She had married at the age of 22, but there was only one child. She lived at home and looked after her husband. Menstruation ceased in 1949. In September, 1950, she had a hysterectomy for carcinoma of the fundus. Recovery from this was complete and satisfactory. In the next 3 months her weight fell from 13 st. to 12 st., but according to a note made in January, 1951, "she felt all the better for having lost some fat." The first sign of further trouble was on Feb. 4, 1951, when she woke up at 8.30 A.M. and went into the bathroom. After that she remembered no more until she found herself downstairs with her husband kneeling beside her. According to the husband's story he found his wife lying unconscious on the bathroom floor, "rolling about, tearing her hair, and talking nonsense." She did not regain full consciousness until about 12.30 P.M. In the afternoon she had severe biparietal headache, but she managed to do various household jobs. By the evening the headache had almost disappeared. On Feb. 9 and Feb. 17, 1951, second and third attacks came on. Both of them closely resembled the first, and both lasted about three hours. In between she felt perfectly well except for some anxiety about what was wrong. On Feb. 21, 1951, the day of admission, there was some clouding of consciousness. She remembered getting up in the morning, but after that her mind was a blank until she woke up in the ward. She was described in the outpatient notes as "rather stuperose."

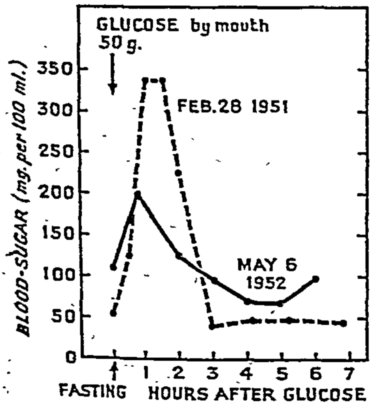

Fig. 2—Sugar-tolerance tests in case 4 before (Feb. 28, 1951) and after (May 6, 1952) removal of islet-cell adenoma of pancreas on March 2, 1951. Test on Feb. 28, 1951, followed small feeds at midnight and at 3 a.m.; there was no coma. On May 6, 1952, patient had fasted since 8 p.m. on May 5.

On admission physical examination revealed nothing of note. Her blood-pressure was 150/90 mm. Hg.

Progress.—Next day was uneventful, but on the day after that she had an attack at 5 A.M. in which she struggled, shouted, and kicked her legs. A few hours later she was quite normal and remembered nothing about it. The C.S.F. was normal on lumbar puncture. On the 4th day after admission she had an attack about noon, when she became drowsy and difficult to rouse. She is said to have murmured "Bread and butter" in answer to every question. Shortly afterwards she became restless and from time to time screamed in a high-pitched voice. Meanwhile her eyes were tightly closed. On Feb. 27, 1951, she was very drowsy and sweating at 8 A.M., when her blood-sugar level was only 33 mg. per 100 ml. At 10 A.M. she was given 60 g. of glucose by stomach-tube. Within 5 minutes she was quite rational.

Operation.—On Feb. 28, 1951, she was transferred to the care of Mr. Alan Perry, who removed a tumour from the lower border of the pancreas on March 2. The remainder of the pancreas was carefully palpated, but no other tumour nodules were felt. During the operation a continuous infusion of 5% glucose was given, but the quantity is not known. At the end of the operation the blood-sugar level was 125 mg. per 100 ml. 3 hours later it was 200 mg. per 100 ml.; and at 9.30 P.M., 7 hours after the operation, it was 300 mg. per 100 ml., and there was much sugar in the urine but no ketones. The result of a preoperative sugar-tolerance test is shown in fig. 2.

Operation Specimen (S.D. 905. 51).—This was a soft, purple, apparently encapsulated nodule, measuring 2·2 × 1·5 × 1·3 cm. and weighing 2·27 g., with strands of connective tissue attached to its surface. On section the cut surfaces were in part purple, soft, and finely granular, the rest being yellowish-white, firm, and almost rubbery. Microscopically a narrow zone of normal pancreas extended over the surface of the tumour in a few places. In its architecture and cytology the tumour closely resembled that in case 3, except that the collagen fibres of the stroma were more prominent and formed broad anastomosing bands throughout part of the tumour. In the interstices here the tumour cells were often in stages of degeneration.

Convalescence and Follow-up.—Recovery from the operation was uneventful, and there had been no further attacks of drowsiness or unconsciousness when the patient was last seen in September, 1952. The result of a sugar-tolerance test on May 6, 1952, is shown in fig. 2.

Case 5 (L.H. record no 11218. 52).—A man, aged 36, was transferred from the Belmont Hospital to the medical unit of the London Hospital on March 31, 1952, with a provisional diagnosis of islet-cell tumour.

Background.—He was married but had no children. His eldest brother had died in 1949 from "cancer of the lymph-glands." His two other brothers and his two sisters were well. He had recently become the manager of a small firm and enjoyed his work. He smoked 30 cigarettes a day and drank spirits occasionally. His previous health was good. There was no history of any important illness. The first symptoms occurred in January, 1952. He got up one morning and sat in an armchair. When his wife brought him a cup of tea, he did not answer her and "appeared to be in a trance." He remained like this for over 2 hours and then gradually came round. He remembered this attack and said that the $2^1/_2$ hours seemed like $2^1/_2$ minutes. Afterwards he felt "very weary." There were no muscular spasms, and he did not pass urine or bite his tongue. In February, returning from work at 6 P.M., after having had his tea at 4 P.M., he complained to his wife of double vision; the images were vertically displaced. The same thing

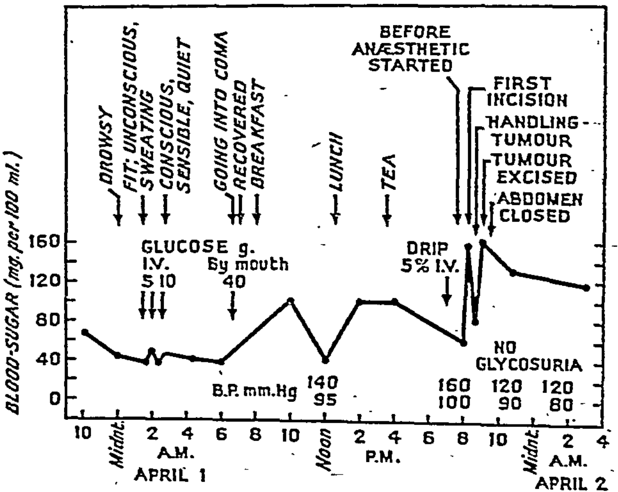

Fig. 3—Immediate preoperative and postoperative blood-sugar levels in case 5.

happened on the 2 following days. As a result of this he saw his own doctor and was referred to a hospital for nervous diseases. After a neurological examination and E.E.G. he and his wife were told the condition was functional. A week later attacks began to occur every morning. They tended to come on earlier and to leave him feeling weaker. When his wife shook him, he only muttered "all right, all right." She noticed that he sweated freely. In his later attacks, which lasted up to 4 hours, he sometimes passed urine in bed. Finally he began to get additional attacks at midday and in the evening. On the last occasion he had an attack on the way home and had to be helped home by two men as he walked "drunkenly" along the road. He knew where to go and recognised his wife. He was relieved to see her and then fell asleep for 10 minutes. When he woke up he said that he had had a dreadful dream and described what had happened. He was advised to go into Belmont Hospital, where Dr. M. N. Pai saw an attack and diagnosed hypoglycæmia.

On admission to the London Hospital the patient seemed quite normal and was described as intelligent and coöperative. His blood-pressure was 140/95 mm. Hg. At midnight he became drowsy and disorientated; he laughed, rolled his eyes, and smacked his lips, and his arms and legs twitched. He was flushed and sweating and finally passed urine. Soon after being given intravenous glucose he was well orientated again, smiling and talking amiably. During the attack his pupils were dilated but reacted to light and accommodation. Immediately after the attack the cranial nerves were normal.

Operation.—In the evening of April 1, 1952, he was transferred to the surgical unit and underwent laparotomy. The spleen and tail of the pancreas were removed. There were many nodules in the liver, and a part of one was removed for examination. The immediate preoperative and postoperative blood-sugar levels are shown in fig. 3.

Operation Specimens (S.D. 1438. 52).—The primary tumour replaced the tail of the pancreas, forming a mass measuring 5·5 × 3·5 × 3·0 cm. (after three portions each measuring up to 1·9 × 0·6 × 0·3 cm. had been removed for fixation in fluids other than formaldehyde) which infiltrated adjacent structures but did not invade the attached spleen. Its texture was firm and rather rubbery. A separate portion, from the liver, included a nodule, measuring 1·3 × 1·0 × 0·8 cm., of firm white granular growth. Microscopically the growth in the pancreas was composed of trabeculæ and solid acini of polygonal cells, which differed from those in the previous cases only in the varying size of the cells and of their nuclei and in a slight aberration in their chromatin-content. Mitoses were rare. There was considerable degeneration in many areas, with advanced pyknosis. The collagenous stroma was abundant, forming large hyaline masses in the centre of the tumour. Groups of the tumour cells infiltrated the adjacent pancreas, extending into the peripancreatic adipose and connective tissues both directly and by permeation of veins, lymphatics, and perineural sheaths. An adjacent lymph-node was almost completely superseded by tumour, in which the disparity in nuclear size was pronounced, some being of giant character, but again mitoses were very scarce. The metastasis in the liver was a solid mass of cells closely resembling those of the parent tumour; the collagenous stroma was scanty. Superficially the tumour abutted on the liver capsule; beneath this the liver parenchyma was well demarcated, and compressed by the tumour, but on the deep surface the tumour was intimately related to the liver cells.

Convalescence and Follow-up.—The patient made a good recovery and had no further attacks and never any glycosuria. He was given a 2000-calorie diet from April 3, 1952, and a 2500-calorie diet from April 11. His blood-sugar level rose and remained over 100 mg. per 100 ml., but his fasting blood-sugar level in the morning on April 17 was 47 mg. per 100 ml., and on April 19 at 8 A.M. 53 mg. per 100 ml. His wife, who was seen on May 20, said he was again having attacks in the morning. They responded rapidly to sugar.

In June he had further attacks of hypoglycæmia: it is hoped to report his subsequent course and treatment with cortisone at a later date.

Case 6 (L.H. record no. 22594. 51).—A man, aged 45, was admitted under the care of Dr. Kenneth Perry to the London Hospital in coma at 12.15 P.M. on June 8, 1951. He died at 1.30 A.M. on June 9, without regaining consciousness. The provisional diagnosis was cerebral hæmorrhage.

Background.—He was a single man employed as a street vendor. His mother died at the age of 40 with "sugar in the water." He lived alone in a room; previously he had lived with his father. His father died in February, 1950, aged 72. Of his three brothers, two were dead and the third, aged 52, was alive and well. He seldom saw his brother. He served in the Royal Artillery in 1942–43 and was discharged as medically unfit. His brother did not know the reason for his discharge from the Army. In 1944 the family first noticed he was having "fits." On the first occasion he got out of bed without any clothes and wished to run across the road. He was stopped and shortly afterwards became "queer and fainted." He was well again within a few hours; he remembered nothing of the attack. He was referred to St. George in the East Hospital. A letter from this hospital stated that he was admitted on May 8, 1946, semicomatose after an epileptiform fit. On May 11, 1946, his blood-sugar level was 30 mg. per 100 ml. A Wassermann reaction was negative; there was no abnormality in the C.S.F.

Operation.—He was readmitted on June 25, 1946, and underwent laparotomy on Oct. 16. No obvious pancreatic tumour was found; so the body and tail of the pancreas were removed. After operation his blood-sugar level was normal. Microscopy of the specimen was inconclusive but suggested "an excessive number of islets of Langerhans."

Follow-up.—He attended as an outpatient and was apparently well until December, 1947. Little is known about him from that time until his death. His neighbours thought he had "fits." In June, 1951, he was not seen for a week; so the police were called. His room was entered; he was found in coma and brought to the London Hospital. He was unkempt and had pressure sores on the left chest and trochanter. His temperature was 97·8°F, pulse-rate 104, and respirations 30 a minute. His blood-pressure was not registrable. His abdomen bore the scar of the previous operation. His pupils were dilated and did not react to light, and the corneal reflexes were absent. So far as they could be examined the other cranial nerves were normal. The left arm was spastic and the right flaccid, and the abdominal reflexes were absent. In the lower limbs the knee-jerks and ankle-jerks were absent and the plantar responses extensor. The urine contained neither sugar nor ketones, but there was a trace of albumin; the blood-sugar level was 437 mg. per 100 ml. (both urine and blood estimations were repeated). Lumbar puncture showed the C.S.F. at low pressure, containing protein 70 mg. per 100 ml. and sugar 306 mg. per 100 ml. (the accuracy of these estimations is open to doubt because they were done at night by an inexperienced house-physician).

Necropsy Findings.—The necropsy was not done in this hospital; the chief findings were bronchopneumonia and a tumour "adherent to the peritoneal surface and the posterior wall of the stomach close to the cardia. It was generally speaking rather soft and hæmorrhagic and in one place was partly calcified." No abnormality was noted about the pancreas. There was no gross disease of the brain. The pathologist wrote that a suggestion had been made in his laboratory that the tumour was composed of islet cells and that death was due to hypoglycæmia. He thought, however, that this was "rather a wild shot." Subsequent microscopy of the tumour confirmed the strong resemblance to an islet-cell adenoma.

Owing to the lack of accurate clinical and pathological details case 6 is not considered in the discussion.

DISCUSSION

The cells of the central nervous system are highly sensitive to a fall in the blood-sugar level. At first the disturbance is only functional; later the damage is irreversible.

In all the present cases the pattern of symptoms suggested widespread damage to the brain, with hypothalamic disturbance in particular. The pronounced vegetative disorders—sweating, pyrexia, tachycardia, flushing, and, possibly, clouding of consciousness—led experienced neurological specialists to place the lesion in the hypothalamus in four cases. It is difficult to decide whether the predominance of the latter symptoms is due to a special susceptibility to hypoglycæmia of this part of the brain, or whether it is the dramatic manifestations in disease of this region which attract attention. In both fatal cases there were pyrexia and tachycardia. In case 2, the only fatal case in the London Hospital, there was terminal hyperpyrexia. There was thus in case 2 a close resemblance during the last stages to the effects produced when the hypothalamus is accidentally damaged during operation on neighbouring parts of the brain. In the brains examined at necropsy this region does not appear to suffer disproportionate anatomical damage.

Hypoglycæmia stimulates the production of adrenaline, which converts liver glycogen into glucose (Cannon et al. 1924). It has been suggested that an excess of circulating adrenaline is responsible for many of the symptoms (*Lancet* 1950, Thorn et al. 1943). The course of the present cases is against this hypothesis. The patients were sweating and flushed, not pale. Their symptoms were unlike those of an adrenaline-producing tumour. There was no evidence of paroxysmal hypertension. There is no mention in the notes of anxiety or of an anxiety type of trembling.

The course was rapid. Case 3 took 10 months to reach the comatose stage, or 7 months if the first solitary attack is excepted. Case 2 reached a stage of permanent coma in 3 months and died a week later. Case 1 reached the stage of permanent coma in 5 months but took another 2 months to die. The early attacks have been consistently in the morning; later, as in case 5, the attacks may come on some hours after a meal. This is a time when there is a functional hypoglycæmia, which probably, in the presence of the tumour, precipitates the attack.

One of the reasons why the diagnosis is missed is that the blood-sugar level is not necessarily low, and there may be no response when intravenous glucose is given. In case 4, who was seen 17 days after the first attack, the symptoms were paroxysmal and there was a prompt response to glucose. Case 5 also responded to glucose 2½ months after the onset of symptoms. In case 3 the response to glucose was only partial; in fact, she did not recover full consciousness until several days after the adenoma had been removed. In both patients with benign tumours who were successfully operated on there was transient postoperative glycosuria. This is a reassuring sign for the surgeon, who must always be anxious lest small adenomas of islet tissue have been left behind.

In cases 1 and 2 there was no biochemical evidence of hypoglycæmia and no response to intravenous glucose. In case 2 no low blood-sugar level was recorded. In case 1 there was a solitary reading of 38 mg. per 100 ml., but this could not be repeated or confirmed. It is difficult to explain this return of the blood-sugar level to normal. Prolonged hypoglycæmia of this severity possibly also damaged the insulin-producing cells of the adenoma.

If cases 1 and 2 had been correctly diagnosed, their lives might have been saved. Possibly, however, they would only have survived as idiots. The structural damage seen in the brains examined at necropsy shows that early diagnosis and treatment are of the greatest importance in the full recovery of the patient. The preoperative and postoperative E.E.G. in case 3 suggest permanent structural damage.

SUMMARY

Six cases with islet-cell tumour are recorded.

The pattern of symptoms, time of attacks, and course of the disease were consistent.

The evidence suggests that a disorder of the hypothalamus, rather than excess of adrenaline, is responsible for some of the clinical manifestations.

In the advanced cases the blood-sugar levels and response to glucose were inconsistent, leading to confusion.

The necropsy findings in two cases are described.

I wish to thank the physicians and surgeons of the hospital who allowed me to use their cases; and particularly Mr. D. W. C. Northfield and Dr. Denys Jennings for their help.

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EXAMINATION OF RIB BONE-MARROW FOR TUBERCLE BACILLI

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Two recent papers in America (Horowitz and Gorelick 1951, Hausmann 1951) as well as the publications of Choremis and Pantazis (1951, 1952) in Greece have drawn attention to the possibility of finding *Mycobacterium tuberculosis* in bone-marrow. It is to be expected that *Myco. tuberculosis* could be demonstrated in bone-marrow in miliary and acute hæmatogenous tuberculosis, but it is generally considered that one would be unlikely to find the bacillus in the bone-marrow of adult patients with the ordinary fibrocaseous or cavitatory type of pulmonary tuberculosis.

Schleicher (1946) found miliary tubercles in aspirated bone-marrow in 8 cases, and Peterson and Canfield (1945) suggested that it was possible to use bone-marrow for the differential diagnosis of miliary tuberculosis and typhoid fever. Horowitz and Gorelick (1951) examined the bone-marrow from various patients with the Ziehl-Neelsen technique and made cultures of it on suitable media, such as Löwenstein, Petragnani, Petroff, and Dubos. These patients had far-advanced pulmonary disease with toxæmia, or had a fever of unknown origin where laboratory investigations had been unrevealing. They claimed to show tubercle bacilli in the bone-marrow of 14 of 20 patients by direct examination of the aspirated material, but in only 5 of these 14 was the diagnosis confirmed by culture.

Choremis and Pantazis (1951) reported a positive blood-culture in 62·4% of 324 cases of tuberculosis, and 5 cases positive out of 17 in which sternal marrow had been cultured. Most of their patients were young children. Later Choremis and Pantazis (1952) got positive bone-marrow cultures from 16 of 65 children, most of whom had a primary complex, tuberculous pneumonia, or miliary tuberculosis. Smears were made of the aspirated material to make sure that it was bone-marrow, but Ziehl-Neelsen staining was not done.

On the other hand, Leitner (1949), in his study of 54 cases of hæmatogenous tuberculosis, obtained only one positive culture from aspirated sternal bone-marrow.

In addition Hausmann (1951) was unable to demonstrate tubercle bacilli by means of direct smear, marrow digest cultures, and surface scraping cultures taken from segments of ribs from 69 consecutive thoracoplasty stages of 34 patients. He therefore suggested that there would probably have been no risk of implanting tubercle bacilli into the recipient's tissues if any of the ribs studied in his series had been used as homogenous bone grafts. In fact, in 5 instances, rib fragments from thoracoplasty patients were successfully used as homogenous bone grafts for tuberculous lesions of bone.

INVESTIGATION

The purpose of the present investigation was to discover whether or not the bone-marrow of the ribs removed at thoracoplasty or pulmonary resection from patients known to have or to have had a positive sputum contained tubercle bacilli. It was also hoped that, if any of the bone-marrow gave a growth of *Myco. tuberculosis*, it might be possible to determine whether or not these tubercle bacilli were resistant to streptomycin, if the patient had a streptomycin-resistant strain of tubercle bacilli in his sputum. Bone-marrow was also aspirated in 3 cases of acute disseminated tuberculosis in adults.

28 men and 14 women had thoracoplasties, and 5 men and 5 women had resections. Additional bone-marrow was cultured from 6 men and 7 women who had had two stages and 1 woman who had had three stages. The total number of cultures from 52 surgical patients was 66. In addition, cultures from the bone-marrow of 3 cases of acute disseminated tuberculosis were set up; these 3 patients had not received chemotherapy at any time during their illness. 25 of the 28 men who had thoracoplasties had positive sputum during their stay in hospital before operation; 13 of these were also positive at operation. Of the 5 who had resections only 1 had negative sputum during his stay in hospital and previous to operation. 6 of the 14 women who had thoracoplasties had positive sputum while in hospital, but only 4 were positive at the time of operation. Of the 5 women who had resections 4 had had positive sputum, and 3 of these were also positive at operation. 19 men who had thoracoplasties had had previous chemotherapy with streptomycin and *p*-aminosalicylic acid before admission to this hospital, and 10 had similar chemotherapy at the time of operation, of whom 4 had had previous chemotherapy while in this hospital. Of the women 14 had had chemotherapy previous to admission, and 5 had it at the time of operation. Of the 5 men who had resections all received chemotherapy at the time of operation and 3 had had it before admission. Of the 5 women who had resections all were receiving chemotherapy at operation and 4 had had it before admission. Altogether 25 patients were receiving chemotherapy at the time of operation. The accompanying table gives these details.

PROCEDURE AND TECHNIQUE

At St. Wulstan's hospital it is usual for thoracoplasties to be done in two stages at fortnightly intervals, and in all seven ribs are removed. One surgeon prefers to do an eight-rib thoracoplasty in three stages.

All the ribs removed at thoracoplasty or resection were sent direct to the laboratory in a sterile container. They were split longitudinally with ordinary carpenter's pincers. Portions of each bone containing the most marrow were placed in a universal container which was then almost filled with sterile distilled water (30 ml.). It was well shaken and placed in the refrigerator at 4–5°C to ensure the separation of the marrow from the bone. The container was again shaken vigorously and the thick bone-marrow suspension poured off into a centrifuge tube, leaving the bone fragments in the universal container. The suspension was centrifuged at 3000 r.p.m. for about 5–8 minutes, the supernatant fluid being discarded, leaving a column of bone-marrow 2 cm. long in the bottom of the centrifuge tube (the actual amount yielded was not constant but was usually about 1·5 ml.). Smears were made from this deposit and stained by the normal Ziehl-Neelsen procedure, after which 3% sulphuric acid was poured on to the deposit in the ratio of 2 parts of acid to 1 of deposit. After thorough mixing with a sterile platinum sputum loop the mixture was allowed to stand at room-temperature for 5–10 minutes, and was next centrifuged at 3000 r.p.m. for 5 minutes. The supernatant fluid was discarded and the deposit was resuspended in a corresponding volume of sterile distilled water and neutralised with 2% sodium hydroxide, phenol red being used as indicator. The neutralised suspension was centrifuged once more, and the deposit was next cultured direct to the Löwenstein slopes, three or four good loopfuls (4–5 mm. loop) being used.

DETAILS OF PATIENTS FROM WHOM BONE-MARROW WAS OBTAINED

Surgical operation	No. of patients	Sex	No. with positive sputum		No. receiving chemotherapy			No. of specimens of bone-marrow examined
			Before operation	At operation	Type A	B	C	
Thoracoplasty	28	M	25	13	19	4	10	34
,,	14	F	6	4	14	0	5	22
Resection	5	M	4	4	3	0	5	5
,,	5	F	4	3	4	0	5	5
Total ..	52	..	39	24	40	4	25	66

Type A = Chemotherapy before admission only.
Type B = ,, after ,, ,,
Type C = ,, at time of operation.

In addition bone-marrow was aspirated from 3 men with acute disseminated tuberculosis who had positive sputum and had never received any chemotherapy. Cultures were negative.

Bone-marrow was aspirated in the region of the spinous processes of the lumbar vertebræ. The material was examined and inoculated in the same way as that removed from the ribs taken at thoracoplasty.

Several controls were set up by inoculating with a known strain of *Myco. tuberculosis* bone-marrow taken at thoracoplasty. From the resulting preparation suitable films were made and stained by the Ziehl-Neelsen technique, and cultures were put up.

RESULTS

In no case was it possible to demonstrate the presence of *Myco. tuberculosis* either by examination of the bone-marrow smear or by culture, but in the controls films showed the presence of *Myco. tuberculosis* and the cultures all proved positive.

Since these patients, undergoing surgical treatment, had neither the acute fulminating tuberculosis that Choremis and Pantazis (1951, 1952) found in their patients nor the widely disseminated tuberculosis that Horowitz and Gorelick (1951) observed among their patients, hæmatogenous dissemination was most unlikely, and therefore one would not expect to culture tubercle bacilli from bone-marrow.

This work thus confirms the results obtained by Hausmann (1951).

It is suggested that ribs removed at thoracoplasty or at resection could be used in orthopædic units for grafting in tuberculous disease of bone without risk of implanting tubercle bacilli into the tissue of the recipient.

I am indebted to Dr. T. W. Lloyd, medical superintendent, St. Wulstan's Hospital, Malvern, where this work was done, for permission to publish these results, and to Dr. *Colin* White for his helpful advice.

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FURTHER LIGHT ON MOUSE HEPATITIS

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THIS note is a postscript to a report (Gledhill et al. 1952) of the resolution of the ætiological agent of mouse hepatitis (Gledhill and Andrewes 1951) into two components—one (S) relatively stable, the other (L) more labile. Neither component inoculated alone into weaned mice caused evident illness, but when they were combined fatal hepatitis was produced. It now appears that the L component is identical with *Eperythrozoön coccoides*—a mouse parasite related to *Hæmobartonella* and variously regarded as a bacterium or a small protozoon. Our interest had already been aroused by finding L present in the blood in very high titre, when histological study led, as described below, to the finding of eperythrozoon in large numbers.

Histological studies of tissues from animals infected with the S and L components, together or separately, have yielded interesting results. With the techniques so far used in this study, no changes have yet been found with the L agent. With S small areas of hepatic necrosis occur, which differ only in degree from the massive lesions caused by the complex infection itself; both infections, and particularly the latter, were accompanied by varied cytological changes which will be described in detail later. The most unusual pathological feature of the experimental disease and of that due to the S component is the appearance of an endothelial and mesothelial reaction throughout practically all the organs and tissues; this begins within 24 hours of inoculation and has practically disappeared by the 5th day. The endothelial reaction is focal and is restricted to venous channels of all sizes; it is characterised by the formation of multinucleated giant-cells which arise directly from the endothelium, project into the vessels, and readily become detached. Examination of films of peripheral blood for these giant cells in animals infected 3 days previously with "mouse-hepatitis virus" revealed the presence of enormous numbers of *E. coccoides*, with characteristic ring forms. Many mice infected with S and L separately and combined have now been examined. In the L series *E. coccoides* appear in the blood within 2–3 days of inoculation In the S series no eperythrozoa have been found. In animals infected with "mouse-hepatitis virus" *E. coccoides* appear within 24 hours and increase in numbers until death, the terminal stage of the disease being accompanied by many small rod and coccal-forms which may preponderate over the typical ring elements. When S and L are combined to produce fatal hepatitis, the same morphological picture is found. So far it has not been possible to dissociate the activity of the L agent from *E. coccoides*, and it seems likely that they are identical. The L agent and the eperythrozoa react similarly to chemotherapeutic agents, including neoarsphenamine.

Many speculations arise immediately from this association; at present it is sufficient to emphasise the following observations:

1. *E. coccoides* occurs in the blood in experimental mouse hepatitis without previous splenectomy; and it can be passed without splenectomy in normal mice more readily than is usually believed.

2: Eperythrozoa in plasma can pass through a collodion membrane of average pore size 0·46 µ and 0·36 µ, and under ideal conditions probably also through membranes of 0·3 µ—a degree of filterability hitherto unsuspected.

3. Mice of the P strain, which are relatively resistant to hepatitis, are carriers of *E. coccoides*, while those of the V.S. strain, in which the disease can be readily transmitted, are not carriers of eperythrozoa and do not yield *E. coccoides* after splenectomy.

We have not yet elucidated the mechanism whereby the S virus and the eperythrozoon act synergistically to produce fatal hepatitis. It appears, however, that the S is present to about a hundredfold higher titre in the livers of mice in which there is concurrent infection with eperythrozoa. It may be that all strains of *E. coccoides* will behave as described here; but this remains to be proved.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Basis of Allergic Reactions

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Dr. W. N. GOLDSMITH said that eczema was an epidermal hypersensitivity reaction of the late or delayed type. The process was chiefly cellular, and in some instances—e.g., fixed drug eruptions—the reaction was strictly localised to circumscribed areas of the skin. Sensitising agents could be simple substances (even elements such as nickel or chromium) or more complex organic chemicals, such as paraphenylenediamine. Many of these substances showed a pronounced affinity for protein, and the actual allergen might be a complex of the substance with protein. Desensitisation had been attempted with mixtures of serum and the sensitising substance. Products of the skin itself—e.g., blister fluid—had been shown to act as sensitisers.

In animals intraperitoneal injection of picryl chloride had produced epidermal sensitisation. Where islands of skin had been created by means of deep incisions, the application of such substances to the islands failed to produce hypersensitivity, whereas application to the surrounding skin produced hypersensitivity both locally and in the islands. It had been suggested that this proved that the antibodies were elaborated centrally. However, a subject who had been sensitised by the application of 9-bromofluorene for 24 hours developed redness and blistering at the site of application 13 days later; and the process extended steadily towards the periphery. Dr. Goldsmith supposed that this was due to the slow diffusion of the allergen, successive areas becoming sensitised after the requisite time interval. This gradual progression was possible only if the antibody was produced locally in the skin.

In this type of reaction, passive transfer by serum usually failed, and where it succeeded the reaction was urticarial, not eczematous. Cross-transplants of skin had been made in uniovular twins, one of whom had been sensitised epidermally. The sensitised transplant lost its hypersensitivity in the normal host, whilst the normal transplant took on the hypersensitivity of the recipient. Similarly, a sensitised animal rendered parabiotic with a normal caused the latter to become hypersensitive. The agent was therefore diffusible, but it did not cross the placenta and its molecules were probably large. It did not reside in the plasma, since passive transfer failed; but possibly it was transported by lymphocytes. Hypersensitivity was not induced by injection of such lymphocytes into the skin itself, but followed intraperitoneal injection in animals. It was not clear how the antibody passed from the lymphocytes to the epidermis.

The injection of histamine did not cause eczema, nor was histamine released by the eczema reaction. Antihistamine substances did not have a preventive action.

In addition Hausmann (1951) was unable to demonstrate tubercle bacilli by means of direct smear, marrow digest cultures, and surface scraping cultures taken from segments of ribs from 69 consecutive thoracoplasty stages of 34 patients. He therefore suggested that there would probably have been no risk of implanting tubercle bacilli into the recipient's tissues if any of the ribs studied in his series had been used as homogenous bone grafts. In fact, in 5 instances, rib fragments from thoracoplasty patients were successfully used as homogenous bone grafts for tuberculous lesions of bone.

INVESTIGATION

The purpose of the present investigation was to discover whether or not the bone-marrow of the ribs removed at thoracoplasty or pulmonary resection from patients known to have or to have had a positive sputum contained tubercle bacilli. It was also hoped that, if any of the bone-marrow gave a growth of *Myco. tuberculosis*, it might be possible to determine whether or not these tubercle bacilli were resistant to streptomycin, if the patient had a streptomycin-resistant strain of tubercle bacilli in his sputum. Bone-marrow was also aspirated in 3 cases of acute disseminated tuberculosis in adults.

28 men and 14 women had thoracoplasties, and 5 men and 5 women had resections. Additional bone-marrow was cultured from 6 men and 7 women who had had two stages and 1 woman who had had three stages. The total number of cultures from 52 surgical patients was 66. In addition, cultures from the bone-marrow of 3 cases of acute disseminated tuberculosis were set up; these 3 patients had not received chemotherapy at any time during their illness. 25 of the 28 men who had thoracoplasties had positive sputum during their stay in hospital before operation; 13 of these were also positive at operation. Of the 5 who had resections only 1 had negative sputum during his stay in hospital and previous to operation. 6 of the 14 women who had thoracoplasties had positive sputum while in hospital, but only 4 were positive at the time of operation. Of the 5 women who had resections 4 had had positive sputum, and 3 of these were also positive at operation. 19 men who had thoracoplasties had had previous chemotherapy with streptomycin and *p*-aminosalicylic acid before admission to this hospital, and 10 had similar chemotherapy at the time of operation, of whom 4 had had previous chemotherapy while in this hospital. Of the women 14 had had chemotherapy previous to admission, and 5 had it at the time of operation. Of the 5 men who had resections all received chemotherapy at the time of operation and 3 had had it before admission. Of the 5 women who had resections all were receiving chemotherapy at operation and 4 had had it before admission. Altogether 25 patients were receiving chemotherapy at the time of operation. The accompanying table gives these details.

DETAILS OF PATIENTS FROM WHOM BONE-MARROW WAS OBTAINED

Surgical operation	No. of patients	Sex	No. with positive sputum		No. receiving chemotherapy			No. of specimens of bone-marrow examined
			Before operation	At operation	Type			
					A	B	C	
Thoracoplasty	28	M	25	13	19	4	10	34
,,	14	F	6	4	14	0	5	22
Resection	5	M	4	4	3	0	5	5
,,	5	F	4	3	4	0	5	5
Total ..	52	..	39	24	40	4	25	66

Type A = Chemotherapy before admission only.
Type B = ,, after ,, ,,
Type C = ,, at time of operation.

In addition bone-marrow was aspirated from 3 men with acute disseminated tuberculosis who had positive sputum and had never received any chemotherapy. Cultures were negative.

PROCEDURE AND TECHNIQUE

At St. Wulstan's hospital it is usual for thoracoplasties to be done in two stages at fortnightly intervals, and in all seven ribs are removed. One surgeon prefers to do an eight-rib thoracoplasty in three stages.

All the ribs removed at thoracoplasty or resection were sent direct to the laboratory in a sterile container. They were split longitudinally with ordinary carpenter's pincers. Portions of each bone containing the most marrow were placed in a universal container which was then almost filled with sterile distilled water (30 ml.). It was well shaken and placed in the refrigerator at 4–5°C to ensure the separation of the marrow from the bone. The container was again shaken vigorously and the thick bone-marrow suspension poured off into a centrifuge tube, leaving the bone fragments in the universal container. The suspension was centrifuged at 3000 r.p.m. for about 5–8 minutes, the supernatant fluid being discarded, leaving a column of bone-marrow 2 cm. long in the bottom of the centrifuge tube (the actual amount yielded was not constant but was usually about 1·5 ml.). Smears were made from this deposit and stained by the normal Ziehl-Neelsen procedure, after which 3% sulphuric acid was poured on to the deposit in the ratio of 2 parts of acid to 1 of deposit. After thorough mixing with a sterile platinum sputum loop the mixture was allowed to stand at room-temperature for 5–10 minutes, and was next centrifuged at 3000 r.p.m. for 5 minutes. The supernatant fluid was discarded and the deposit was resuspended in a corresponding volume of sterile distilled water and neutralised with 2% sodium hydroxide, phenol red being used as indicator. The neutralised suspension was centrifuged once more, and the deposit was next cultured direct to the Löwenstein slopes, three or four good loopfuls (4–5 mm. loop) being used.

Bone-marrow was aspirated in the region of the spinous processes of the lumbar vertebræ. The material was examined and inoculated in the same way as that removed from the ribs taken at thoracoplasty.

Several controls were set up by inoculating with a known strain of *Myco. tuberculosis* bone-marrow taken at thoracoplasty. From the resulting preparation suitable films were made and stained by the Ziehl-Neelsen technique, and cultures were put up.

RESULTS

In no case was it possible to demonstrate the presence of *Myco. tuberculosis* either by examination of the bone-marrow smear or by culture, but in the controls films showed the presence of *Myco. tuberculosis* and the cultures all proved positive.

Since these patients, undergoing surgical treatment, had neither the acute fulminating tuberculosis that Choremis and Pantazis (1951, 1952) found in their patients nor the widely disseminated tuberculosis that Horowitz and Gorelick (1951) observed among their patients, hæmatogenous dissemination was most unlikely, and therefore one would not expect to culture tubercle bacilli from bone-marrow.

This work thus confirms the results obtained by Hausmann (1951).

It is suggested that ribs removed at thoracoplasty or at resection could be used in orthopædic units for grafting in tuberculous disease of bone without risk of implanting tubercle bacilli into the tissue of the recipient.

I am indebted to Dr. T. W. Lloyd, medical superintendent, St. Wulstan's Hospital, Malvern, where this work was done, for permission to publish these results, and to Dr. Colin White for his helpful advice.

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FURTHER LIGHT ON MOUSE HEPATITIS

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THIS note is a postscript to a report (Gledhill et al. 1952) of the resolution of the ætiological agent of mouse hepatitis (Gledhill and Andrewes 1951) into two components—one (S) relatively stable, the other (L) more labile. Neither component inoculated alone into weaned mice caused evident illness, but when they were combined fatal hepatitis was produced. It now appears that the L component is identical with *Eperythrozoön coccoides*—a mouse parasite related to *Hæmobartonella* and variously regarded as a bacterium or a small protozoon. Our interest had already been aroused by finding L present in the blood in very high titre, when histological study led, as described below, to the finding of eperythrozoon in large numbers.

Histological studies of tissues from animals infected with the S and L components, together or separately, have yielded interesting results. With the techniques so far used in this study, no changes have yet been found with the L agent. With S small areas of hepatic necrosis occur, which differ only in degree from the massive lesions caused by the complex infection itself; both infections, and particularly the latter, were accompanied by varied cytological changes which will be described in detail later. The most unusual pathological feature of the experimental disease and of that due to the S component is the appearance of an endothelial and mesothelial reaction throughout practically all the organs and tissues; this begins within 24 hours of inoculation and has practically disappeared by the 5th day. The endothelial reaction is focal and is restricted to venous channels of all sizes; it is characterised by the formation of multinucleated giant-cells which arise directly from the endothelium, project into the vessels, and readily become detached. Examination of films of peripheral blood for these giant cells in animals infected 3 days previously with "mouse-hepatitis virus" revealed the presence of enormous numbers of *E. coccoides*, with characteristic ring forms. Many mice infected with S and L separately and combined have now been examined. In the L series *E. coccoides* appear in the blood within 2–3 days of inoculation In the S series no eperythrozoa have been found. In animals infected with "mouse-hepatitis virus" *E. coccoides* appear within 24 hours and increase in numbers until death, the terminal stage of the disease being accompanied by many small rod and coccal-forms which may preponderate over the typical ring elements. When S and L are combined to produce fatal hepatitis, the same morphological picture is found. So far it has not been possible to dissociate the activity of the L agent from *E. coccoides*, and it seems likely that they are identical. The L agent and the eperythrozoa react similarly to chemotherapeutic agents, including neoarsphenamine.

Many speculations arise immediately from this association; at present it is sufficient to emphasise the following observations:

1. *E. coccoides* occurs in the blood in experimental mouse hepatitis without previous splenectomy; and it can be passed without splenectomy in normal mice more readily than is usually believed.
2. Eperythrozoa in plasma can pass through a collodion membrane of average pore size 0·46 μ and 0·36 μ, and under ideal conditions probably also through membranes of 0·3 μ—a degree of filterability hitherto unsuspected.
3. Mice of the P strain, which are relatively resistant to hepatitis, are carriers of *E. coccoides*, while those of the V.S. strain, in which the disease can be readily transmitted, are not carriers of eperythrozoa and do not yield *E. coccoides* after splenectomy.

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The injection of histamine did not cause eczema, nor was histamine released by the eczema reaction. Antihistamine substances did not have a preventive action.

Cortisone was more effective in epidermal than in dermal reactions; but local application was ineffective, although patch-test reactions might be inhibited.

Dr. W. S. Feldberg, F.R.S., described a substance—'48/80'—which on injection caused the release of histamine without tissue damage. It caused an increase of capillary permeability, which resulted in local œdema, and permitted the escape of colloidal dyes from the blood into the tissues. Animals so injected showed regional differences in response to the drug; the most œdematous areas corresponded with those which normally contained most histamine. Injection of histamine did not produce this pattern of œdema, which seemed to be due to the action of histamine at the site of release. Animals injected with increasing quantities of 48/80 became depleted of histamine so that the induction of anaphylaxis was no longer accompanied by œdema. Also, animals rendered light-sensitive with hæmatoporphyrin did not react to exposure to light after histamine depletion with 48/80. Nevertheless not all the effects of allergic reactions should be attributed to histamine alone, since it had been shown that antigen-antibody reactions released another pharmacologically potent substance—5-hydroxy-tryptamine (serotonin).

Prof. J. R. Marrack discussed the antibodies involved in allergic reactions, limiting his remarks to those found in reactions of the hay-fever type. These were incomplete antibodies, which did not precipitate or agglutinate when mixed with antigen. In-vitro work with them was difficult because of the impurities present in antigen.

Even recrystallised ovalbumin might have several antigenic components. This could be shown by adding a solution of the antigen to a tube containing a column of antiserum solidified with agar; if the antigen were impure, a number of zones of precipitation could be made out. It was therefore often uncertain that the antibodies detected or measured in vitro were those responsible for the biological reaction, and in-vitro tests should always be checked against the biological reactions.

Dr. J. F. Ackroyd described the experimental steps by which the mechanism of 'Sedormid' purpura had been elucidated. The drug caused in hypersensitive people thrombocytopenia with hæmorrhages throughout the body; this hypersensitivity persisted for 12 years or more.

If sedormid and the whole blood of a hypersensitive patient were mixed, there was no clot retraction (this was not so with normal blood); the platelets were seen to be agglutinated and lysed, and complement was used up in this stage. Normal platelets were unaffected by the abnormal serum unless sedormid were added, and platelets from the sensitised case suspended in normal serum were not lysed by sedormid. The serum component was found to be present in the gamma-globulin fraction of the proteins.

His hypothesis was that sedormid combined with the platelets to form an antigen which was, however, of low antigenicity, so that only a few people became sensitised by it. In this small minority, taking sedormid rendered the platelets antigenic and thus capable of union with the specific serum antibody: their resulting agglutination and lysis led to the thrombocytopenia. In such people patch-testing with sedormid produced local purpura without thrombocytopenia, so that the vascular element appeared to be independent of the platelet effect. A similar mechanism possibly affected the vascular endothelium.

Dr. R. R. H. Lovell discussed the effects of cortisone and A.C.T.H. on cutaneous allergy. Patients had been given 200 mg. of cortisone or 150 mg. of A.C.T.H. for a week before testing. Reactions to tuberculin (P.P.D.) were significantly diminished, as were reactions to local applications of atropine. There was some reduction of the reaction to a direct irritant—manganese butyrate. Triple-responses to histamine, morphine, and grass pollen were not diminished. It seemed clear that the hormones affected the chain of events comprising the delayed type of reaction.

Supervoltage Therapy

The radiology section of the Royal Society of Medicine met on Nov. 21, under the chairmanship of Dr. Constance Wood, president of the section, to hear two accounts of the therapeutic use of powerful X rays.

Mr. G. W. Blomfield (Sheffield) has for three years used a van de Graaff machine. This is an electrostatic moving-belt generator that builds up a high potential of frictional electricity which is applied in increasing stages along an accelerator tube. The electron beam is passed through this tube and thereby speeded up to produce 2-million-volt X rays from the target—ten times more powerful than conventional X rays. Mr. Blomfield said that three years was too short a time in which to collect statistically valuable clinical results with a stable technique, particularly since the follow-up of treated cancer had to cover many years. But survival statistics were not the only criterion in radiotherapy. The rate at which radiation could be given, its penetration of the tissues, and the shape of the isodose curves in them were all important. So was the patient's comfort and the avoidance of high-dose effects, such as skin burns and necrosis or radiation sickness. They had chosen the 2 MeV instrument as the largest which still had some manœuvrability and was likely to be economic. In fact the total annual running cost, including salaries as well as replacements (chiefly new belts), was about £3700, which worked out at about £8 10*s.* per patient or 14*s.* a treatment, which he thought was reasonable. The instrument produced only slight skin reactions, gave a sharply defined beam with little lateral spread, which meant greater precision in irradiating malignant tissue only, and delivered a bigger dose to the deeper tissues. At 10 cm. the depth dose was twice that from a conventional 200 kV apparatus. These characteristics made supervoltage therapy a useful adjunct to radium in the treatment of carcinoma of the cervix, since it could reach secondary growths in the parietal pelvic lymph-glands without harming the head and neck of the femur. A lead filter was used to reduce the dose in the centre of the beam, and two applications of about three minutes from different positions ensured that the glands received an effective dose, while the filter spared the uterus to some extent. During 1950 112 cases were treated with 55% survival so far, including 2 patients with a stage-4 carcinoma who had received supervoltage therapy alone. Other patients treated in 1950 included 26 with infiltrating and fixed bladder carcinoma (11 still alive without recurrence); 20 with intracranial tumour (7 still alive); and 13 with carcinoma of larynx (5 still alive), who received 6000r in five weeks. In general about 1000r a week was a large enough dose, but in each of 50 patients artificial menopause was successfully induced with single doses of 350–450r.

Prof. J. S. Mitchell, F.R.S., and his team at Cambridge are using a synchrotron which is over ten times more powerful than the van de Graaff instrument, and works on a different principle which requires no moving parts. The electron beam is made to circle faster and faster inside a hollow ring by means of a powerful oscillating magnetic field, and is given further speed from passing at one point through a small coil in which a radio-frequency alternating current flows. When it hits the target 30-million-volt X rays are emitted.

Professor Mitchell explained that the synchrotron had presented so many problems that most of the time since its installation in November, 1949, had been spent on working out techniques and simplifying the controls. Only 5 patients had been treated between May, 1951, and March, 1952. It was difficult to make the machine reliable, and its low output of 5–10r per minute at a focal skin distance of 1 metre meant that treatment times were long and therefore that extensive clinical trials would be hard to achieve. He had chosen 30 MeV as a useful power from calculations made in 1946 which showed that as the power was increased above the conventional level the skin would be more and more spared while a greater proportion of the total radiation would be delivered centrally where it was wanted. From this point of view the synchrotron was even better than the 2 MeV van de Graaff accelerator, and it gave an even sharper beam. Thus it was easy to give a high dose to a tumour while largely sparing surrounding tissues. This also simplified treatment technique, since a single field of application often sufficed. But since the skin was spared it was difficult to gauge how the tumour inside was reacting to irradiation, and this lack of clinical control was disturbing. The fact that the beam occupied a fixed position was very inconvenient. Noise was less than expected, and patients did not seem to mind it.

They had worked out the isodose curves in phantoms, measuring the dose in various ways and also using a new audible dose-rate meter which sounded off in proportion to the dose-rate. It was doubtful whether the r unit could still be used in this high-power radiotherapy, because of secondary effects of unknown magnitude in the tissues—for instance, the production of positrons, neutrons, and induced radioactivity. Measurements suggested that some of these effects were negligible in soft, and probably in all, tissues. Absorption of radiation per unit mass by horse-bone was the same as by water to within 1%, but there was back scatter from bone which increased the soft-tissue dose locally by about 10%. Another factor which might prove important was that the instrument emitted its X rays in brief rapid pulses and not continuously.

For making collimators and applicators they used lead shot packed in plastic holders. The instrument was isolated in a room with walls up to 6 ft. thick, and the patient was observed through a water window by means of mirrors and could signal to the operator with a bell. The cases so far treated included a parotid carcinoma which had recurred after two separate courses with 220 kV X rays, a malignant glomus jugularis tumour at the skull base which had recurred after operation, and an inoperable glioblastoma where the patient was still alive fifteen months after irradiation. In this case radiation left no mark on the skin; and Professor Mitchell wondered what had gone on within the skull, particularly as in a case of pharyngeal carcinoma treatment left no sign externally on the face and neck but produced a visibly fierce reaction inside the mouth in the tumour area. There was no doubt that the 30 MeV synchrotron had a place in therapy for such cases as these, and also perhaps for carcinoma of the bronchus and the bladder; it would not be suitable for the treatment of breast cancer.

CENTRAL SOCIETY FOR CLINICAL RESEARCH AND AMERICAN FEDERATION FOR CLINICAL RESEARCH

THE Central Society for Clinical Research and the midwestern section of the American Federation for Clinical Research met in Chicago on November 6–8. Some 58 papers were given.

Thyrotropin in Diagnosis of Obscure Hypothyroidism

R. D. LEVY and W. JEFFRIES (Cleveland, Ohio) had measured I^{131} uptake over the thyroid gland with and without injection of pituitary thyrotropin in normal people, and in patients with hypothyroidism, with pituitary myxœdema, and with exophthalmos developing after removal of the thyroid gland. They found that a single injection of thyrotropic hormone (T.S.H.) produced a significant increase in the rate of uptake of I^{131} in people with normal thyroid function whether or not they had been taking thyroid. Euthyroid people, even after having taken as much as 0·26 g. of thyroid for over eighteen months, uniformly had a significant response to T.S.H., whereas in those with primary hypothyroidism there was little if any increase in uptake. Normal response to T.S.H. was also seen in pituitary myxœdema and in postoperative exophthalmos.

Nature of Circulating Thyroid Hormone

W. P. DEISS, E. C. ALBRIGHT, and F. C. LARSON (Madison, Wisconsin) had given I^{131} to euthyroid and hyperthyroid persons, and thereafter separated the plasma-protein fractions by paper electrophoresis. The pattern of radioactivity in the fractions was measured after cutting the paper into strips. In three days virtually all the radioactivity appeared in an area just ahead of the α_2-globulin peak; the radioactivity at this site gradually increased. The same sequence of localisation appeared in the hyperthyroid subjects. In them, however, the radioactivity appeared sooner, increased more rapidly to much higher levels, and then declined sharply. Radioactive thyroxine added to serum in a test-tube was bound to a protein in the α-globulin section.

Raben-Westermeyer Growth Hormone

JEROME W. CONN and his colleagues (Ann Arbor, Michigan) said that Raben and associates had reported the isolation of a hog-pituitary fraction which was growth-promoting in animals, was not diabetogenic in adult dogs, and caused nitrogen retention without effecting carbohydrate metabolism. Conn studied the metabolic effects of this preparation in a 17-year-old boy with panhypopituitarism due to a calcified craniopharyngioma who also had diabetes mellitus—a rare association. He described a metabolic state resembling that in the Houssay rat. A detailed metabolic balance study over a twenty-four-day period showed: (*a*) significant anabolism of body protein with the Raben pituitary-growth preparation; (*b*) no intensification of the diabetic state; (*c*) no intensification of the anabolic effect of growth hormone by administration of insulin; (*d*) a definite protein-anabolic effect of insulin alone in the diabetic pituitary dwarf, who without insulin maintained nitrogen equilibrium. Conn believed that the Raben preparation, when given intramuscularly at a pH below 4, could be expected to induce growth in human pituitary dwarfism without inducing diabetes mellitus.

A.C.T.H., Cortisone, and Aspirin in Rheumatic Fever

H. B. HOUSER and other colleagues of C. H. RAMMELKAMP (Cleveland, Ohio) gave a preliminary report of their long-term study of the comparative effects of A.C.T.H., cortisone, and aspirin on the course of acute rheumatic fever. 152 young airmen with acute rheumatic fever were observed for nine weeks. Treatment with the three agents was started during the first week of illness and was continued for six weeks. The daily dose of A.C.T.H. was 120 mg. initially and was reduced at specified intervals so that at the beginning of the sixth week the dose was 20 mg. daily. Intramuscular cortisone was reduced gradually from 300 mg. on the first day to 50 mg. per day during the sixth week. Aspirin was reduced during the first week from gr. 1 per lb. body-weight per day to a maintenance dose of gr. $^1/_2$ per lb. per day. Aspirin was most effective in relieving symptoms and signs of joint involvement. Fever subsided most promptly after aspirin therapy, although there was no great difference among the groups in the prevalence of fever after the fifth day of treatment. A.C.T.H. was most effective in returning the erythrocyte-sedimentation rate to normal. Abnormal auriculoventricular conduction occurred with similar frequency among the three groups, but the duration of abnormalities was longer in the aspirin group. There was no distinct difference between the three groups in the appearance or disappearance of murmurs or of other signs of acute carditis. After treatment clinical or laboratory relapses occurred in the majority of patients in all groups; with few exceptions these relapses subsided promptly. None of the drugs used had any great advantage over the others in the early treatment of rheumatic fever.

Conversion of Mesobilirubinogen to Stercobilinogen

PAUL LOWRY, R. ZIEGLER, and CECIL WATSON (Minneapolis, Minnesota) said that Baumgartel, in Germany, had claimed that cellular dehydrogenases converted bilirubin to mesobilirubinogen in the liver, and that fæcal bacteria converted bilirubin directly to stercobilinogen. Since the keystone of Baumgartel's hypothesis was the supposed inability of fæcal bacteria to convert mesobilirubinogen to stercobilinogen, Watson and his colleagues studied the effect of such organisms on N^{15}-labelled crystalline bilirubin. They showed convincingly that fæcal bacteria reduced both bilirubin and mesobilirubinogen to stercobilinogen. Since Watson had repeatedly crystallised mesobilirubinogen from human fæces, there was little reason to postulate an extra-intestinal site for its formation, or to doubt its intermediary relationship between bilirubin and stercobilinogen.

Refractory Macrocytic Anæmia

D. L. HORRIGAN and ROBERT W. HEINLE described a new disease entity—a refractory macrocytic anæmia with a defect in vitamin-B_{12} binding which responded to normal plasma. A patient who had had unexplained anæmia for eighteen years did not respond to crude liver-extract, nor to iron. Free HCl was present in fasting gastric contents. Hæmatological findings during relapse included macrocytic anæmia, reticulocytosis, and normoblastic bone-marrow hyperplasia. Slight but significant remissions were obtained with *single* injections of normal human plasma or with *single* injections of vitamin B_{12}. Such remissions were not maintained either with vitamin B_{12} intramuscularly every one to two weeks, or with oral folic acid 10 mg. daily. Normal blood levels were maintained, however, when the patient was given vitamin B_{12} combined with fresh human plasma, at short intervals. Healthy persons and the patient were studied after intramuscular administration of 0·5 µg. of Co^{60}-labelled vitamin B_{12}. In the normals 0–10% of the injected vitamin was excreted in the urine, and altogether 60% was excreted in twenty-four hours. These observations suggested that: (*a*) the anæmia in this patient resulted from deficiency of vitamin B_{12} caused by failure of proper binding of the vitamin; and (*b*) normal plasma contained a factor which corrected this defect.

Hæmophilia-like Disease after Pregnancy

PAUL G. FRICK (Minneapolis, Minnesota) described an instance of a hæmophilia-like disease following pregnancy with transplacental transfer of an acquired circulating anticoagulant. The disease appeared in a woman three months after her first normal pregnancy and was studied from the time of its onset until recovery two and a half years later —sixteen months after sterilisation by X rays. The venous clotting-time was markedly prolonged, and the prothrombin consumption was minimal. Bleeding-time, prothrombin-time, prothrombin concentration, platelet-count, clot retraction, tourniquet test, and plasma-fibrinogen concentration were all within the normal range. There was no evidence of parenchymal liver dysfunction. The lack of response of the clotting abnormality to fresh blood or plasma led to the suspicion of a circulating anticoagulant, which was demonstrated by the delaying effect of the patient's blood on the coagulation-time of normal blood. Cohn's fraction I containing active antihæmophilic globulin had no effect on the patient's clotting mechanism. The anticoagulant was therefore believed to inhibit the action of the antihæmophilic globulin (thromboplastinogen). The patient delivered a second child fifteen months after the onset of the disease, and the anticoagulant was demonstrated in the baby's blood during the first two and a half months of its life. The findings strongly suggested an immunological mechanism in the development of the anticoagulant.

Endothelial Permeability to Albumin

J. A. SCHOENBERGER, H. V. KROLL, and ROBERT M. KARK (Chicago, Illinois) reported on their studies in man on endothelial permeability to radioactive-iodine-tagged albumin injected intravenously or intraperitoneally. They used I^{131}-tagged human albumin to study endothelial permeability in health and in various diseases associated with ascites and œdema. The material was injected in tracer doses first intravenously and a few weeks later intraperitoneally. In healthy volunteers the intraperitoneal injections were made through the posterior vaginal fornix or through the anterior abdominal wall after a small pneumoperitoneum had been established. The studies disclosed a dynamic equilibrium between albumin in intramuscular and extravascular sites. Mathematical analysis of the curves yielded quantitative estimates of the rate of exchange of albumin across the peritoneal membrane and also out of the vascular endothelium. Quantitative differences in permeability between healthy individuals and patients with ascites were found. In patients with ascites repeated studies were made during reablement. These disclosed changing permeability which was correlated with electrophoretic studies of the passage of various-sized protein molecules from the plasma to the ascitic fluid. Large protein molecules (such as globulins) distributed themselves equally between plasma and ascitic fluid when permeability was poor, but did not pass the endothelial barrier freely when permeability was improved.

Concentration of Antibiotics in Brain

W. E. WELLMAN and his colleagues (Rochester, Minnesota) had sought to find out whether neopenil (the diethylaminoethyl ester hydriodide salt of penicillin G), a new form of penicillin for parenteral use, was concentrated in the brain. The patients they studied were in hospital because of psychiatric disorders, and prefrontal lobotomy was done for therapeutic reasons. Before operation, these patients received for prophylaxis one of the following drugs: neopenil, procaine penicillin G in aqueous suspension, aureomycin, terramycin, dihydrostreptomycin, or erythromycin. They found that only neopenil and aureomycin were consistently detectable in significant amounts in brain tissue.

L.E. Phenomenon in Penicillin Hypersensitivity and Serum-sickness

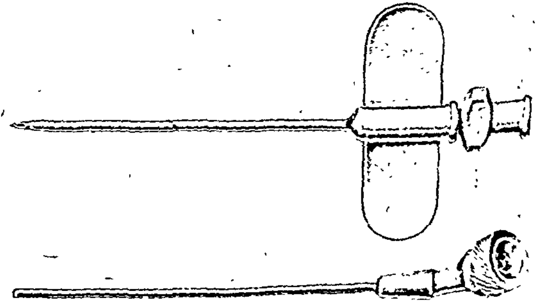
JOHN R. WALSH and HYMAN J. ZIMMERMAN (Omaha, Nebraska) had studied 8 patients with penicillin reactions and 1 with serum-sickness following the administration of tetanus antitoxin. Of the 8 patients with penicillin reactions, 4 had mild disturbances characterised only by urticaria; the other 4 had fever, adenopathy, joint pain, and skin lesions which ranged from erythema multiforme to a generalised exfoliative dermatitis. In each of these 4 patients with severe penicillin reactions the plasma L.E. factor was demonstrated, and, furthermore, L.E. cells were found in the concentrated heparinised bone-marrow. Study of the 4 patients with mild penicillin reactions failed to reveal the L.E. plasma factor or L.E. cells in heparinised marrow. Likewise, study of the heparinised bone-marrow of the patient with serum-sickness revealed L.E. cells; but an attempt several days later to demonstrate the L.E. plasma factor was unsuccessful.

New Inventions

AN ADAPTER FOR AN INTRAVENOUS NEEDLE

MANY anæsthetists consider that a cannula of the Guest type is the easiest to introduce into a vein, and that it causes less damage to the vein wall than an intravenous needle.

The use of the adapter shown in the accompanying figure will allow this cannula to be used for intermittent injections and yet remain patent should an intravenous infusion be required. The adapter consists of an inner cannula with a rubber diaphragm at one end, similar to a Gordh needle.



Venepuncture is performed with the cannula and introducing needle connected to a syringe. The syringe and needle are then steadied and the cannula pushed on up the vein. The needle is then removed and the adapter inserted. Should the adapter become blocked (though there is very little tendency for this to happen) it may easily be replaced. Two sizes of adapter have been used, one to fit a standard case Guest cannula and one to fit a 19-gauge cannula of similar design, which is used for the back of the hand in adults and for children.

My thanks are due to Dr. J. Challis and the anæsthetists of the London Hospital for their encouragement in the design of this needle, and to Messrs. A. L. Hawkins who have made the cannula sets.

Formerly of
Department of Anæsthetics,
London Hospital

J. MIDDLETON PRICE
M.B. Lond.

Reviews of Books

Fitness for the Average Man

Sir ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P., honorary medical adviser to the British Olympic Athletic Teams. London: Christopher Johnson. 1952. Pp. 170. 10s. 6d.

THIS is in the main what its title suggests—a book about health for ordinary men—but it is also in part a book about athletes and athletics as seen at close quarters by a physician. "Moderation in all things, including moderation," says Sir Adolphe, and follows at least the first part of this dictum. Sober, sobering, and not unduly familiar facts, and sane reflections upon them, fill the very readable pages; and the average man who wants sound, well-based advice on food, exercise, alcohol, cold baths, tobacco, and health will find it here. Medical readers may be more interested in the later chapters on women and athletics, infant prodigies, champions among athletes, and the psychology of record-breaking. They will seldom find grounds for disagreement; but there is a passage seeming to imply that, in training, the very cells of "heart, lungs, muscles, nerves, and the rest" are replaced by new ones better suited to athletic needs —surely a questionable piece of physiology? Such qualities and faculties as "will-power, judgment, courage and self reliance" are placed where the layman, but not Sherrington, puts them—in the central nervous system.

Phosphorus Metabolism

A Symposium on the Role of Phosphorus in the Metabolism of Plants and Animals. Vol. I. Editors: WILLIAM D. MCELROY and BENTLEY GLASS, the McCollum-Pratt Institute of Johns Hopkins University. Baltimore: Johns Hopkins Press. London: Oxford University Press. 1952. Pp. 762. 80s.

LIFE depends on the mechanisms by which energy is released, transferred from one system to another within the cell, and utilised for special purposes. Realisation, during the past few decades, that many of these mechanisms depend on the reactions of relatively few types of phosphorus compounds has made the study of phosphorus metabolism of immense importance, and caused it to advance with bewildering rapidity. This book contains the communications made when American experts on phosphorus metabolism met for a symposium at Johns Hopkins University in June, 1951.

An introduction by Otto Meyerhof is followed by four dozen separate contributions, in ten main groups dealing with such topics as the metabolism of polysaccharides and disaccharides, of hexosephosphates, of pentose and triose phosphates, and of phosphorus-containing coenzymes; active acetate; oxidative phosphorylation during electron transport; the chemistry and thermodynamics of phosphate bonds; and the utilisation of phosphate-bond energy in biological systems. (Phospholipids, phosphoproteins, and nucleic acids were left for a later symposium.) Each main topic is presented by a well-known authority, and shorter papers follow on special parts of the field: general discussions, reported in detail, close each section. There is a subject index and an index of the participants. A most valuable feature is an 80-page summary by one of the editors of the ground covered by the symposium.

L'insuffisance cardiaque chronique

Études physiopathologiques. ANDRÉ COURNAND, cardio-pulmonary laboratory, Columbia University, New York; JEAN LEQUIME, Université de Bruxelles; PAUL REGNIERS, Université de Gand, Clinique Médicale. Paris: Masson. 1952. Pp. 262. Fr. 1400.

IDEAS on the mechanism of cardiac failure have been much modified by new methods of clinical investigation —methods which can bring to diagnosis the precision of the laboratory.

The first part of this work is devoted to the detailed description of procedures which for the most part are still little known to the clinician. Successive chapters are devoted to catheterisation of the heart and great vessels, the recording of intracardiac pressures, the determination of cardiac output, blood volume, and circulation-rates, and finally modern tests of lung function. The second part deals with the problem of chronic cardiac insufficiency. After reviewing usefully the physiological factors affecting the regulation of the circulation in health, the authors analyse their results and describe fully their studies over a wide range of acquired diseases of the heart and lungs, comparing their findings with those of all the principal workers in this field who have published their work. Isolated failure of the left or right ventricle and combined failure of both ventricles are separately considered. The inadequacy of cardiac output studies alone and the importance of the blood volume and of intracardiac and venous filling pressures are clearly explained, and modern concepts of various syndromes are discussed—e.g., that of cor pulmonale and the importance of anoxæmia in the development of pulmonary hypertension in emphysema. Finally the authors formulate a coherent theory of cardiac insufficiency.

This is an important book, authoritative and up to date. It should be warmly welcomed by all who are actively engaged in the investigation of the hæmodynamics of the heart and circulation in health and disease, by all cardiologists, and by all who wish to keep abreast of modern work and are interested in the underlying basis of their clinical observations and treatment. The French is easy to understand; and the bibliography is full, and derived from Continental, British, and American sources.

New Knowledge of Hygiene in Diet

J. SIM WALLACE, M.D., D.SC., F.D.S., R.C.S., F.A.C.D., vice-president, Food Education Society. New York: Dental Items of Interest Publishing Company. London: Henry Kimpton. 1952. Pp. 264. 36s.

THIS book by the late Dr. Sim Wallace sets out at length his theory of the relationship between diet and dental caries. In the closing decades of the last century he came to the conclusion that dental decay was a disease of civilisation, resulting from over-refinement of food and consequent dysfunction of the masticatory apparatus.

Since we do not need to chew our food in order to digest it, the natural tooth-cleansing from vigorous mastication does not occur and the teeth become clogged with food, much of it in the form of sticky, easily fermentable carbohydrates, from which acids are produced to attack and disintegrate the hard tooth substance. From this view he argued that the only way to prevent the ravages of dental caries was to institute a counter-revolution in the community's dietary habits. He believed that it was essential to popularise a régime of coarser foodstuffs, resembling the primitive diet for which our jaws and teeth were evolved.

It seems unlikely that such a far-reaching reform of entrenched habits could ever be effected on a large enough scale to influence the dental health of the community as a whole; and it is by no means certain that the change would not reintroduce digestive ills to which our forefathers were subject. Our best hope of solving this serious problem would seem to lie in the pathologist and biochemist discovering the nature of the process or processes covered by the term dental decay. We shall have to know more about the disease and its causation than we do at present before we can usefully attempt to find a cure. This is not to say that Dr. Wallace's contribution to the theory of the disease was not of great value, nor that we cannot with advantage follow his advice on dietetics.

Biologie d'anopheles gambiæ. Recherches en Afrique-Occidentale française.

World Health Organization Monograph Series No. 9. M. H. HOLSTEIN, Dr. ès Sc. Geneva: World Health Organisation. 1952. Pp. 176. 10s.

Anopheles gambiæ carries malaria with the greatest ease. The acknowledged model and pattern of her profession in Africa, she is not over-fastidious in her choice of breeding-places, and therefore multiplies prolifically in sun or shade; she seeks man rather than animals for the blood-meals she needs, and she picks up and matures man's malaria parasites to a degree hardly paralleled by other species in other continents. She needs a hot climate, it is true, but, as in Brazil twenty years ago, if she invades suitable new territory she can convert a modest malaria incidence into a raging epidemic. She responds to D.D.T. with a degree of irritation and repulsion which makes control by the methods of D.D.T. residual spray, so successfully used from South America to India and beyond, somewhat problematical. She is probably the most formidable factor in malaria at present known, and needs much study if we are to find and exploit her biological weaknesses.

This monograph surveys the vast literature (388 references) which clusters round this pest, and covers morphology, biology of all stages of development, the rôle of the mosquito in transmission of malaria, and the question of various races. *Anopheles melas*, of course, has long been differentiated, but Dr. Holstein now describes and distinguishes two other forms, one multidentate and man-loving, the other paucidentate and animal-loving. This distinction may be important.

He also describes his investigations, carried out in French West Africa, into the ability of the female to survive the long dry season by æstivation, the differentiation of races, and other biological problems. No serious student of African malaria can afford to be without this book; and, though the French text is clear and lucid, English readers will be interested in the announcement on an accompanying leaflet that an English edition is being prepared.

Metabolism and Function in Nervous Tissue

Biochemical Society Symposium No. 8. Editor: R. T. Williams. 1952. Cambridge: University Press. 1952. *Pp. 102. 12s. 6d.*

In this symposium, held at the end of last year, eight biochemists read papers which show how actively research is being pursued into the metabolism of the brain. As Sir Rudolph Peters, F.R.S., said in his opening remarks, it is only recently that sustained work has been carried out in this field, more than half a century after the fundamental studies of Thudichum; but the present lively interest promises a great deal. The contributors were Dr. R. V. Coxon, of Oxford, on carbohydrate metabolism; Dr. H. Weil-Malherbe, of Runwell Hospital, on glutamic acid; Mr. H. M. McIlwain, D.Sc., of the Institute of Psychiatry, Maudsley Hospital, on phosphates and nucleotides; Mr. G. H. Sloane Stanley, Ph.D., of the same institute, on lipids; Dr. Derek Richter, of Whitchurch Hospital, Cardiff, on the relation of metabolism to cerebral function; Mr. R. M. C. Dawson, Ph.D., also of Cardiff, on the use of radioactive isotopes in studying metabolism of nervous tissue; and Prof. H. A. Krebs, F.R.S., and Mr. R. E. Davies, Ph.D., of Sheffield, on biochemical aspects of the transport of ions by nervous tissue. The papers are severely technical and are not concerned with clinical matters, but they raise many questions in the clinician's mind, and they have clearly great potential importance for the pathology of some, and the treatment of almost all, forms of mental disorder.

Phantasy in Childhood

Audrey Davidson and Judith Fay. London: Routledge & Kegan Paul. 1952. Pp. 188. 18*s*.

Dr. Davidson and Miss Fay wish to pass on in simple language some of Mrs. Melanie Klein's psycho-analytical hypotheses, using as illustrations the remarks and behaviour of little children whom they have looked after. The children seem to have been mostly separated from their parents, or the luckless offspring of marriages that had failed; and it is not always clear whether we are meant to regard the reported fantasies as dependent on emotional privation (e.g., in a child who longs for his divorced mother) or as the inevitable and normal accompaniments of a stage of development. The prominence given to the mouth, the breasts, the excreta, and the genitals is, of course, to be expected in a psycho-analytical work; but a sceptical reader might wonder whether the suggestions made to the child were as correct an interpretation of what he or his unconscious meant as the authors assume. The book will be found most informative by those who would like to know how psycho-analytically trained psychiatrists and teachers approach the task of caring for young children and understanding them: it will be touch and go whether the reader then considers the book tedious and the mode of thought uncritical, or, on the other hand, discerns a genuine insight and a profound body of truth in it.

Food and Population and Development of Food Industries in India

Director: V. Subrahmanyam. Mysore: Central Food Technological Research Institute. 1952. Pp. 357. 10s.

Dr. V. Subrahmanyam, the director of India's new food technological research institute at Mysore, organised there two symposia in May, 1951. The subject of the first was Food and Population and of the second Development of Food Industries. This book records 45 contributions made by chemists, agriculturalists, industrialists, doctors, Civil Servants, and politicians; and the very variety of the contributors emphasises that Indians are now fully aware of their food problems and are working out all manner of solutions.

The production of a nutritious substitute for rice from tapioca-starch and defatted groundnut cake is an ingenious technical advance which may have far-reaching effects on both agriculture and health. Enormous strides are being made in the vegetable-oil industry, and new methods of preserving and storing foodstuffs are being developed. An energetic "grow more food" campaign is educating the people in methods of self-help. Improved seeds are giving higher yielding crops. Plans are being made to meet the food emergencies which must inevitably arise in an uncertain future. Many see the need for family planning, and urgent pleas were put forward for the establishment of birth-control clinics on a large scale.

This is a stimulating and exciting book. The new India is making enormous strides in applied science, and setting about her urgent problems in human biology with energy and ingenuity. A great fight against poverty and disease is in progress, and this book records a promising start. It is a disappointment that none of the speakers found time to pay tribute to Sir Robert McCarrison: thirty years ago he was fighting this their battle almost alone.

Renal Function (*Transactions of the Third Conference October 18–19, 1951*. New York: Josiah Macy Foundation, 1952. Pp. 210. $3.50.).—This record, edited by Stanley Bradley, of the third Josiah Macy Foundation conference on renal function, follows the pattern of the two preceding publications in presenting informally the views of the experts in this field and the trends of their research. The accent of the conference was on the physical factors relating to kidney function. Five of the seven topics discussed have a physical bias, and to understand much of what is presented requires a special knowledge of physics and mathematics. Some of the sections, and particularly those concerned with the processes of filtration and diffusion, will interest workers concerned with capillary circulation through other organs.

The Principles of Line Illustration (London: Burke. 1952. Pp. 212. 25*s*.).—Articles for publication often arrive with really beautiful drawings which are totally unsuitable for reproducing because the artist has studied neither the block-maker's requirements nor the effect of reduction on his work. Mr. L. N. Staniland, A.R.C.S., shows how this waste of effort may be avoided, for he sets out lucidly almost everything that need be known about drawing for print. He describes the different kinds of line drawings, how to produce them both on ordinary paper and on scraper board, how to illustrate flowers, animals, and other biological specimens, and how to make graphs, diagrams, maps, and lettering. The book is well written, well printed, and, of course, well illustrated.

Must Man Wage War? (London: Watts. Thrift Books. 1952. Pp. 93. 1*s*. 6*d*.).—This is a clear-headed, humane, and factual study, by Prof. F. A. E. Crew, F.R.S., of the problem of war, its effects, its preparation, and its significance for the human race. In its lucid exposition of the strategems by which men are led to accept war as a pattern of behaviour, and its unhysterical but forthright speaking on such subjects as propaganda and atomic and germ warfare, it is a courageous and a disturbing stimulus to thought and action. We know most of the facts to which Professor Crew points; and the survival of humanity may depend on our ability to respond rationally to them. One can only wish this book the widest possible circulation in the shortest possible time.

THE LANCET

LONDON: SATURDAY, NOV. 29, 1952

Hospital Costs

The number of noughts in the national budget makes it increasingly meaningless to the citizen and removes it from the reality of daily life. The cost of the National Health Service is perhaps more easily appreciated if it is described as 10% of the money at the Government's disposal for all national purposes. Of this 10% half goes to the hospitals, and the individual hospital consultant is largely responsible for a medical service costing, on the average, some £30,000 to £40,000 a year. The N.H.S. does not include representatives of the community elected to safeguard the taxpayer's pocket, and the public has to trust all those who work the service to watch its interests. Actually, members of our profession have good reason to favour economy, both because they are taxpayers themselves and because they know how much needs to be done with the limited allowance of money. Both the sharp increase in hospital costs and the state of the national purse make it important for every consultant to accept responsibility for the financial as well as the professional efficiency of his unit. It has become only too clear that, for a nation situated as ours, further progress in medical and other social services can be achieved only by getting better value for the money spent.

The business efficiency of hospitals is relatively low, and whenever a spotlight is focused on, for example, catering or laundry it is found that reorganisation may save thousands of pounds a year and still provide better service. The purely medical routines, too, often benefit by critical scrutiny, for the combination of a busy consultant and junior assistants is not always conducive to changes. From a financial standpoint, there is a twofold need: (1) to assist management by providing hospital staff with a stimulus to combine efficiency with reasonable economy (i.e., good housekeeping); and (2) to provide regional boards and the Ministry of Health with figures that will enable a comparison to be made between hospitals doing similar work. Hitherto it has been difficult to assess and contrast the financial needs of hospitals; and, indeed, the necessity did not become generally apparent until they were united on a national scale. A partial solution of the problem was attempted by the Ministry in its Costing Returns, consisting of hundreds of pages of closely printed figures, purporting to compare the hospitals of the country under many headings of expenditure; and, though these tabulations contain as many fallacies as there are holes in a sieve,[1] they have served a purpose in that they drew public attention to the need for a better system of costing in hospitals and for comparing units. Long before their publication, the Ministry had invited both the Nuffield Provincial Hospitals Trust and King Edward's Hospital Fund to advise on how to do better. The reports of these bodies,[2,3] published this week, form a very valuable contribution, and it is interesting that, approaching the subject independently, they both make the same major recommendations. They suggest that the accounting system for hospitals should be based on the departments and services of the hospital, and, to permit of comparisons, that the expenditure of departments should be broken down, where appropriate, to costs per unit of work. Thus, instead of having returns based on expenditure on salaries, maintenance, provisions, and so on, we should have figures related to the actual cost of specific hospital departments; for example, expenditure on the general surgical wards would be related to inpatient days, expenditure on the electrocardiographic department to the number of electrocardiograms, and expenditure on the boiler-house to the number of thousand pounds of steam raised. Furthermore, they propose that, in all hospitals with more than 50 beds, budgets should follow the same pattern, and that normal accountancy principles should be introduced into the preparation of the annual balance-sheet. These recommendations by the two great hospital foundations are backed by their practical experience in a variety of hospitals over an appreciable period. It will be remembered that the recently published report of the committee of Regional Hospital Board Treasurers[4] was willing to retain the present Ministry costing returns while also introducing departmental budgeting; but this decision has been severely criticised by the *Accountant.*[5]

There are many advantages in the proposals of the Fund and the Trust. Returns produced on such a basis would restore a measure of confidence in comparative costs, which has been lost under the former system. They would also introduce into hospital administration a basic lesson from industry—i.e., the need to link executive and financial responsibility. The efficiency of a large industrial unit depends on each head of a department being responsible for the economical working of his section,[6] and on the ability of the board of directors to observe his efforts from the departmental returns. The present administrative hierarchy of hospitals under the N.H.S. has seriously undermined the status of departmental heads, such as the chief pharmacist, the chief engineer, and the catering officer, who may be almost unknown as individuals to boards of governors or hospital management committees. This arrangement is not conducive to getting their best contribution to proper housekeeping, and the introduction of departmental costing would do much to give them the recognition that is their due. The recent

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1. See *Lancet*, 1952, i, 1243.
2. Costing Investigation for the Ministry of Health. King Edward's Hospital Fund, 10, Old Jewry, London, E.C.2. 1952. Pp. 87. 6*s.* (7*s.* post free).
3. Report of an Experiment in Hospital Catering. Nuffield Provincial Hospitals Trust, 12, Mecklenburgh Square, London, W.C.1. 1952. Pp. 227. 5*s.* (5*s.* 6*d.* post free).
4. See *Lancet*, Aug. 16, 1952, p. 327.
5. *Accountant*, Aug. 16, 1952, p. 177.

emphasis has been on joint staff consultative committees, which may be valuable for improving morale but as means of ensuring economy are far less effective than is personal responsibility. The concept of departmental costing also has particularly important repercussions on the hospital's annual budget—a point made very clearly in the King's Fund report:

> "The budget of a hospital or group is at present regarded as a sum of money to cover the estimated expenditure to be incurred during the next financial year; as a document laying down limits which must not be exceeded. This, in our opinion, is not a budget; it is an appropriation of funds. We regard a budget as a constructive plan of action, which has, in its several parts, been agreed by the heads of all departments concerned and approved by the management. It is an expression, in accounting terms, of the plan and future policy of the hospital and a pre-requisite to sound management. This view of a budget places emphasis on the financing of the cost of care rendered to patients rather than on that of financing the hospital as an institution. Within a hospital or group it must be flexible to meet changing conditions in the volume and incidence of service rendered, and to allow of just comparisons."

There are certain technical differences between the two reports, the chief of which concerns the method of distributing the cost of general services. The Nuffield Provincial Hospitals Trust prefers to express the departmental figures in terms of "prime cost"—i.e., expenditure on salary and wages of staff working in a department and on the materials actually used in the department. Thus a medical department would include only medical salaries and salaries of nurses and ward orderlies and the cost of all materials used in the wards, such as dressings, linen, and crockery. This system means that each responsible member of the staff is made aware of the expenditure incurred by him for his department and of variations in the expenditure that can be controlled by him: costs over which he has no control are excluded. This simple system does indeed seem preferable to the technique advocated by the King's Fund, whereby a proportion of general service charges (e.g., heating, laundry, and catering), is allocated to each department according to its claims on these services. Allocations that might be based on semi-arbitrary decisions would tend to undermine a sense of individual responsibility and also reduce confidence in comparative figures. The King's Fund report suggests a greater number of departmental units to be costed—an arrangement not favoured by the Trust. Certainly it seems undesirable to cost each ward separately, because a position might arise in which ward sisters sought to avoid patients who made expensive demands on their stock. There are in fact too many variables to allow a useful comparison between individual wards.

The proposed costing system would be a further step away from the method of Treasury control formerly exercised, which could hardly have been better designed to inhibit economy. The essence of the Treasury system was control of payments (not expenditure) by reference to detailed yearly estimates which were broken down into many inelastic groups. As the Fund clearly points out, this system left the way open for waste and inefficiency; for, in a last-minute scramble to spend balances in hand, money was frittered away on short-term palliative maintenance work, pieces of equipment, furniture, and so on—orders small enough to be completed within the financial year. It was also especially stultifying to long-term planning and to the careful husbanding of resources towards this end, since there was an absolute prohibition against carrying forward unspent balances. Working and budgeting in terms of departmental medical services to the community is a sensible and logical approach, and would go far to release hospital services from the sterilising Treasury system.

One essential test to apply to any proposed change in the N.H.S. is whether or not it will facilitate the growth of the dangerous virus of national uniformity. There is, in fact, a risk that the proposed system of costing might facilitate this growth; but the advantages of the system seem to outweigh its dangers, though these must be kept constantly in mind. We may add that it would have been a virtual impossibility for any Government department to have undertaken the surveys worked out by the Nuffield Provincial Hospitals Trust and the King's Fund, and their efforts afford yet another example of the value of the independent observer. The reports of the two foundations will provide medical historians with further evidence of the valuable contribution they are making to the British hospitals services. A tribute should also be paid to the Ministry of Health for its perspicacity in seeking independent assistance in a difficult and contentious field.

Transplantation

THOUGH the human body is often beset with autonomous new growths of great vigour, it is seldom able to transgress the rules and to support life from the tissues of another individual. Only quite limited grafts of highly specialised tissues have so far been a success—for example, blood-transfusion, corneal grafting, and the transplantation of homologous cartilage, bone, and blood-vessels, which are now an accepted part of surgical practice. The career of most of these implants as distinct pieces of tissue is short; indeed it is questionable whether they need be alive at the moment of grafting. Most of our knowledge of transplantation is based upon experiments in animals; but these, it seems, differ as much from man in their response to homografting as in the diseases from which they suffer. The only explanation of these phenomena that is based upon observed facts, rather than on abstractions, is that of MEDAWAR.[1] He has shown that skin homografting evokes an immune response in the host. If this response has already been produced by a preliminary exposure to skin or white blood-cells from the same donor, the survival-time of a second graft is much shorter. There is also evidence that if the reticulo-endothelial system of the recipient is inactive at the time of grafting, the survival period is significantly prolonged.[2] Total body radiation or the administration of nitrogen mustard will depress the activity of the reticulo-endothelial system, but as a result the body also loses its resistance to bacterial infection during the phase of marrow aplasia. Under these circumstances antibiotics alone are seldom sufficient to control a massive infection; but when they were used in the treatment of people irradiated by the explosion of the atomic bomb at Hiroshima[3] they did, in borderline cases, allow time for the reticuloendothelial system to recover. JACOBSON et al.[4] found that the recovery-rate in irradiated pure-strain mice was greatly increased by the intraperitoneal insertion, after exposure, of splenic homografts from one-week-old mice of the same strain, and hæmopoiesis in the marrow and spleen returned to normal much sooner than in the few control mice that survived. It remains to be seen whether animals of mixed strain will respond in the same way. Homologous rat ovaries have been implanted in the spleen, where they developed into tumours, which in some cases metastasised to the liver.[5] More limited "takes" were obtained by FAWCETT,[6] who placed fertilised ova under the renal capsule of adult mice. The cheek pouch of the golden hamster (a highly inbred species) has also been described[7] as a favourable site for homografts and even heterografts, though no explanation has been suggested. In general it seems that fœtal tissues have a better chance of surviving as homografts, but are their antigenic properties necessarily less than those of adult tissues? Some evidence to suggest that they are was provided by KEMP[8] who observed that red-cell agglutinogens could be demonstrated in the human fœtus at 37 days, and that the sensitivity of these cells to immune sera increased progressively thereafter.

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[1] Medawar, P. B. *J. Anat., Lond.* 1944, 78, 176; *Ibid.* 1945, 79, 517.

[2] Dempster, W. J., Lennox, B., Boag, J. W. *Brit. J. exp. Path.* 1950, 31, 670.

Organ transplantation occupied CARREL in his most active years; using a precise technique, as he did in tissue-culture work and in vascular surgery, he advanced the subject far ahead of his time. Endocrine transplants interested HALSTED; he believed that they would "take" more readily if the recipient was in physiological need of them. The endocrine basis for this law is now quite familiar; for example, A.C.T.H. is found to be present in excess in Addison's disease. BROSTER's case[9] of adult-adrenal transplantation and other instances in which fœtal adrenals have been used are later examples of this possibility. Kidney homografts function only for a short time, even though their vascular pedicle may remain intact for very much longer. DEMPSTER has developed the technique of this operation in dogs, using autogenous kidneys; but the disposal of the ureter is a difficult point, even with autografts, and hydronephrosis is a common cause of late failure. Homotransplanted kidneys usually fail after only a few days, during which they produce a urine of fixed specific gravity. DEMPSTER describes a "toxic hypertensive state" which develops in dogs at this stage if they lack their own kidneys. Extensive degenerative changes are found in the transplant, and the tubules are damaged much earlier than the glomeruli. In the few examples[10][11] of human kidney homotransplants that have been recorded, the graft has survived very much longer than in the dog; but these kidneys did not function normally, and it is uncertain whether they served to clear away the products of previous renal failure during their period of activity, or whether resolution was due to recovery of the patient's own kidneys. Skin homografts in man also survive longer than in animals—for periods of from three to six weeks. Under favourable circumstances therefore, skin donors can be a great help in providing skin cover for extensive burns, particularly in children. WOODRUFF[12] made the interesting observation that the areas of homologous skin were not affected in an intercurrent attack of chickenpox, while the autogenous strips were. He agrees with most other authorities that ABO blood-groups apparently play no part in the compatibility of other tissues. He adds, however, that, as in MEDAWAR's experiments, blood-transfusion in humans may produce immunity to that particular donor at least. An exception to these general rules is provided by grafts inserted into the anterior chamber of the eye. Homologous skin[13] and thyroid[14] can survive indefinitely here, though, in the case of the skin, vascularisation of the transplant is a prelude to its destruction. Moreover, a surviving piece of homologous thyroid in the eye is also destroyed soon after another piece from the same donor is inserted subcutaneously. It seems that antibodies, once formed, can reach the anterior chamber, though a homograft inside the chamber need not evoke an immune response. WOODRUFF, however, has also found that long-established anterior chamber transplants are no longer affected by a subcutaneous graft from the same donor, though this itself is destroyed in the usual way. He therefore believes that there is a critical period during which recent homografts in the eye, and perhaps in other sites, are most readily destroyed by the antibodies of the host. There may thus be some way of maintaining conditions which are favourable to the graft until the critical period is over, after which it should have a better chance of permanent survival.

Should homografting fulfil its promise to surgery, the collecting and storing of donor tissues will become of the greatest importance. The Corneal Grafting Act, 1952, allows eye banks to be operated much more easily than before, and comparable legislation may soon be needed for other tissues to be collected in similar circumstances. Storage difficulties have already set a limit to the scope of arterial grafting, for fresh grafts, like stored blood, should not be used after three to four weeks. PEIRCE,[15] in a year's work, collected 50 grafts, but only 3 of these were actually used in patients. The most practical method of husbanding these scarce commodities has so far been to freeze them to −70°C, and to keep them at that temperature by means of solid carbon dioxide. In this way storage may be prolonged indefinitely. Various tissues are known to survive this kind of treatment: arteries,[16] spermatozoa,[17] red blood-cells,[18] and skin[19] can all function successfully when thawed. Techniques for frozen storage of living tissues are complicated, and homograft survival is limited and uncertain, but enough has already been accomplished to illustrate the abundant surgical applications that may finally prove possible.

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[3] Hersey, J. Hiroshima. London, 1946; p. 104.
[4] Jacobson, L. O., Simmons, E. L., Marks, E. K., Gaston, E. O., Robson, M. J., Eldredge, J. H. *J. Lab. clin. Med.* 1951, 37, 683.
[5] Biskind, M. S., Biskind, G. R. *Proc. Soc. exp. Biol., N.Y.* 1944, 55, 176; *Ibid.* 1945, 59, 4; *Cancer Res.* 1950, 9, 35.
[6] Fawcett, D. *Anat. Rec.* 1950, 108, 83.
[7] Lemon, H. M., Lutz, B. R., Pope, R., Parsons, L., Handler, A. H., Patt, D. I. *Science*, 1952, 115, 461.
[8] Kemp, T. *Acta path. microbiol. scand.* 1930, 7, 146.
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[11] Hume, D. M., Merrill, J. P., Miller, B. F. Clinical Congress of the American College of Surgeons. 1952.
[12] Woodruff, M. F. A. *Ann. R. Coll. Surg.* 1952, 11, 173.
[13] Medawar, P. B. *Brit. J. exp. Path.* 1948, 29, 58.
[14] Woodruff, M. F. A., Woodruff, H. G. *Phil. Trans. B.* 1950, 234, 559.
[15] Peirce, E. C. *Ann. Surg.* 1952, 136, 228.
[16] Hufnagel, C. A., Eastcott, H. H. G. *Lancet*, 1952, i, 531.
[17] Polge, C., Rowson, L. E. A. *Nature, Lond.* 1952, 169, 626.
[18] Mollison, P. L., Sloviter, H. A., Clapham, H. *Lancet*, Sept. 13, 1952, p. 501.
[19] Billingham, R. E., Medawar, P. B. *J. exp. Biol.* 1952, 29, 454.

Kwashiorkor

In 1933 Cicely Williams[1] drew attention to a nutritional disease common among the children of the Gold Coast, where it was known by the vernacular name of kwashiorkor. Since then there have been numerous reports from all parts of Africa, and also from Asian, American, and even European countries, describing clinical syndromes which resemble kwashiorkor in greater or less degree. Some authors have emphasised similarities to the condition originally observed in the Gold Coast: others have laid stress on differences. Unfortunately, most of them have been able to speak from experience of only one area, and their accounts of varying ætiological factors and clinical features have made it hard to know whether the disorders they are describing are essentially the same disease. But whether they are the same or not, they are certainly very important as causes of misery and loss. The time is more than ripe, therefore, for an attempt to correlate the items of knowledge gained in the past twenty years, and we hope for useful results from the conference on kwashiorkor now in progress at Fajara in the Gambia, at which delegates from more than twenty African territories are meeting under the presidency of Prof. B. S. Platt, director of the Medical Research Council's field research station in that place.

It may be recalled that in 1950 a joint expert committee of the World Health Organisation and the Food and Agricultural Organisation recommended the subject for study by the United Nations[2]; and from this initiative comes a report[3] by Dr. J. F. Brock, professor of medicine at Cape Town, and Dr. M. Autret, of F.A.O. Having made an extensive African tour, they define kwashiorkor as a nutritional syndrome, common among the natives of many parts of Africa, in which characteristically there occurs: "(*a*) retarded growth in the late breast-feeding, weaning, and post-weaning ages with (*b*) alterations in skin and hair pigmentation, (*c*) œdema, (*d*) fatty infiltration, cellular necrosis, or fibrosis of the liver, (*e*) a heavy mortality in the absence of proper dietary treatment and (*f*) the frequent association of a variety of dermatoses." Perhaps it is this variety of the dermatoses, determined partly by local vitamin deficiencies and partly by environmental trauma, that has chiefly delayed agreement on the nature of the disease. Clearly there are local variations, related both to local dietary deficiencies (notably the varied intake of the B group of vitamins) and to local prevalence of tropical infections; but Brock and Autret showed that behind these variations there is a clinical entity at least as distinct as beriberi or pellagra. Pragmatically anyhow, the use of the word kwashiorkor has been justified, for it has led to the recognition and treatment of individual cases and to the devising of means of prevention. Physicians who have used it in the same sense as Brock and Autret include such authorities as Clark[4] and Trowell[5] in East Africa, Pieraerts[6] and Dricot et al.[7] in the Belgian Congo, and Bergeret[8] and Bergouniou and Trémolières[9] in French West Africa. Nevertheless there are dissidents, represented by Kahn,[10] of Johannesburg, who recently asked in this journal whether we are justified in "bundling together cases with and without œdema, with and without mucous membrane changes, with and without dermatosis, and so on?" He would restrict the term kwashiorkor to the pigmentary changes in the hair, which in some areas turns from black to russet; but he seems to be in error (with Cicely Williams) in believing that on the Gold Coast kwashiorkor means "red boy" and is solely descriptive of these changes. MacPherson[11] says that in fact it means "possessed by red devils" and is a sinister word knit with Gold Coast magic.

The first task before Brock and Autret was to establish whether or not kwashiorkor was a real medical problem, affecting large numbers of children in many parts of Africa. To this question their answer was an emphatic "yes." They went on to produce much evidence that a widespread lack of protein (particularly animal protein) in the diet during the early years of life is the all-important ætiological factor: as the Governor of the Gambia said in opening the Fajara conference,[12] the general opinion is that the main contributory cause is a deficiency in protein foods, especially at the time of weaning. The relation of deficiency in the diet to the deficiency in pancreatic function which was observed some years ago in children with kwashiorkor[13] and is now being further investigated[14][15] still needs to be worked out; but so far as treatment is concerned, the efficacy of proteins (particularly milk proteins) is almost beyond dispute. The problem of prevention, however, has no equally simple solution. We know that, apart from the heavy mortality, vast numbers of African children are retarded and stunted, both physically and psychologically, by this form of malnutrition: indeed it is no exaggeration to say that the African peoples will never be able to take their proper place in a free world so long as they are thus handicapped. The recent work of Dean[16] encourages the hope that proteins from vegetable sources will suffice for prevention; but before the African child of the future can receive a sufficiency of these there will have to be a revolution in African standards of mothercraft, and several revolutions in African agriculture. This is the kind of fact that we hope the conference, like the W.H.O.–F.A.O. report, will help to drive home.

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[2] *Lancet,* 1950, ii, 580.

[3] Kwashiorkor in Africa. F.A.O. Nutritional Studies no. 8 and W.H.O. Monograph Series no. 8. Rome and Geneva, 1952. Pp. 78. 5s.

[4] Clark, M. *E. Afr. med. J.* 1951, 28, 229.

[5] Trowell, H. C. *Trans. R. Soc. trop. Med. Hyg.* 1949, 42, 417.

[6] Pieraerts, G. *Bull. Soc. Path. exot.* 1950, 43, 120.

[7] Dricot, C., Beheyt, P., Charles, P. *Ann. Soc. belge Méd. trop.* 1951, 31, 581.

[8] Bergeret, C. *Bull méd. Afr. occid. franç.* 1948, 5, 257.

[9] Bergouniou, J. L., Trémolières, J. *Bull. Soc. Path. exot.* 1952, 45, 113.

[10] Kahn, E. *Lancet,* Sept. 20, 1952, p. 588.

[11] MacPherson, A. *Ibid,* 1951, i, 53.

[12] See *Times,* Nov. 20, 1952.

[13] Davies, J. N. P. *Lancet,* 1948, i, 317.

[14] Thompson, M. D., Trowell, H. C. *Ibid,* 1952, i, 1031.

[15] Srinivasan, P. R., Patwardhan, V. N. *Ibid,* Nov. 1, 1952, p. 864.

[16] Dean, R. F. A. *Brit. med. J.* Oct. 11, 1952, p. 791.

Annotations

A NEW NEUROSURGICAL UNIT

It is a far cry from the simple equipment of the psycho-analyst to the complicated machinery of the neurosurgeon. Some may see symbolism in the differences; but if ever the various disciplines are to be brought together in a single, comprehensive psychiatry, there is a lot to be said for bringing them together in a single, comprehensive hospital. A new step in this direction has been taken by the Maudsley Hospital where a neurosurgical unit was opened by Lord Waverley on Nov. 20. This joint enterprise between that hospital and Guy's—named the Guy's-Maudsley Neurosurgical Unit—is the first combination in London between an undergraduate and a postgraduate teaching hospital; for the university has hitherto felt that the demands of the two types of student would conflict. At the Maudsley Hospital the unit will have the great advantage of easy access to the laboratories of the Institute of Psychiatry, which is attached to the hospital.

The idea originated some years ago with the late Prof. Edward Mapother's intention to set up a specialised neurological department at the Maudsley Hospital. His death, and the war, prevented this from being put into effect. During the war it was suggested that a unit should be set up at Dartford. Finally, the present scheme took shape. The result is a stimulating example of coöperation among several bodies with different responsibilities. These bodies are Guy's Hospital, the joint Bethlem Royal Hospital and Maudsley Hospital, the South-east Metropolitan Regional Hospital Board, and the Institute of Psychiatry, which is part of the Postgraduate Medical Federation of the University of London. With so many associations nobody could accuse the new unit of parochialism; but to clinch the matter it has obtained from New Zealand its first director—Mr. Murray Falconer.

The unit consists of two ward wings, each of fourteen beds and a cot, and a third wing containing the operating-theatres; all the wings are on ground level. The wards, formed from a building which was already in existence, are in the form of a W, with the theatre block extending from the central point. The theatre block is designed so that the main theatre is in the centre, with the other rooms grouped round it. There is a smaller theatre; the usual anæsthetic, changing, and sterilising rooms; and also electro-encephalographic equipment for electrocorticography as well as routine testing. There is diagnostic X-ray equipment, a small pathology laboratory for quick sections and smears, and a conference room. The buildings were charged to the National Health Service; and the equipment and furnishings were bought from the endowment funds of the two hospitals.

These two hospitals have advantages which put them under an obligation not only to the rest of their region, but to the whole country and, indeed, to the Commonwealth. Their past histories suggest that they will not fail the future.

DWARFISM AND AORTIC MALDEVELOPMENT

CONGENITAL agenesis of the ovary gives rise to a well-recognised syndrome characterised by stunted growth, absent axillary and deficient pubic hair, amenorrhœa, underdevelopment of the sex organs, and increased excretion of gonadotropin and decreased excretion of 17-ketosteroids in the urine. Further clinical features include a barrel-chest, osteoporosis of spine and pelvis, wrinkled skin, cubitus valgus, and webbing of the skin of the neck.[1] In such cases coarctation of the aorta is not uncommon; and in the opinion of Albright et al.[2] this lesion, and not the ovarian insufficiency, accounts for the retardation of growth. On the other hand, van Buchem et al.[3] found that 115 reported cases of ovarian agenesis included only 12 with typical aortic coarctation (a combination that has been named Turner's syndrome). The part played by coarctation in retarding growth seemed questionable; but they found that distinct endocrine disturbances were commonly associated with electrocardiographic abnormalities, and they concluded that surgical treatment for coarctation in a patient with agenesis of the ovary should be preceded by œstrin therapy, which may improve the myocardium and thus reduce the risk of operation.[4]

In most patients with coarctation of the aorta but no other abnormality, the physical development is rather above average. Rokitansky,[5] however, noted an association between infantile aorta and hypogenitalism; and hypoplasia of the aorta commonly accompanies other congenital cardiac defects, such as atrial septal defect, which may cause skeletal and genital maldevelopment. Some patients with aortic hypoplasia die suddenly, and post mortem gross enlargement of the heart is usually found. In many of such cases the only satisfactory explanation seems to be an endocrine disturbance. The relation of developmental aortic insufficiency to endocrine disturbances should be further studied.

TERRAMYCIN

AMONG the newer antibiotics aureomycin and terramycin are often mentioned together as inseparable companions. But the first may appear as Mary, while the other often plays the subordinate rôle of Martha, though terramycin can fairly claim an audience in its own right. It was first isolated in Messrs. Pfizer & Co.'s research laboratories in Brooklyn, after an exhaustive search of thousands of soil samples, in one of which the responsible micro-organism, *Streptomyces rimosus*, was eventually discovered. Now that its structural formula has been established [6] it is possible that its mode of action may be more fully elucidated. There is nothing in the molecule to disturb our faith in the drug. The association of an amino group and a benzene ring usually raises doubts about agranulocytosis, but the modification in terramycin is such that few will entertain fears on this account alone.

In the pure state terramycin is a crystalline amphoteric substance of remarkable stability. It is usually prepared as the hydrochloride, and the dry compound shows no appreciable loss in activity even after prolonged storage at 25°C; the solution, too, maintains its potency over a wide range of pH, especially when kept at 5°C. Absorption from the gastro-intestinal tract is rapid, and what have been described as "significant, continuous blood plasma concentrations" are achieved with doses of 0·25 g. every six hours.[7] It is distributed through most of the body-fluids, though in the absence of meningeal inflammation the amount that reaches the subarachnoid space is probably not very great. The drug is readily excreted in the urine, still in its active form and in high concentrations; and relatively large quantities are also passed in the fæces. The commonest side-effects are nausea, vomiting, and diarrhœa; and occasionally stomatitis and epigastric pain are troublesome. These reactions can be minimised by giving the drug with milk, which in no way impairs absorption. Sometimes monilial infections arise and the drug has to be withdrawn. The remarkable alterations in intestinal flora which have been observed are probably due to the comparatively large amounts of terramycin which remain unaltered in the bowel.

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2. Albright, F., Fraser, R., Smith, P. H. *Amer. J. med. Sci.* 1942, 204, 625.
3. van Buchem, F. S. P., Homan, B. P. A. A., Dingemanse, E., Huin In't Veld, L. G. *Acta med. scand.* 1952, 143, 399.
4. Scherf, D. *Klin. Wschr.* 1938, 17, 44.
5. Rokitansky, C. *Handb. allg. path. Anat.*, *Vienna*, 1844, 2, 585.
6. *J. Amer. chem. Soc.* 1952, 74, 3708.
7. Finland, M., Gocke, T. M., Jackson, G. G., Womack, C. R., Kass, E. H. *Ann. N.Y. Acad. Sci.* 1950, 53, 290.

Its antibacterial activity is certainly comprehensive though it is on the gram-positive organisms that it exerts its greatest effect. The conditions which respond to terramycin include pneumococcal pneumonia, primary atypical pneumonia, pneumonia of mixed bacterial ætiology, hæmolytic streptococcal infections, brucellosis, the spirochætal and rickettsial diseases, gonorrhœa, lymphogranuloma inguinale, Vincent's angina and intestinal amœbiasis. On the other hand, it has no action at all on proteus and *Pseudomonas aeruginosa*, or in typhoid and salmonella infections, mumps, measles, chickenpox, smallpox malaria, and trichinosis. Its action on the staphylococcus is of particular interest because so many strains with a high resistance to penicillin are being encountered. In some cases terramycin provides the answer; in others it unhappily fails altogether. On the whole, staphylococcal infections can be controlled well enough by terramycin, but quite often the results are unsatisfactory. Moreover, instances have been reported in which staphylococci have appeared in the sputum of patients who were having terramycin for a pneumococcal pneumonia. But the question-mark before staphylococcal infections is a relatively small blot on the record of a drug that is clearly a valuable addition to our antibiotic resources.

HYALURONIDASE FOR CHRONIC LIMB ŒDEMA

LONG-STANDING œdema of the legs embarrasses patient and doctor alike. When the general causes of œdema—such as heart-disease, anæmia, and hypoproteinæmia secondary to liver or kidney disease—have been excluded, we are left with a large group of œdemas presumed to be of local origin. Sometimes these are familial; sometimes they are associated with obesity, varicose veins, or "poor circulation" in young women. An occult thrombosis of the deep veins of the leg may cause local circulatory failure, even without spectacular superficial varicose veins.[1] Little is known of the pathological anatomy or physiology of these chronic limb œdemas; and even if the initial exodus of fluid from the capillaries is easily reversed by elevation of the limb, changes in the connective tissue ensue and are associated with swelling which no longer pits easily on pressure, nor resolves on elevation of the limb. At this stage the results of treatment are not such as to dull our interest in revolutionary proposals.

Ferrero[2] has published a preliminary report on intra-arterial injections of hyaluronidase in twenty patients with chronic limb œdema. He gives 6–10 injections, each of 250–500 units of hyaluronidase, into the artery supplying the affected limb. A sphygmomanometer cuff on the limb is kept at venous pressure during the injection, and raised to arterial pressure just after the injection, to prevent excessive dilution of the injected material. The cuff is then tightened and relaxed intermittently. Treatment is given either daily or on alternate days. Good results are claimed both in postphlebitic and in "cryptogenic" œdemas. There is said to be no local pain and no general reaction. The sense of weight in the limbs is decreased, mobility improved, and the girth of the limb diminished; in some of the cryptogenic œdemas there was complete resolution. Ferrero suggests that in connective tissue there is a balance between hyaluronic acid and hyaluronidase; in chronic œdema this is upset in the direction of increased hyaluronic acid, with increased "gelation" of the tissues. Injection of hyaluronidase makes the tissue more fluid, and allows resolution of the œdema. Arterial injection, says Ferrero, seems a logical way of promoting what is essentially a local tissue action.

The results and the hypothesis do not necessarily stand or fall together. Confirmation of either or both can come only from further work; and neither can be dismissed out of hand, from what we already know of the action of hyaluronidase on the physical status of connective tissue,[3] the permeability of capillaries,[4] and the absorption of subcutaneous infusions.[5]

THE IRISH NUTRITION SURVEY

DURING and immediately after the late war the people of Ireland seemed to enjoy a relatively high standard of nutrition. But there was the inevitable doubt: is this prosperity, in part, an illusion, and is a section of the population improperly nourished? To answer this question the Irish Medical Research Council sponsored the National Nutrition Survey, which in 1946–48 systematically investigated food consumption and made a widespread clinical survey. The report of the survey has appeared in seven parts. The first four, describing the majority of the dietary investigations, were published in 1949.[6] The remainder[7] have now been issued. Parts five and six describe a dietary survey of farm-workers' families, and of a small group of rural families not engaged in agriculture, but for the most part prosperous. Part seven describes the clinical survey.

The diets of 2893 families were investigated. The over-all average weekly diet for the country comprised: milk 7·1 pints, eggs 5·1, cheese 0·8 oz., fats 10·6 oz., meat 30·7 oz., fish 3·5 oz., flour and bread 88·6 oz., other cereals 10·0 oz., potatoes 135·4 oz., vegetables 30·7 oz., fruit 7·1 oz., sugar 11·6 oz., and preserves 4·5 oz. Such a diet fully meets the most exacting nutritional standards. The calorific value is 3105 and the protein content 99 g., of which 42 g. is from animal sources. The calorific figure agrees with one of 3260 obtained from Ireland's agriculture and trade statistics for the F.A.O. food-balance sheet. This figure relates to production levels, whereas the survey figure is for consumption levels—i.e., after the inevitable losses in distribution and retail sale.

The report includes a separate analysis of 317 families whose economic position was likely to be precarious on account of unemployment or the death of the head of the family. In the unemployed groups the consumption of milk and meat was low, and in some the daily caloric intake was little over 2000. Clearly, although most of the population had ample good food, a small minority was subsisting on unsatisfactory diets.

In the clinical survey nearly 15,000 school-children, 570 adolescent boys and girls, and 320 expectant and nursing mothers were all examined by a single observer. Of all the children examined, the proportion reported to be in good nutritional state was 75%, while those in poor nutritional state came to less than 2½%. This judgment was based on subjective impressions derived from assessment of muscle development and tone, the quantity of subcutaneous fat, the strength of the hand-grip, and the colour of the mucous membranes. These are notoriously hard to judge, but no doubt the employment of a single observer made for consistency. His or her account (anonymity is preserved throughout the report) confirms the conclusion from the dietary study that the well-nourished population contained a small number of under-fed children. In most groups evidence of rickets was found in over 15% of children, and in one group such evidence was found in 29%; but unfortunately diagnostic criteria are not described in detail. Presumably in most children the lesions were old and long healed, and their detection was not incompatible with good, or at least fair, nutrition. Perhaps many of the children had developed rickets during the period February, 1942, to

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[1] Anning, S. T. *Lancet*, Oct. 25, 1952, p. 789.

[2] Ferrero, R. *Minerva med.* 1952, ii, 801.

[3] Day, T. D. *Nature, Lond.* 1950, 166, 785.

[4] Benditt, E. P., Schiller, S., Wong, H., Dorfman, A. *Proc. Soc. exp. Biol., N.Y.* 1951, 75, 782.

[5] Gaisford, W., Evans, D. G. *Lancet*, 1949, ii, 505.

[6] *Lancet*, 1950, i, 861.

[7] National Nutrition Survey, *Parts 5–7*. Obtainable from Government Publications Sale Office, G.P.O. Arcade, Dublin. 1s., 1s. 6d., 3s. 6d.

April, 1943, when Ireland consumed 100% extraction flour without added calcium and there was a high incidence of active rickets in children aged 1–4 years.[8] After the return to 85% extraction flour and the addition of calcium, the incidence of the disease declined greatly. In the towns height and weight showed a statistically significant, but not striking, relationship with social class. In rural areas this correlation was not distinct.

The survey has provided a simple answer to a simple question. The reports, though uniformly silent about names, make clear that the survey depended on an excellent organising committee of the national Medical Research Council, the goodwill of the various public-health departments, and a team of ten women field investigators and one full-time clinician backed by continuous expert statistical advice. Significantly, there was no biochemist and indeed no laboratory work of any sort.

PERSPECTIVE OF DIABETES

Prof. Elliott P. Joslin and his collaborators have perhaps had the opportunity of assessing more cases of diabetes than any other group of physicians in the world. In a preface to the ninth edition of their famous textbook,[9] they mention the 40,000 patients who have consulted them for diabetes, and draw some important lessons from this vast experience. Before the discovery of insulin, coma and tuberculosis were major causes of death in diabetics; now deaths from coma at the New England Deaconess Hospital have fallen to 1·1%, and from tuberculosis to 0·9%. In 75% of deaths nowadays the cause is cardiovascular-renal disease; but they say that when they began treating diabetes they were more hopeless of reducing the death-rate from coma and tuberculosis than they now are of postponing, reducing, or even eradicating premature cardiovascular-renal disease. From 12,281 fatalities they have drawn the firm conclusion that "of those complications which have ravaged our diabetics most can be explained by failure to control the disease." Retinitis, nephropathy, and neuritis, they are able to assert, are among such complications: their prevention depends on continuous control, and the aim of the book is to make such control possible.

The danger, Joslin and his colleagues say, lies in the fact that today almost any diabetic, young or old, will live ten years if he is given a moderately restricted diet plus insulin. But the patient who designs to live two, three, or four decades after the onset of his disease must make the effort to live a model diabetic life. This is especially important with children; for though the measures needed to defeat coma and tuberculosis were relatively simple, the conquest of neuritis, retinitis, nephritis, and cardiovascular degeneration depends not only on diet, exercise, insulin, and education, but also on control of the patient's human nature. Nor is it sufficient merely to convert the patient: his doctor too, "with missionary zeal," must be converted. A charming aspect of this kind of enthusiasm led the Boston Safe Deposit and Trust Company to offer the Quarter Century Victory Diabetes Medal to those who live twenty-five years with their disease and are perfectly well at the end of it. In 1948 insulin itself was only twenty-six years old, and Joslin and his team knew only 1 such patient; now there are 34 holders of the medal, and the number is expected to increase by leaps and bounds. But these observers say they have never seen a diabetic with the disease uncontrolled for twenty-five years who could meet the criterion. On the other hand, a time may come, they suggest, when the diabetics with their diseases well controlled and their health carefully maintained will outlive their contemporaries.

LOCAL TREATMENT OF LEG ULCERS

Celsus used plasters for leg ulcers and Galen applied wine, but both recognised the importance of firm bandaging. Guy de Chauliac in the 14th century tried waxed cloth or diachylon or some cold adhesive plaster, and 200 years later Paré was using ointments to clean the ulcer, pressure pads soaked in wine or oxycrate, and sometimes a lead plate. He insisted, as did Galen, that the ulcer should not be dressed too often and that firm bandaging was essential. Though a variety of dressings were later used for the local treatment of leg ulcers, the principles of treatment remained much the same until Lister's time, when the control of micro-organisms on the surface of the ulcer by means of antiseptics became an increasingly important consideration.

Dickson Wright,[1] however, showed that a leg ulcer would heal, although infected, if the œdema was abolished. He wrote: "There is no need to invoke a stubborn bacterial infection to account for the chronicity of varicose ulcers; it is purely a matter of hydraulics." Nevertheless, an ulcer sometimes becomes offensive and extends rapidly as a result of secondary infection, which, after bacteriological investigation, may be controlled by an appropriate antibiotic. Streptomycin [2,3] and aureomycin [4,5] have been found useful, but there is no advantage to be gained from applying them for more than a few days. Moreover, there is some risk of sensitising the surrounding skin, particularly if penicillin cream is used. Various antibacterial substances have proved effective: *p*-chlorophenol, phenoxyethanol ('Phenoxetol'), silver dinaphthylmethane disulphonate,[6] and ozonide of olive oil.[7] More recently Sommerville and Devine [8] have described the use of 'Furacin' (5-nitro-2-furaldehyde semicarbazone) in a carbowax and propylene-glycol base. Some patients were ambulant and wore supporting bandages; others were kept in bed. The results seem promising, but a furacin dermatitis developed in 8 of the 25 patients they treated. Moreover, it is impossible to assess such treatment without comparing the results with those in a similar group of patients treated by rest or bandages, but without furacin. Local protective dressings are sometimes helpful, and adhesive tape [9] and boiled human amnion [10] have been used for this purpose. Ointments containing unsaturated fatty acids seem to have no value except as soothing dressings. There is a danger that drugs may be absorbed from the raw area, and ointments containing resorcinol have caused myxœdema.[11]

Although various kinds of local treatment may improve matters, it is important that they should be used only as ancillary measures. Anning [12] lately stressed that if attention is given to the circulation of the limb as a whole, the base of the ulcer and its flora may usually be ignored. To cure a leg ulcer, the œdema must be abolished, whatever local treatment may be used, and too often in the past concentration on local treatment has led to neglect of this fundamental principle.

MR. J. D. KING, D.SC., F.D.S., director of the Medical Research Council's dental research unit at King's College Hospital, London, died on Nov. 22, at the age of 45.

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Special Articles

THE CAT OR THE CAUSE?

Proposed Return to Corporal Punishment

THERE are dangerous possibilities about the mounting agitation in some quarters for a return to corporal punishment for crimes of violence. An air of emotional fervour about this movement, of a type to which Parliament has sometimes responded in the past and which is in sharp contrast to sober Ministerial statements, means that there is some risk of the sudden passage of new legislation, which, under pressure of strong emotion, may not be wise.

Notoriously, in the dispute about corporal punishment, reasoned argument has failed to sway the issue. It might almost be concluded that people either deeply wish that violent criminals should be flogged and murderers hanged (for these wishes often go together), or they do not; and there is an end of the matter. Perhaps a majority of the judges on the Queen's Bench, some of the magistrates, but not the Law Lords or the Secretary of State, share this wish; most of those engaged in works of social amelioration and reform do not; religious leaders appear to be divided. How can the hypothetical man-in-the-street be other than confused and uncertain in his attitude?

The popular press is often blamed for giving so much lurid publicity to crime and for being selective, conducting campaigns about certain types of crime. There is no evidence that such campaigns affect the incidence of crime, but they must to some extent poison the public attitude. In one sensational incident in New York in which public anxiety over a so-called wave of sex crimes became intense under a vivid press campaign, it was found later that there had been no more than an unusual sequence of similar crimes, the incidence for the year being normal. What harm was done to the public by this experience is a matter for speculation; but certainly little good. Experience indicates that, though publicity may suggest to a criminal a certain detail of action, it will scarcely cause a crime to be committed. However, positive good might follow if the press were to pay more attention to St. Paul's injunction to think on those things which are true, lovely, and of good report.

The parties to this dispute naturally differ as to whether corporal punishment is or is not a deterrent. Proponents often back their argument, implicitly or explicitly, with the concept of corporal punishment as punishment or retribution; opponents back theirs with humanitarian considerations and their concept of civilised behaviour. They agree that prison will protect the public from the criminal for the duration of the sentence, but they differ in regarding prison as being on the one hand primarily a punishment and a deterrent, and on the other hand as a potential opportunity for reform. Some who are uneasy about corporal punishment will pin their faith on making prison a most unpleasant place in which the criminal will spend a very long time.

A DETERRENT?

The defects of statistics as a means of proof have often been emphasised, but it is at least impressive that nobody seems to have produced figures to show that corporal punishment can be a deterrent to crime. Table I, based on Home Office figures for England and Wales, contains several points of interest. It will be seen that the offences for which corporal punishment used to be authorised have actually decreased since corporal punishment was abolished in 1948—this in a period when all other forms of indictable offence, including all other forms of violent crime, have increased. In 1947, of convicted persons liable to corporal punishment, only 6% were sentenced to receive it, and these represented only about 0·01% of all the indictable offences known to the police. One may wonder whether the prospect of corporal punishment appeared more than very remote to the criminal as he went out to commit his crime.

The figures for the war-time whipping of boys under 14 (table II) are truly remarkable, for in 1940 the amount of whipping suddenly rose sixfold to reach a peak in 1941 at eleven times the 1938 level, only to decline as abruptly to reach half its 1938 level in 1945. Meanwhile indictable offences rose by nearly two-thirds between 1938 and 1940 and remained at that level throughout the war. It strains credulity to believe that increasing whipping from 0·3% of offenders in 1938 to 1·3% in 1941 (and reducing it to 0·1% in 1945) warded off a much bigger rise in juvenile crime and held the level steady for two years after the policy was abandoned. It is easy to understand how, under the pressure of increasing crime and of war-time magisterial uneasiness, this form of punishment was adopted. It is less easy to see why it as suddenly disappeared; but at least there is no hint in these figures that whipping was regarded by the magistrates at *that* time as a successful deterrent.

TABLE I—CRIMES OF VIOLENCE AMONG ADULT MALES

—	1945	1946	1947	1948	1950	1951	First 6 months, 1952
Offences for which corporal punishment could be ordered before September, 1948:							
Armed robbery and robbery with violence	..	804	842	..	812	633	359
No. of convicted persons sentenced to corporal punishment	..	35	50	..	..	..	..
Percentage of convicted persons sentenced to corporal punishment	..	4·4	5·9	..	..	..	..
Offences for which corporal punishment could not be ordered in 1945–48:							
Felonious wounding	..	..	..	646	..	1078	..
Malicious wounding	..	..	..	3547	..	4445	..
Rape	..	..	..	252	..	335	..
Indecent assault on females	..	..	..	5659	..	7287	..
Total no. of indictable offences known to the police ..	478,394	..	..	..	..	524,506	..
Percentage of convicted persons sentenced to corporal punishment ..	0·01	..	..	..	..	..	..

Statistics of murder for the years 1939 to 1945 (table III) show some of the reasons why hanging, which was practised at that time without some of the hesitations which have lately appeared, may equally *not be an* effective deterrent. First, people were brought to trial for only about half the known murders; presumably many of these had evaded punishment by committing suicide. Secondly, while 174 guilty persons were deemed to be sane, 209 were, at some stage of the proceedings, deemed to be insane. Thirdly, only about half of the sane persons convicted of murder were executed: of those charged with murder the proportion executed was only 1 in 6, and for every 11 murders there was only 1 execution. 12 executions per year among 40 million people; for 900 murders, 82 executions: what a problem in calculating risks for the 19% of murderers caught and deemed sane!

TABLE II—WHIPPING IMPOSED BY MAGISTRATES' COURTS, BOYS UNDER 14 YEARS OF AGE

—	1938	1939	1940	1941	1942	1943	1944	1945
Number of sentences	48	58	302	531	314	165	37	25
Number of boys found guilty of indictable offences	14,724	16,724	23,167	23,083	20,382	21,058	22,525	22,922
Proportion of offenders per 100,000 of age-group	798	930	1304	1324	1184	1234	1330	1361
Percentage of convicted offenders sentenced to whipping ..	0·33	0·35	1·30	2·31	1·54	0·79	0·17	0·11

Figures, excluding calculations of percentages and proportions, taken from the Home Office's *Criminal Statistics for England and Wales*, Cmd. 7227. H.M. Stationery Office. 1947.

For a deterrent to be effective, either there must be an appreciation and dislike of the consequences, combined with self-control, or else there must be sheer fear of those consequences. Common sense and psychology agree that if all men possessed the qualities of intellectual appreciation, self-control, and foresight, there would be fewer murders and crimes of violence. Criminals who are capable of calculating risks are far more likely to go in for confidence tricks, fraud, and the like. Violent crime is largely a matter of primitive emotional forces, of very great strength. Moral standards and the adult's positive desire for good come from the child's birthright of love and trust in the home, which, if denied or betrayed there, may engender such hatred and hostility in an individual that the forces of morality, with all their strength, are swept aside. Violent crime is not merely a matter of low moral standards, of slackness, or of work-shyness, but arises from intense antisocial emotions. How can it be hoped that a problematical punishment in the future—a highly abstract eventuality for the primitive person concerned—will have a strong deterrent effect?

RETRIBUTION?

When all the available evidence is to the contrary, adherence to the opinion that these punishments are deterrents can only signify a deep need to justify a belief held for emotional reasons. If it could now be recognised that corporal punishment is advocated out of sympathy for the victim, because of a need for revenge, a primitive desire to mete out to the thug what he has done to another, a notable advance would have been made. Then the British people would be faced with a clear-cut issue—whether direct acts of retribution are or are not a desirable principle of justice. They could consider whether society can afford to sink to the level of, and to take revenge on, its criminal members; whether, in striving to return to more civilised standards of behaviour after a war, even a small matter like the flogging of fifty men each year may not be undesirable. If there is no justification in expediency, there is no escape from the moral issue, unless some bold spirits should wish to attempt to justify the expediency by flogging ten or a hundred times the number of criminals in an attempt to secure a deterrent effect.

TABLE III—MURDER OF PERSONS AGED ONE YEAR AND OVER, SEVEN YEARS, 1939–45 INCLUSIVE

Murders known to the police:		
Total no. of murders known to the police..	900	
Average number of murders per year ..	129	
No charge preferred (murderer committed suicide, &c.)	426	
Total number of persons brought to trial..	474	
		Percentage of the persons brought to trial
The trial:		
Found insane on arraignment	84	18
Found not guilty	102	21
Found guilty but insane by the jury ..	114	24
Found guilty	174	37
		Percentage of sane persons convicted
The sentence:		
Aged under 18 years and detained during H.M. pleasure	14	8
Sentenced to death	160	92
Sentences quashed by Court of Criminal Appeal	11	6
Found insane on enquiry and sent to Broadmoor Asylum	11	6
Reprieved by action of the Secretary of State	56	32
Executed	82	47
Average number of executions per year ..	12	..
Total number of guilty persons found insane..	209	
Total number of guilty persons found sane ..	174	
Proportion of known murders to executions	11 : 1 (approx.)	
Proportion of charges of murder to executions	6 : 1 ,,	
Proportion of convictions of murder to executions	2 : 1 ,,	

PREVENTION?

The essential distinguishing feature of the cool calculating criminal—the conscienceless rogue—is that he is conscienceless; and of the violent thug that he has emotional reactions and relationships more appropriate to a child of two or three than to his adult body. No-one would dream of blaming a child for having rickety legs, and modern research is now showing that psychological medicine, too, has its deficiency diseases. To hold that criminals are just "plain wicked" is a counsel of despair; and the present-day need of society is for research into causes, not for "cats."

The incidence of crime in a community shows some relation to the rate of change of social institutions therein. A rise in the level of crime is associated with rapid industrialisation, social revolution, and war, and the war-time training in and approval of violent behaviour among the young males is no doubt associated with the steeper secondary rise experienced when peace returns. The effect of war-time disturbances of home life is likely to last for many years—indeed so long as the young men and women involved are active in crime. Other factors that produce more local and temporary variations in the crime-rate include social injustice, political tension, and the moral attitudes of the community.

The prevention of criminality thus requires a many-sided approach. The main object must be to improve the mental hygiene of family life, which may be attempted through economic, sociological, and religious activities. But one of the very important tasks is to improve the quantity and quality of recruits to the police forces and to seek a reorientation towards the more truly preventive aspects of their work.

Even effective prevention, however, does not solve the problem of the existing criminal, for whom, it must be stated, the approved-school and borstal systems are giving only mediocre results and prison is often almost disastrous. A long sentence may give merely a respite from criminal activity and is more likely to demoralise than rehabilitate the criminal. From the very conditions of prison life, psychological treatment in prison does not hold out any great hope of success; but a more concerted effort to raise, not lower, the prisoners' self-respect deserves serious trial. The Home Secretary has pointed out that the Criminal Justice Act envisages such efforts, but that there has not yet been opportunity to bring them into being.

Only organisational difficulties—and they are formidable—appear to stand in the way of attempting to make prisons self-supporting, to make inmates work for their living. To introduce a new spirit of this type might breathe new life into the Prison Service and counteract the demoralising effect on staff of the purely custodial care of caged human beings. Continued neglect of such an experiment is perilous for society.

A CHANGE OF ATTITUDE

It would be well if the current agitation for an arbitrary change in the law, with no thought for principle, were quickly brought to an end. The public needs a respite from fears aroused by the fantasy that the country is being overwhelmed by violent lawlessness, a fantasy which is far removed from the fact. Much good would follow from more objectivity in the press, and less exploitation of the situation for the sake of the circulation; more circumspection, especially in public utterances, by leading judges and magistrates; and more thought by the general population about the moral and spiritual values of our civilisation, including recognition of the effect of the more primitive emotions on our thoughts and conclusions.

GENERAL MEDICAL COUNCIL

OPENING the 185th session last Tuesday, Prof. DAVID CAMPBELL, the president, remarked that the Dentists Bill had not gone further than the first reading in the House of Commons before the close of the Parliamentary session. It would, therefore, have to be renewed in Parliament as though it were being introduced for the first time; and it appeared probable that the council would have to continue to carry out its duties in relation to the dental profession for an indefinite period.

The next edition of the *British Pharmacopœia* would be published on March 1, 1953, and have effect from Sept. 1, 1953. A quarter of a century ago the Macmillan Committee, whose report was accepted by the council, urged that the body preparing future issues of the *British Pharmacopœia* should not only be composed of thoroughly qualified persons but should also be such as to command the confidence of all the interests concerned. The committee to select the new Pharmacopœia Commission would, therefore, consist of representatives of the council, the Pharmaceutical Societies of Great Britain and Ireland, and the Medical Research Council.

The council had decided to put into operation that part of the Act of 1950 which empowered them to appoint visitors, not being members of the council, to medical schools and examinations. It proposed to select men of special qualifications and of experience on particular subjects, and to arrange for them to visit both the schools and the examinations.

The Appointed Day for introducing the compulsory period of service as a house-officer was to be Jan. 1, 1953. Approved hospitals and institutions numbered 634—456 in England and Wales, 104 in Scotland, 24 in Northern Ireland, and 50 (approved by the Medical Registration Council of the Republic) in Eire. The total number of posts was 3048—280 in Eire and 2768 in the United Kingdom. Of the United Kingdom posts 926 were in general medicine, 972 in general surgery, 342 in midwifery, and 528 in the various specialties (171 primarily medical and 357 primarily surgical). Holders of recognised Commonwealth or foreign diplomas would be able to claim registration if they had been employed for the prescribed period in hospitals approved by licensing bodies of this country, and if they satisfied the council that they had rendered satisfactory service under the conditions applicable to holders of diplomas granted in the British Isles. Applicants holding recognised Commonwealth or foreign diplomas who could not claim full registration on this basis could claim such registration if they had acquired otherwise substantially equivalent experience of the practice of medicine and surgery.

No doubt, at the beginning some of the machinery might creak; but, given the coöperation of student, medical school, and hospital authority, it should soon run smoothly. The student might be assured that the authorities of his school would do everything they could to help him to secure suitable posts; but that would not free him from using his own judgment and himself seeking employment, as those before him had done. It was certain that all licensing bodies and schools would prefer each student to take posts for 6 months in general medicine and 6 months in general surgery; and if that was impracticable, they would insist that 6 months should be spent in either general medicine or general surgery. Before accepting any particular post included in the list published by the council, the applicant should consult the authorities of his school as to whether the combination of posts he proposed would be recognised by his licensing body to enable him to qualify for full registration. Hospital authorities could help greatly by synchronising as far as possible their appointments with the periods at which final examinations were held. By effecting a revision of existing staff arrangements and providing the requisite residential accommodation, they might also secure the recognition of hospitals not yet approved and thus add to the number of suitable posts. The ultimate responsibility lay with the licensing bodies. The council's sole object was to perfect the administrative machinery and to do all in its power to enable these bodies to ensure that this measure would lead to a higher standard of medical care and practice.

DENTAL TREATMENT OF CHILDREN

THE British Dental Association found, from the answers to a questionary, that private practitioners were willing to set aside about 10,000 hours per week for the dental treatment of school-children; and in a memorandum[1] to the Government it suggested that this might help to provide a short-term solution to the problem of obtaining enough treatment for this priority group. In their reply the Ministers of Health and Education and the Secretary of State for Scotland state "certain principles which they consider to be fundamental to the proper organisation of a dental service for the priority classes and to which in their view both short term and long term policy must have regard.

"The first is that as has been shown by experience the most effective way of providing treatment for school-children is in clinics closely associated with school routine so as both to ensure the attendance of children in need of it and to cause the least interruption of their education. Treatment for younger children can most effectively be provided by a clinic service forming part of the local health authorities' general arrangements for the care of mothers and children, so as to encourage attendance and meet the convenience of the mothers.

"Secondly, it is imperative, particularly in present economic circumstances, to achieve the utmost economy in expenditure and here again experience has shown that children can be treated in clinics at a substantially lower cost than when treated by private dentists remunerated for each item of treatment on the scale of fees in operation under the general dental service.

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[1] *Brit. dent. J.* Oct. 21, 1952, suppl. p. 53; see leading article, *Lancet*, Oct. 25, 1952, p. 811.

"Thirdly, one of the fundamental difficulties facing all branches of the dental services at the present time is the shortage of dentists. In the treatment of children dental manpower can be used more economically in clinics than in private practice. As the Association themselves recognise the public dental officer working in a clinic can make the best possible use of ancillary help such as chairside assistants and oral hygienists. In such a system the public dental officer can play his full part and achieve a most useful and satisfying position with responsibility for the full care of the child's teeth. Under the Association's proposals it would seem that responsibility would be divided, the volume of treatment the public dental officer could undertake would be materially reduced, and he would be able to do little more than 'act as co-ordinator.'

"The Ministers therefore feel that the improvement of the special priority service for children must be sought on the lines of expanding the existing clinics rather than of transferring part of the service to private surgeries; and it is for this reason that clauses 5 and 6 have been included in the Education (Miscellaneous Provisions) Bill now before Parliament.

"The Ministers, however, are most anxious that the maximum number of dentists should have an opportunity of working in these clinics either whole or part time and as the Association know circulars were issued to all local health authorities and education authorities earlier this year urging them to invite dentists to give their services in this way. The Ministers are therefore particularly glad to see that the questionnaire circulated by the Association has elicited that there are a total of 583 practitioners willing to work part time in the clinics and the Association have already been invited to ascertain the names and addresses of these practitioners and to supply them to the Departments so that every effort can be made to secure their services.

"The Ministers note from the results of the Association's questionnaire that a large number of dentists share their views that the dental care of the priority classes should take first place in the public provision of dental treatment. They would like to see the private dental practitioners of each district together agreeing to accept collective responsibility for the dental care of the district's children (in so far as might be necessary to supplement the services already provided by the local authorities) and for this purpose offering part time service in the dental clinics organised by the responsible health and education authorities."

TRIALS OF INFLUENZA VACCINE

The Medical Research Council, in conjunction with the Ministry of Health, is organising trials this winter of a vaccine against influenza A.[1] This vaccine, selected as a result of investigations last winter, is suitable to the strain most likely to give rise to influenza in the coming months.

The trials are due to start early in December in volunteer groups throughout the United Kingdom. The volunteers involved are likely to total about 15,000 and will include smaller groups in hospital nursing staffs and the universities with larger groups in industry and the Services. In addition a special trial is to be carried out in villages in the Isle of Lewis, Scotland.

Two vaccines will be used—one the new vaccine, and the other (as a control) a vaccine of the type which has been available for a number of years. Half of the volunteers will be inoculated with the one vaccine and half with the other. They will then be supervised for 3 months. In many cases, particularly in the industrial groups, responsibility for treating illness during this period will rest with general practitioners. All general practitioners called in to see volunteers are asked to fill in the simple record form with which they will be provided. All concerned are asked to make effective use of the laboratories of the Public Health Laboratory Service for diagnosis and the determination of virus strains.

More detailed information is obtainable from the secretary of the Medical Research Council's committee on clinical trials of influenza vaccine, at the Ministry of Health, 14, Russell Square, London, W.C.1 (tel.: Museum 6811, ext. 23).

Medicine and the Law

Negligence Claim Settled

If allegations of negligence are made against hospitals or medical practitioners and are presently withdrawn on the offer of an agreed sum, the medicolegal interest of the proceedings disappears, unless it be worth while to record the kind of mistake which was alleged and the amount of the agreed damages.

In Ross *v.* Tunbridge Wells Group Hospital Management Committee and another (*Times*, Nov. 21), the plaintiff's claim arose out of the death of her husband. His age was 40; it was stated that he had never consulted a doctor in his life or suffered anything worse than a common cold. He entered hospital on his dentist's advice for extraction of a wisdom tooth. His heart, it was said, stopped on the operating-table; it was got going again, but he died after 48 hours. Counsel for the plaintiff widow, opening the case as one of the most extraordinary that could come before the courts, stated that the deceased was given a preliminary anæsthetic by injection before being brought into the theatre. For anæsthesia in the theatre a Boyle's apparatus was used with a combination of nitrous oxide and oxygen. It was suggested that carbon dioxide was somehow mixed with the oxygen. When a further gas—cyclopropane—was administered, the patient collapsed. It appeared most likely, said counsel, that the patient was asphyxiated by the introduction of the carbon dioxide.

The defendant hospital's committee and the second defendant denied the negligence. On the morning of the second day of the hearing, counsel (who had first seen the judge in his private room) announced a settlement. Plaintiff's counsel said that a substantial sum (representing in his view the amount which his client might have expected, if successful, to recover) had been offered by the defendants. This sum the plaintiff was prepared to accept, and accordingly the allegations were withdrawn. He asked for an order that £1000 be paid to her immediately. It was a term of the settlement that her costs should be taxed as between solicitor and client. The judge observed that in his opinion the parties had been well advised to come to terms. He added that the sum mentioned was almost exactly the figure which he himself had provisionally assessed as the amount the plaintiff might recover if she succeeded in establishing the defendant's liability.

A Varied Claim

For surgeons perhaps the main interest in the case of Moon *v.* Bristol United Hospitals and Fairman[1] was that an allegation was made against a professional man on somewhat speculative grounds, that his evidence was not challenged, and that the claim against him was dismissed with costs before the end of the trial.

Mrs. Moon asked for damages against the hospital defendants and the surgeon on various grounds. Her husband underwent tonsillectomy on Feb. 1, 1949. At 2 A.M. next day he complained that his arms and legs were useless. He also suffered a burn on the abdomen from a hot-water bottle. The paralysis having been mistakenly attributed to hysteria, he was removed to a mental hospital but was soon brought back, the records diagnosing his case as "complete spinal cord lesion following extraction of tonsils." Later he was able to go home, but had daily treatment at the hospital. His condition deteriorated; he was admitted to the Bristol Royal Infirmary where he died on Dec. 27, 1950. Post-mortem examination revealed widespread cancer in the pelvic region. The allegation of negligence in the mistaken diagnosis, resulting in the removal to the mental hospital, was disposed of by an offer of compensation which the widow accepted. The allegation of negligence on the part of Mr. H. D. Fairman, the operating surgeon, took the form of suggesting that the patient was allowed to slip or fall or slide off the operating-table head first into a bucket. Mr. Fairman's evidence repudiated this suggestion; a witness who had assisted him said he did not remember that there had been any untoward incident. The judge asked plaintiff's counsel whether in the circumstances he alleged want of care against Mr. Fairman or not. Counsel replied that he did not reject Mr. Fairman's evidence. The judge then told the jury that there was no evidence against Mr. Fairman and the case against him was dismissed. Counsel for the defendant hospitals contended that Mr. Moon died of cancer and that the death had nothing to do with the operation. The paralysis, he argued, was just misfortune and nobody's fault. It was stated that the deceased had a protruding intervertebral disc; the jury were shown X-ray photographs of the spine taken before and after the operation. As regards the burn caused by the hot bottle, there was evidence that the deceased had asked a fellow-patient to fill his bottle; the fellow-patient had done so "with good intent"; the burn resulted from this action more benevolent than wise.

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[1] See *Lancet*, Nov. 15, 1952, p. 993.

[1] *Manchester Guardian*, Nov. 10, 13, 14, 15, 19, 20.

Summing up to the jury, the judge commented on the absence of evidence from the anæsthetist. In the end the jury awarded £2000 on the claim of negligence against the hospital and £2000 for the loss of expectation of life. The judge gave judgment on the first £2000, with costs against the hospital, Mr. Fairman also to have his costs from the hospital board. No final judgment, however, was given on the second £2000. The judge is to hear legal argument in London (probably next year) as to the widow's right to damages for loss of expectation of life if the cancer had not supervened.

Another Hot-water Bottle Case

In Hickey *v.* North Liverpool Hospital Management Committee the plaintiff was a young married woman who went to hospital for the birth of her second child. According to the judge's findings, at some stage of her labour and the subsequent surgical treatment the patient was burned on the left hip by a hot-water bottle, the burn causing an indolent ulcer. Apparently at one time there were four stone hot-water bottles, filled from the hot-water tap, in the bed, each enclosed in a flannel jacket. There was evidence of the custom to place the bottles not actually in contact with the patient but with a blanket between it and her. At the stage mentioned there was a bottle at either hip and two bottles in the region of the plasma drip. The judge seems to have drawn the inference that as only one bottle had caused a burn, there must have been some negligence in respect of that bottle. If in cases of extreme shock, he thought, the blood-vessels do not dilate, the condition should have been the same in one as in another part of the body, supposing that heat of a similar degree were applied in similar conditions. He awarded special damages of £2 and general damages of £150 with costs. The patient had required some treatment as an outpatient after leaving hospital; a small operation under an anæsthetic had been necessary to clean the ulcer and encourage healing.

The judge referred guardedly to expert evidence from witnesses who, in his words, "frankly agree that their opinion is not the generally accepted opinion of the medical profession although of course their prophecies may in due course be believed." This seems to be an allusion to the theory that in very severe shock heat may be useless and even injurious.

Parliament

The Preregistration Year

IN the House of Commons on November 19, Mr. IAIN MACLEOD, Minister of Health, formally moved an order, which prescribes 12 months as the period of preregistration service made compulsory for newly qualified doctors, by the Medical Act, 1950. No objection to the proposed span of service was raised, but support was offered with discrimination as well as goodwill, and the debate ranged widely and usefully over practical difficulties that may need adjustment.

Mr. ARTHUR BLENKINSOP suggested that on the introduction of the intern year the opportunity should be taken to examine the whole medical curriculum so that too severe an extra strain should not be imposed on the student. The Goodenough Committee, he recalled, in sponsoring the preregistration year, had recommended that the training period should be no more than four and a half years. He also wondered whether the country as a whole was ready for the operation of this proposal. Was the Minister satisfied, he asked, that suitable posts were available for all who would need them? He hoped that the posts would not merely be a continuance of the old house-officer appointments but would enable the interns to move around in the hospital and get a valuable extra training.

Dr. BARNETT STROSS was also concerned that the student should make the best use of this extra year. What the student needed was not more theory, but further practical education with limited responsibilities. The intern, Dr. Stross suggested, should not be limited to surgery for six months and medicine for six months, but should go widely round the departments and learn more about treatment. Dr. Stross also pointed out that a medical student with a family might be receiving over £500 a year in grants at present, and it would be anomalous if under this scheme he dropped in the first six months to £350, with exactly the same responsibility, and his total remuneration for the second six months was only £400.

SATISFACTORY SERVICE

Mr. JOHN HYND believed that if an intern had completed 12 months' service it should be assumed that he had been satisfactory. In his view interns were no longer students; they were practising doctors taking the first stage of their practical experience in a hospital, which provided special facilities and opportunities not afforded in ordinary practice. Could there be some provision that any intern not considered satisfactory should be warned? Perhaps the best solution would be to drop the reference to satisfactory service altogether. It was also important that there should be some arrangement to carry the young doctor over the period when his education grant finished on qualification to the time when he obtained a post.

Mr. SOMERVILLE HASTINGS was anxious that the interns' time should be fairly divided between medicine and surgery. They must also have time, not only for study and thought, but for rest and recreation as well. Personally he had never been so tired as he was when he held his first six months' surgical appointment. The Goodenough report had made this point strongly and had suggested that in a teaching hospital the young doctor should only be in charge of perhaps 20 beds, and in a non-teaching hospital of perhaps 30. He felt that if an intern's services were not regarded as satisfactory during one of his two appointments he should be given another chance. Litigation for alleged neglect in hospitals had increased enormously since the introduction of the National Health Service, and he was afraid that those who lived on litigation would soon learn that there were such things as unregistered interns and would be ready to apply for compensation where these junior people had been involved. He thought every intern should be insured in a medical protection society.

POSTS AND ALLOWANCES

Mr. MACLEOD said it was everybody's opinion that by and large there would be enough posts next year in the preregistration service, but they might not be in exactly the right places. Only 200 students would qualify in the first three months of next year and it would be easier to start the scheme and deal with any teething troubles at a time when comparatively few people were qualifying. How the students were to get the posts, and whether they should apply for them and perhaps be interviewed before qualification, were difficult problems. In many things they would have to learn from experience. Often the qualified student would be able to spend part, or, with luck, all his preregistration year in the hospital where he had studied as an undergraduate. Mr. Macleod had invited hospital authorities to coöperate with the universities and medical schools to ensure that the newly qualified doctors should not have to wait an unreasonable time before they took a hospital post. Most of the interns would be ex-Service students who had been eligible to receive modified allowances from the Ministry of Education as house-officers after qualification. That system was to be continued for preregistration service, and a married man with one child would probably get about £414 compared with the £427 that he had been receiving during training. The Minister of Education would also pay for a period not exceeding two months a sum, based on the usual vocation allowance to newly qualified men who could not get a house-post as soon as they qualified.

Mr. Macleod was sympathetic to the suggestion that the unsatisfactory intern should be warned, but he was not responsible for deciding what form the medical curricula, and indeed this certificate, should take. The point raised by Mr. Hastings about the way in which the preregistration year should be spent was also important, but here again the responsibility rightly lay with the General Medical Council and not with him. But he promised to see that the views expressed by the House were brought to the attention of those responsible. He would examine the possibility that every resident officer should be compulsorily insured by a medical protection society. So far as he knew there had not been any inquiry about the length of general medical training, but there were a number of committees on allied subjects to this which were due to report in the near future.

Army Medical Services

In the House of Commons on Nov. 21, Mr. AUSTEN ALBU raised the question of the efficiency of medical services in the Army, and asked for reassurance that there was adequate supervision of the young doctors engaged in this work. If National Service was to be maintained for any length of time parents must have confidence that their sons would not be subject to unnecessary hazards due to carelessness in medical treatment.

Mr. J. R. H. HUTCHISON, under-secretary of State for War, said that the Army Medical Services were responsible for about 750,000 people, including not only soldiers but also many of their families. The health of the Army had never been better. Statistics of admission to hospital showed a continuous decline, and the health of troops in overseas stations was also impressive. All the National Service medical officers were fully qualified and most of them had had six months' hospital experience. Next year that period would be extended to 12 months. The National Service doctors were doing an extremely good job under the circumstances. There were 900 of them out of a total of 1550 medical officers. He agreed that, owing to the war, there was a shortage of medical officers with five to ten years' practical experience, many of whom were specialists. Measures to improve the situation were under review. The number of administrative commissioned officers in the R.A.M.C. had been expanded to free medical officers for purely medical duties.

Besides the R.A.M.C. officers honorary consultants to the Army were appointed by the Secretary of State for War, after consultations with the Royal Colleges, and the Army owed much to their generous help. Close links also existed with the local civilian services both at home and abroad, and these facilities worked both ways. Mr. Hutchison pointed out that there were fewer patients per doctor in the Army than in civil life, and the doctor was generally within easy reach of his Service patient. There were no waiting-lists for admission to Army hospitals, and we had military hospitals in all our major overseas theatres. For example, in B.A.O.R. there were 1750 beds—enough for 2·1% of the troops—which compared favourably with the beds available per head of the population in civil life. Taken all in all, parents and relatives could have confidence that their boys and husbands were getting the best medical attention.

QUESTION TIME

Reduction of Hospital Staffs

Mr. N. N. DODDS asked the Minister of Health if he would make a statement in view of the widespread concern at the suggestion by his department to regional hospital boards for reducing hospital staff levels.—Mr. IAIN MACLEOD replied: I am anxious that all proper economy should be observed in staffing the hospitals, and am considering what further guidance I should give on this subject to employing boards and committees.

House-officer Posts in Sheffield

Mr. GEORGE JEGER asked the Minister why many non-teaching hospitals in the Sheffield regional hospital area were excluded from the list of approved hospitals and institutions and recognised house-officer posts under the Medical Act, 1950, having regard to the inclusion in the list of hospitals of comparable size and status in the other regions; what advice he gave to the licensing body in the Sheffield region relating to the list of approved hospitals and recognised house-officer posts which resulted in the adopting of criteria different from those applied in other regions, as evidenced by the abnormally low proportion of posts approved in that region; and whether he was aware of the damage to the prestige of many major non-teaching hospitals in the Sheffield region and to their ability to attract medical staff which would be caused by their exclusion from the first published list of hospitals and institutions approved under the Medical Act, 1950.—Mr. MACLEOD replied: Section 2 of the Medical Act, 1950, gives me no jurisdiction in the approval of these posts. The Act leaves the approval of posts for this purpose entirely to the licensing bodies—i.e., the universities and, in England, the Conjoint Board of England (representing the Royal Colleges), and the Society of Apothecaries.

Mental Hospital Staff and Accommodation

In answer to questions Mr. MACLEOD stated that of the 294 mental hospitals and mental-deficiency institutions in the National Health Service 235 reported shortages of nursing staff at Sept. 30 last. 162 were short of male staff and 220 of female staff. All but 12 of the 107 mental hospitals in England and Wales were overcrowded.

Male Nurses

Replying to a question Mr. MACLEOD stated that about 7000 male nurses are employed in hospitals in England, of whom 5500 are in general hospitals, 400 in fever hospitals, and 1100 in sanatoria.

Patients' Access to the Minister

Sir WILLIAM DARLING asked the Minister why he approved Statutory Instrument 1811 under which patients at Broadmoor might not write directly to him, the Board of Control, or any Commissioner without having their correspondence previously inspected by a medical attendant; and if he would reconsider this proposal in the interests of the patients concerned.—Mr. MACLEOD replied: Statutory Instrument 1811 gives effect to one of the recommendations of the Broadmoor Inquiry Committee. The recommendation was accepted by the Government and I cannot agree to reconsider it now.

Hæmophilia Research

Replying to a question, Mr. A. H. E. Molson stated that recent work on hæmophilia by the Medical Research Council had been concerned chiefly with the preparation and clinical trial of concentrated blood-fractions which it is hoped will be more effective in treatment than the transfusions of whole blood or plasma used at present. These products were being tested in a number of different centres and preliminary results had been encouraging.

commend it. The success of this technique seems to depend entirely on the nursing staff. Sister Unsworth, of the Royal Alexandra Hospital for Sick Children, Brighton, who has charge of a ward from which 36 operations are performed each week, tells me that the practice there is to empty the capsules of quinalbarbitone ('Seconal'); the drug is then given with orange juice and concealed on the back of a spoon. In this hospital a failure is very rare. It would be interesting to learn the views and the methods of other ward sisters.

A long-acting preparation of atropine is also valuable when the anæsthetist has a long list of cases.

Dr. Bullough advocates the use of the intravenous route for the induction of anæsthesia. In this case I think it is preferable to add a suitable dose of gallamine triethiodide to the thiopentone, after which anæsthesia may be maintained with nitrous oxide, oxygen, and the minimum of ether.

Hove, Sussex. REX BINNING.

THE CAUSE AND TREATMENT OF LEG ULCERS

SIR,—Dr. High (Nov. 8) introduces an interesting point in regard to the occupation of patients with leg ulcers. While standing still the tonic contraction of the leg muscles has no pumping action on the blood and the venous pressure in the limb remains high. Normal people after standing for some time (e.g., surgeons operating) may develop a little œdema of the ankles, which disappears on walking. The standing policeman occasionally bends his knees. The result of long-continued standing, on individuals who have inherited the tendency, is dilatation of the superficial or deep veins of the lower limbs, the valves becoming incompetent.

I see no reason to believe, like Dr. High, that the benefits of walking when wearing compressive bandages are only psychological. The massaging effect of muscular movement helps to reduce œdema when the limb is compressed. Clearly compression cannot make a valveless pump efficient; but if valves are still present, though incompetent through dilatation of the veins, compression of the limb may help them to function. We know that in the non-thrombotic group dilated veins may contract after a period of rest, regurgitation disappearing for a time. Superficial varices may disappear temporarily after an illness spent in bed.

The striking difference, commonly seen, between patients with severe superficial varicosities but no œdema or skin changes and those with signs of venous insufficiency provides a clue to the cause of this latter trouble. If only the superficial leg veins become dilated, and their valves incompetent, no œdema or ulceration results. If, however, the deep veins (which carry about 90% of the venous blood from the lower limb) become dilated, the venous return is seriously affected. I use the term "varicose ulcer" exclusively in regard to this latter group, in which ulceration results from dilatation of deep veins and not from superficial varices which are probably also present.

Any series of patients seen in hospital and consulting practice is selected by the colleagues who refer them. Only the family doctor sees an unselected series, as I know from six years' experience in general practice. The important point is that, as other workers have also found, the majority of ulcers are post-thrombotic.[1]

Dr. Rivlin (Nov. 8) considers me to be sadly out of touch with contemporary specialist opinion, though how he can judge this I do not know. Probably he means that my views are not acceptable to such practitioners as concentrate on the treatment of superficial varicose veins. Dr. Rivlin also considers that I am putting the clock back. I wonder whether he thinks there has been much advance since he wrote in 1948: "The only certain way of healing a chronic varicose ulcer is to use the elastic-compression-bandage technique."[2]

Leeds. S. T. ANNING.

ARSENIC AND LEAD IN CIGARETTES

SIR,—To destroy insect pests, tobacco plants are often sprayed with lead arsenate. In view of the current interest in possible carcinogens in tobacco-smoke, it may be useful to record an investigation I have made into the lead and arsenic content of ten popular brands of cigarettes. Each sample analysed was the equivalent of one-fifth of the contents of each box (i.e., 2 out of 10, or 4 out of 20), duplicate samples being taken for examination for necessary confirmation. The results were as follows:

Brand no.	*Arsenic (parts per million)*	*Lead (parts per million)*
1	21	138
2	5	57
3	7	68
4	24	122
5	6	55
6	6	73
7	3	53
8	3	61
9	21	124
10	24	139

Except nos. 9 and 10, which were American, the cigarettes analysed were all of popular English brands sold as "Virginian." No doubt many of them contain tobacco which is in fact grown elsewhere than the United States.

In relation to carcinogenesis the wide variation in arsenic content may be important; but I would also call attention to the figures for lead, which are consistently high for all brands examined.

Both arsenic and lead were determined after oxidation with sulphuric and nitric acids, the former being completed by the Gutzeit method and the latter as sulphide colorimetrically in ammoniacal solution in the presence of potassium cyanide. Where the lead figure was very high and confirmation was required, extraction with diphenylthiocarbazone in chloroform was carried out, but this elaboration was generally found unnecessary.

EDWIN H. BUNCE

East Molesey, Surrey.

Consulting chemist; formerly Public Analyst, Government of Burma.

A NEW ANTISEPTIC

SIR,—We were interested to read your annotation on this subject (Nov. 15), particularly as our preparation 'Bradosol' was mentioned. We would like to query the statement that the quaternary ammonium compounds "have no appreciable effect on the pseudomonas group, the tubercle bacillus, or bacterial spores." Whilst this may be true for some of these compounds, bradosol is, *in fact, active in high dilution against Pseudomonas pyocyanea.*

Neipp and Gross,[3] Seidenberg,[4] and independent workers in this country all give figures of the order of 1 : 10,000 for bacteriostatic action over 24 hours and 1 : 100 bactericidal action in 2½ minutes. We appreciate that in these cases bactericidal tests may not be entirely satisfactory, for there is no indication that an inhibitor was used when transferring samples to the final culture medium, but they do at least show that this compound has an efficient bacteriostatic action.

According to Berry,[5] in ordinary circumstances this bacterio-static action is irreversible and leads to death of the organism due to a steady leakage of nitrogen and phosphorus compounds through the bacterial wall on to which the antiseptic com-pound had been adsorbed. This process can only be arrested or reversed if a specific inhibitor is present or if the adsorbed layer is in some way removed. The same writer also points out that revivers are now known for bacteria which have been apparently killed by iodine and formaldehyde, among other compounds, and yet this does not appear to have precluded the widespread use of these older antiseptics. One would therefore feel that quaternary ammonium compounds cannot be condemned solely on this count.

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[1] Anning, S. T. *Brit. med. J.* 1949, ii, 458, 811.

[2] Rivlin, S. M. *Ibid.* 1948, ii, 723.

[3] Neipp, L., Gross, F. *Schweiz. med. Wschr.* 1949, 79, 980.

[4] Seidenberg, S. *Ibid*, p. 978.

[5] Berry, H. *J. Pharm.* 1951, 3, 697.

Neipp and Gross also quote satisfactory figures for the action of bradosol against *Bacillus subtilis*, a spore-forming organism. Further, Eisman et al.[6] reported on the activity of an aqueous 1 : 1000 solution of bradosol on surgical instruments contaminated with suspensions of various organisms in blood and pus. These included pseudomonas, *Bact. coli*, and the anthrax and tetanus bacilli. Even when the instruments were dried before testing, sterilisation was complete in a little over 10 minutes. The same arguments on inactivators apply also to spore-forming organisms, and here again bradosol is likely to prove at least a highly efficient bacteriostat.

May we also draw your attention to a paper by Gabriel,[7] in which he speaks highly of bradosol as an antiseptic dressing in rectal surgery, a field notoriously liable to postoperative infections. He concludes that, in addition to being a good antiseptic, bradosol seems to inaugurate rapid wound healing by granulation.

We agree with the closing sentence of your annotation and would be only too happy to supply trial material to anyone who is interested in investigating the properties of the quaternary ammonium compounds.

Ciba Laboratories,
Horsham, Sussex.
A. R. G. CHAMINGS.

RÔLE OF THE BRONCHIAL VEINS IN MITRAL STENOSIS

SIR,—I should like to make a few comments on the very interesting paper by Dr. Gilroy and his colleagues (Nov. 15).

The term *Lungenstarre* ("lung rigidity" seems to be a better translation than "stiff lung") was coined by von Basch [8] on the basis of clinical, pathological, and experimental evidence. Engorgement of the small pulmonary vessels, in his view, leads to increased tension in their walls, and this hypertension in turn to impaired elasticity of the lungs (*Starre*), owing to the comparatively large volume which the vascular tree occupies within the lung tissues. von Basch's concept long dominated Austrian and German opinion on pulmonary congestion in mitral disease.

There is another point I should like to raise regarding the mechanism of acute œdema of the lungs. Supposing that Dr. Gilroy and his colleagues are right in their views on the decompressive function of the pleurohilar veins, then acute pulmonary œdema is much more likely to be due to interruption of this mechanism by a neurovascular reflex rather than to acute left ventricular failure. It is difficult to reconcile the maintenance or even exaggeration of a high systolic systemic blood-pressure, so often present in cardiac asthma, as well as the prompt beneficial effect of morphine, particularly if given intravenously, with the idea of sudden weakness of the left ventricle.

It might seem strange that a feature commonly associated with chronic left ventricular strain should be discussed under the heading of mitral stenosis; but dynamically, in long-standing hypertensive or aortic heart-disease, the left atrium is put under similar conditions in view of the increased pressure and increased residual volume in the left ventricle resulting from its reduced output.

Even in acute myocardial infarction when acute pulmonary œdema accompanies or, occasionally, replaces the status anginosus, a coronary-pulmonary reflex may very possibly act as the initial causative agent before—if ever—the left ventricle begins to fail.

Leicester.
LEO HAHN.

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6. Eisman, P. C., Rodbart, M., Kull, F. C., Mayer, R. L. *Fed. Proc.* 1947, 6, no. 1.
7. Gabriel, W. B. *Proc. R. Soc. Med.* 1952, 45, 389.
8. von Basch, S. S. K. Physiologie and Pathologie des Kreislaufs, Vienna, 1892.

DENTAL TREATMENT OF CHILDREN

SIR,—Consideration for your limited space prompts me to reply selectively to your annotation (Nov. 15) and to "School Dental Officer's" rejoinder to my letter.

It is an established fact that the very high wastage factor inherent in the New Zealand dental nurses' scheme nullifies the advantage of her shorter training. It is not clear why this should be so, but it is an entirely unwarranted assumption that wastage among women dental surgeons is of a similar order. The conclusions drawn by your correspondent from this assumption are mere shadow-boxing.

He also attributes an opinion to me which I did not intend to express—i.e., that "children's dentistry can be learnt by gaining skill and experience in treating adults." The point that I wished to make was that *before* any person is permitted to practice fillings and extractions on children she should have undergone that basic training in dentistry which is acquired through working in the conservation department of a dental school, where she will learn to cope with conditions which no amount of academic instruction on manikins, &c., can anticipate. She will learn to appreciate and be thankful for a high degree of coöperation from her first patients, who may sense and make allowances for a beginner's difficulties, even though the work is done under close supervision. Conservation work on children differs from that on adults inter alia in that it is more exacting and must be done in a smaller mouth on smaller teeth with larger pulps in less time than would be acceptable in adults.

The impracticability of teaching extraction on children is so obvious that an amendment to the Dentists Bill was carried in the House of Lords which would have confined such practices to deciduous teeth only. By all means let us teach children's dentistry, but we must not consider children as so much expendable "teaching material" to be practised upon by the raw beginner!

Your belief that the limited number of suitable candidates makes any substantial long-term increase in numbers of dental surgeons impossible is unsupported by facts. The chairman of the Dental Board, Dr. E. W. Fish, stated earlier this year that "there are nearly two and a half times as many applicants to enter the profession as the schools can absorb," and this although not many of these applicants could expect such generous allowances as are made to the New Zealand nurse, who has all her training fees and maintenance paid for her. Present fluctuations in certain dental school intakes do not disprove the fact that about 900 potential recruits to the dental profession must have been lost annually for a number of years through lack of training facilities. (These fluctuations are apparently connected with certain new arrangements recently introduced at school level, and no hasty conclusions should be drawn as to their significance.)

What makes you think, Sir, that the fifty million of these islands cannot—given enlightened public support—produce as many recruits to the dental profession (per capita) of adequate intelligence, as do, for example, the people of the United States of America, where almost four times as many boys and girls apply each year for admission to the dental schools as can be accepted? The training facilities in that country have been sufficient to give their people a ratio of dentists to population of about 1 : 1750 without any reduction in standards, while further expansion of dental schools is under way and a ratio of 1 : 1000 is the declared goal. This must be compared with the present ratio in this country of 1 : 4400!

Dare one suggest as a possible cause of our dilemma that at present, far from having lowered our basic science requirements, particularly in physics and biology, we have in fact been expecting from our dental students similar knowledge to that expected from the student who takes an honours course, in say, nuclear physics or advanced botany ?

London S.W.15. E. ROSENSTIEL.

*** Mr. Rosenstiel confuses the number of applicants for admission to the dental schools with the number of suitable candidates. Before the General Certificate of Education examination results are known each summer, most dental schools no doubt have more applications for the next course of training than they can accept, and some have far more. But the results of the school-leaving examinations reduce the number by weeding out applicants who fail to reach the level of scholastic attainment required for admission to the dental course. Those directly concerned with student selection in the schools find that, when it comes to enrolling students for each course, the number of suitable candidates, taking the country as a whole, is roughly equal to the number of available places. A candidate may not be able to enter the school of his choice ; but if he has reached the requisite scholastic level he seldom fails to find a place somewhere.

The implication of Mr. Rosenstiel's final paragraph is that the standards for admission to the dental schools are set too high and ought to be lowered. We oppose this view on the ground that lowering these standards would entail lowering the standards of dental training. A tutor in one of the dental schools recently traced the fortunes of a score of students and found that only 10% succeeded in completing the course without mishap : about an equal number failed to complete their training, and the rest qualified only after failing at least one of their qualifying examinations. In this particular course this last group of students between them required 32 academic years more than they should have done to qualify as dental surgeons. Had the standards of admission to this school been lower, the wastage of time and training facilities would have been even greater. Though the number of entrants to the schools could no doubt be increased by easing the criteria for admission, it is probable that the additional students admitted could complete the dental course only if the standards of training were also lowered. This seems to us an unacceptable solution of the problem of the shortage of dentists.—ED. L.

"WISDOM IS NOT ENOUGH"

SIR,—In your issue of Nov. 15 Prof. Robert Platt concludes that reason should influence the choice of the ends towards which our endeavour is directed. He adds that for him rationalism means the ability to avoid self-deception. He then goes on to say that there is no need to appeal to supernatural authority to cultivate kindly feeling and veracity—the two qualities he considers would make the world a better place if more generally practised.

With all this most Christians would agree. But his philosophy raises certain problems.

It seems that Professor Platt is preaching the religion labelled humanistic rationalism. He makes human reason the god of this religion. The question arises, how is one to decide whether a particular act is right or wrong when the standards of kindly feeling and veracity of different men vary ? For example, Hitler presumably felt that his standards of kindly feeling and veracity, from the point of view of the good of the German nation, involved the extermination of the Jews. Stalin presumably argues that the State is the arbiter of kindly feeling and veracity, and therefore the State is entitled to remove to Siberia those whom it considers transgress these standards. If there are no supernatural sanctions to evil human acts, why should any State or individual bother about any standard of conduct other than expediency ? (I do not mean that fear of God should be the only motive for conduct—this is contrary to Christian teaching—but that it seems reasonable to suppose that we shall each one of us h to render an account of our deeds some day, for it seems cl that many evil men get away with their misdeeds on this planet).

Philosophical or religious conclusions (the name is immaterial) should be based on a submission of *all* available evidence to rational analysis. No Christian can avoid asking the question "What do you make of the historical evidence, based on long and close investigation, that Jesus Christ was God and claimed that all authority in heaven and earth had been given to him, and that his *resurrection from the dead is part of the evidence in support of his claim ?*" (Lunn gives the matter detailed consideration in his book *The Third Day*, in which will be found references to the important work of Sir William Ramsay).

I am not doubting for one moment Professor Platt's sincerity ; but by his own standards the evidence for such a momentous claim as Christ's must be submitted to careful scrutiny. Professor Platt may well have done this and rejected that claim, but in view of the fact that so many doctors and/or natural scientists are unaware that Christians base their claims on *rational analysis of evidence*, I feel it right to make this point. It has always seemed to me that those who ignore evidence unfavourable to their case are deceiving themselves ; for, as Professor Toynbee has pointed out in his *Civilization on Trial*, religion is the serious business of mankind, whether you call it philosophy or not.

Dundee. A. T. MACQUEEN.

CAROTENÆMIA

SIR,—With reference to Dr. McConaghey's most interesting article (Oct. 11), I would like to record the case of a *young woman*, aged about 20, who had been having mild epileptiform attacks for approximately $4^1/_2$ years.

During these attacks her circumoral region especially, but also to a most striking extent the other parts of her body, became "reddened." When she was first seen, her whole body presented the appearance of generalised "sun tan" pigmentation. The patient had received large doses of vitamins, including riboflavine, from her family practitioner. Two days before an attack about which my opinion was sought, *there* had been an increase in the general pigmentation and a yellow colour had developed around her mouth. *Her* urine was deep-yellow with bright-green fluorescence.

No further investigations were carried out *in this* case. At the time I was unable to discover any previous record of such a syndrome.

I am indebted to Prof. N. L. Edson and Mr. C. M. Todd, of the department of biochemistry in the *Medical School*, Dunedin, New Zealand, for information about the case described here.

Hill End Hospital,
St. Albans. HAROLD PALMER.

BUTAZOLIDINE

SIR,—Clinical trials in *Australia support* the observations of Dr. Currie (July 5) on the antirheumatic action of butazolidine. Striking relief, in all forms of rheumatic disease, develops 24–36 hours after oral treatment has begun and persists for 36 hours after cessation. The maintenance dose is about half the initial dose. With initial doses of 0·6–0·8 g. per day few complications have *occurred*.

Butazolidine, as the first specifically antirheumatic drug, marks a new advance in therapeutics and opens large fields for research into the mechanism of its action. Our thanks are due to Dr. Currie, whose conservative estimate confirms his preliminary report of more than a year ago.[1] And it is fitting that Glasgow, for long the seat of Ralph Stockman's research, should be in the fore-front of this advance.

Melbourne, Australia. MICHAEL KELLY.

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1. Proceedings of European Congress of Rheumatology. Barcelona. 1951 ; p. 417.

DEATH AFTER ANÆSTHETIC WITH HYPOTENSION

SIR,—The following case may be of interest to your readers.

A fit man of 76 was operated on for the removal of an epithelioma of the left ear. The growth was 2 in. in diameter and attached to bone. Two deep cervical glands were palpable. The preoperative blood-pressure was 160/85 mm. Hg, and the temperature and pulse-rate were normal.

Anæsthesia.—'Omnopon' gr. $^1/_6$ and scopolamine gr. $^1/_{300}$ subcutaneously were given as premedication, and anæsthesia was induced at 9.20 A.M. with thiopentone (0·5 g.) followed by pethidine (50 mg.) and *d*-tubocurarine (15 mg.). The cords were sprayed with 10% cocaine, and a no. 9 cuffed tube was passed. Nitrous oxide (4 litres) and oxygen (2 litres) were given through a circle absorber, and the respiration was assisted at first. The table was tilted to about 20° head up, and pentamethonium bromide (50 mg.) was given intravenously before the surgeon started. The pulse was palpable at the wrist throughout the operation, which took 50 min., and the blood-pressure, measured by this means, remained between 50 and 60 mm. Hg during this period. Electrocardiograms taken before, during, and after the hypotensive phase showed no change.

Operation.—The growth and the left pinna were removed, and a block dissection of the glands of the neck on the left side was carried out. The left jugular vein was tied. The defect in the skin was covered with a flap from the occiput and a skin-graft from the abdomen. The operation site was bloodless throughout.

Postoperative Course.—The table was levelled at the end of the operation, and the systolic pressure rose to 70. Atropine (0·6 mg.) followed by neostigmine (2·5 mg.) were given intravenously, although the patient was breathing spontaneously at this time. An hour later the blood-pressure was 90/60. When the patient returned to the ward his skin was a good colour, warm, and not sweating, and the pulse at the wrist was fair. The pharyngeal reflex was absent. The blood-pressure continued to rise steadily, but the patient took longer than usual to recover consciousness. By 3 P.M. he was awake, and his blood-pressure was 120/80. For the rest of the day he seemed perfectly normal, talking lucidly, taking fluid by mouth, and in full control of his limbs. He was quite well when seen again at 9 P.M. The following morning, however, he was lethargic and his speech was slurred. He had a left facial palsy, a flaccid left arm, and a weak left leg. The plantar response was extensor. He was incontinent. His condition deteriorated throughout the second postoperative day, although the blood-pressure was maintained. He lost consciousness, developed a terminal bronchopneumonia, and died on the third day.

Necropsy.—I am indebted to Prof. T. F. Hewer for the report from which the following is taken :

"Thrombosis of left internal carotid artery due to atheroma. Atheromatous narrowing of right internal carotid artery. . . . Cerebral softening due to thrombosis of right middle cerebral artery. There is patchy atheroma in the arch of the aorta, and very marked calcified ulcerated atheroma of descending thoracic and abdominal aorta. At the commencement the left internal carotid artery is completely occluded by blackish brown thrombus lying on top of calcified atheroma. This local thrombus extends for 1·8 cm., beyond which the lumen is merely pin-point. On the right side there is a similar plaque of calcified atheroma, which has reduced the lumen considerably, but there is no thrombus. After fixation, the brain shows recent infarction of the periphery of the right parietal lobe with irregular small hæmorrhages. The right middle cerebral artery shows a recent thrombus fairly near its origin . . . . With marked atheromatous narrowing of the right internal carotid artery and complete occlusion of the left internal carotid artery, the cerebral circulation was obviously impaired, depending mainly on vertebral supply. Artificially induced hypotension during an operation diminished cerebral blood-supply sufficiently to cause thrombosis in an already impaired circulation."

There are two important points, one general and one particular. The first is the delay in recovery of consciousness : if it is a common finding that lowering the blood-pressure during operation prolongs narcosis (and Enderby and Pelmore [1] admit that "the immediate postoperative recovery is a little slower than normal"), then it is difficult to escape the inference that this is due in part to a stagnant anoxia of the cerebral cortex. The second point is the occlusion of a carotid artery by atheroma. This condition was first demonstrated by Egas Moniz et al.[2] who diagnosed 4 cases by cerebral angiography ; since then a definite clinical syndrome has been established,[3] [4] and Denny-Brown [5] says "any severe fall in systolic pressure . . . is likely to provoke a catastrophic necrosis of a large part of the area supplied by the middle cerebral artery." He suggests that this condition is a not uncommon cause of cerebral thrombosis. It is interesting to note that in one of Fisher's patients [4] occlusion followed a fall in blood-pressure after an operation for "radical neck dissection," and one of Ameli and Ashby's patients [3] was a blood donor who had just given a pint of blood. It may be that carotid-artery disease is another hazard sent, like coronary-artery disease, to plague the anæsthetist.

Hillingdon Hospital,
Middlesex.

R. I. BODMAN.

BOOKS INFECTED BY SCARLET-FEVER PATIENTS

SIR,—Although we think it premature to discuss our findings, regarding the recovery of streptococci from library books used by scarlet-fever patients, until our paper is published, it is worth while pointing out in reply to Dr. Glaisher (Nov. 8) that the "control" books from patients with Sonne dysentery were examined for streptococci and not *Shigella sonnei*. This was stated correctly in your report (Oct. 18) of the investigation.

E. H. GILLESPIE
Director, Public Health Laboratory, Sheffield.
Formerly Director, Public Health Laboratory, Leicester.

A. I. ROSS
Deputy Medical Officer of Health, Leicester.

SOCIETY FOR SPASTICS

SIR,—The medical profession is often charged with inertia and complacency ; and, while these charges may sometimes be justified, they are not always so. From your annotation last week on the new National Spastics Society it would appear that this body, set up by parents of cerebral-palsied children, is preferring (very tactfully) just these charges jointly against the medical profession and the education authorities. One must ask whether these charges are justified.

It is certainly true that both medical and education authorities are fully aware of the need for improved facilities for cerebral-palsied children. The Ministry of Health and the Medical Research Council are both involved in research into the problem with the collaboration of the London County Council which, having started the first cerebral-palsy clinic [6] and the first parents' advice clinic in this country, is still taking a lively interest even though the hospitals concerned have now passed under the control of the health service. Invaluable information has been gathered by Craig,[7] Holoran,[8] Dunsdon,[9] and many others. But it is true that action on a large scale has not followed. Is this the result of inertia or of prudence ?

Dunsdon has shown that worth-while results do not necessarily follow the setting up of a special school for cerebral palsy. Yet that good results can be obtained from treatment has been known since the time of Little. The present urgent need seems to be for the training of personnel: these could use, to a large extent, facilities already available. Recognising this, the Chartered Society of Physiotherapy has placed infantile cerebral palsy on its syllabus for students, and I have recently been privileged to arrange for the society two post-graduate weekend courses. Such measures, however, cannot do more than provide an introduction to the subject; more valuable are the 6-week courses open to any personnel concerned with the diagnosis or treatment of cerebral palsy, which have been held three times a year for several years at Queen Mary's Hospital for Children, Carshalton. The deans of the Institutes of Neurology and of Child Health have under consideration arrangements for a jointly organised course for doctors.

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[1] Enderby, G. E. H., Pelmore, J. F. *Lancet*, 1951, i, 663.

[2] Egas Moniz, Almeida Lima, de Lacerda, R. *Pr. méd.* 1937, 45, 977.

[3] Ameli, N. O., Ashby, D. W. *Lancet*, 1949, ii, 1078.

[4] Fisher, M. *Arch. Neurol. Psychiat.* 1951, 65, 346.

[5] Denny-Brown, D. E. *New Engl. J. Med.* 1952, 246, 839.

[6] Evans, E. S. *Proc. R. Soc. Med.* 1946, 39, 15.

[7] Craig, W. S. *Arch. Dis. Childh.* 1950, 25, 325.

[8] Holoran, I. M. *Brit. med. J.* 1952, i, 214.

[9] Dunsdon, M. I. The Educability of Cerebral Palsied Children. London, 1952.

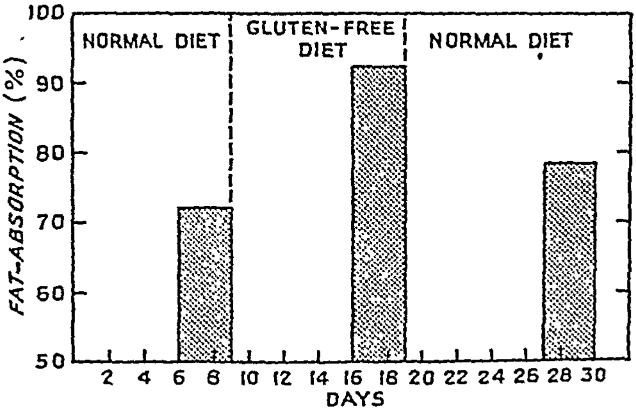
It would appear, then, that much is being done to improve the facilities for the child with cerebral palsy. I hope that the National Spastics Society will see their way to coöperate in measures which should, in a few years, make some of their tasks—e.g., the setting up of a residential special secondary school—unnecessary.

London, W.1. WILLIAM DUNHAM.

MANAGEMENT OF CŒLIAC DISEASE

SIR,—The article by Dr. Sheldon and Dr. Lawson (Nov. 8) poses a query concerning the period for which a gluten-free diet should be continued. The following case suggests that in some instances, if major complications are not to arise later in life, such a diet should be continued for a very long time, or even indefinitely.

A housewife, aged 53, gave a history of attacks of diarrhœa, distended abdomen, and "bowel trouble" in childhood. She was admitted because of severe backache due to a collapsed lumbar vertebra; there was generalised osteomalacia with spontaneous rib fractures. She had also moderate diabetes mellitus of 19 years' duration and hypertrophic hepatic cirrhosis. There was no evidence of hæmochromatosis; the urine could be made acid, and abnormal amino-aciduria was not constantly present. The serum-bilirubin level was 2·6 mg. per 100 ml.; thymol turbidity 8 units; alkaline phosphatase 30 units; serum-albumin 3·6 g. and serum-globulin 3·9 g. per 100 ml; fæcal urobilinogen 55 mg. per 100 g.; serum-calcium 9·0 mg. per 100 ml.; serum-phosphorous 3·4 mg. per 100 ml.; 24-hour urinary calcium output 30·5 mg. The effect of a gluten-free diet on fat absorption is shown in the accompanying figure. There was no evidence of creatorrhœa, and splitting of fat was normal.



Fat absorption on a normal diet and on a gluten-free diet, each containing 70 g. fat per day.

Despite the diabetes and cirrhosis a diagnosis of idiopathic steatorrhœa following cœliac disease is reasonable.

In this case the fact that fat absorption is very much improved on a gluten-free diet, taken in conjunction with the patient's history, suggests that had she been on a gluten-free diet all her life she might not now have osteomalacia. If the cirrhosis is secondary to amino-acid malabsorption she might even have avoided that too.

Manchester Royal Infirmary. R. S. SAVIDGE.

DOWNWARD TREND IN BREAST-CANCER MORTALITY?

SIR,—In his Dorothy Platt lecture, on Progress in the Treatment of Breast Cancer, published in your issue of Sept. 13, Professor Smithers says:

> "There are also difficulties with death certification since the tendency to record death as due to breast cancer in any patient who has once had the disease is so strong. Until 1940 in fact, the Registrar-General's office often changed the recorded cause of death to cancer when this was mentioned as a subsidiary cause by a doctor who had himself attributed the death to something else. It is going to be difficult to judge the effect of treatment by changes in mortality-rates if we are never going to let a patient who has once had breast cancer die of anything else."

If, in females under 60 years of age, any appreciable proportion of deaths from diseases unrelated to breast cancer has been charged to breast cancer, the decline in mortality from these diseases should have caused a decline—though admittedly a small one—in the recorded breast-cancer mortality of that age-group. The lack of any such decline is evidence that deaths charged erroneously to breast cancer in those age-groups were relatively few. This is consistent with general clinical experience. The rates for older ages have been more subject to error. In considering them due allowance for it must be made—and can be made when age-specific rates are used as a basis of comparison.

Professor Smithers then says: "With all these difficulties, however, if correction is made for the growth of the population and its increasingly adverse age composition a slight downward trend in mortality-rate for England and Wales appears." He doubtless refers to a trend line based on age-adjusted "corrected" data of the short and variable period 1930–48, as presented by Smithers et al.[1] In this connection the Registrar-General has cautioned that "the study hitherto made of mortality trends for cancer sites by means of standardised rates at all ages combined was of limited value since it obscured great differences in the behaviour of rates at different periods of life, and these may be important in any attempt to elucidate the causes underlying the trends."[2] In breast cancer the trend based on age-adjusted figures combines the artificially changing trends in older age with the persistently level trends in other age-groups. These significant and reliable level trends are in this way obscured. Hence the basis for comparison used by Smithers et al. is fallacious.

Though changes due to a drastic change in book-keeping in 1940 were also confined largely to the older age-groups, Smithers et al., in an effort to eliminate discontinuity produced by that change in book-keeping, used a "correction factor" for the aggregate of all ages. Like age-adjusting, the use of this correction factor imposes on the aggregate the artificial changes largely confined to older age, and thus gives a distorted impression of the real situation.

There are two other, but minor, objections to the basis they used.

An abrupt decline in the rate for all causes (combined) in the older age-groups about 1940 in England, at variance with the past and with other experience, suggests some artificial factor. Whatever that factor may be, there is no reason to assume that it would not similarly affect breast-cancer mortality. Indeed the nearly 15% drop between the rates of 1936–39 and 1940–44 in the older age-group—a difference quite independent of the change in book-keeping—is fairly confirmatory evidence that such a factor did affect recorded breast-cancer mortality. Further, it is not likely that the full effect of the change in book-keeping in 1940

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1. Smithers, D. W., Rigby-Jones, P., Galton, D. A. G., Payne, P. M. *Brit. J. Radiol.* 1952, suppl. no. 4; Introduction, p. x.
2. Registrar-General's Statistical Review, 1940–45. Text. Vol. I. Medical. H.M. Stationery Office; p. 142. Registrar-General's Statistical Review, 1946–47. Vol. I; p. 144.

would be evident in the space of 2–3 years: it is more likely that the change would be progressive for some longer time and would thus interfere with even the internal comparability of the rates subsequent to 1940. While the validity and the weight of these two admittedly minor objections can be determined only by later experience, they cannot be disregarded when the rates most involved in them—i.e., those for older age—are included indiscriminately as a basis of comparison, as they are in the age-adjusted corrected rates.

The refutation of Professor Smithers's implication need not rest solely on showing that the basis of his comparison is fallacious, nor yet on analysis of the age-specific rates up to 1939, with the later data excluded.[3]

The Registrar-General himself has applied appropriate age-specific conversion ratios to the age-specific rates of the years preceding the change in book-keeping, so as to allow for that change and thus make the rates of those years fairly comparable with those of subsequent years. These converted rates, in summary form, taken from the Registrar-General's Statistical Reviews [4] are shown in the accompanying table along with the rates up to 1949. While age-specific rates have their weaknesses, they, unlike age-adjusted "corrected" aggregate rates, do not obscure those weaknesses; nor, when due allowance is made for the latter, do they distort the facts of the case. They show the full picture, and in their own characteristics reveal much of their fallacies and their reliability. They allow fair separation of the false and the true so that the true, freed from the false, can be used for comparison.

It is apparent from the table that in the past 20–30 years departures from a level trend are largely confined to the rates of older age. Checking these rates with the rates for all cancer, for other causes, and for all causes combined, demonstrates that such departures from the general level are artificial. On the other hand, the rates in the other age-groups remain fairly constant over the same period. Some small leeway must, of course, be allowed for the effect of possible changes in the age distribution within the specific age-groups, and too much must not be made of small fluctuations.

Interpreted with due regard for their quality, the figures in the table show indubitably that there has been no real decline in breast-cancer mortality in England and Wales. This finding, based on the full picture of age-specific rates converted to reasonable comparability through the use of appropriate age-specific conversion ratios, must take precedence over that of Smithers et al.

Professor Smithers makes two other statements that seem to me to lack support. He says: "Those who are most persistent in telling us that there is no evidence of improvement in survival due to treatment also maintain that early diagnosis makes no difference to the prognosis. This is not so." In examination of highly representative examples of all types of evidence usually supposed to support his dogmatic four-word negation, none was found clear-cut or conclusive; much was based on ambiguous figures and was inconsistent, and some was patently a misinterpretation of data—a failure to distinguish between stage (type) and duration.[5] If he has unequivocal evidence to warrant his statement, it is unfortunate that he did not present it. Secondly, he says: "With the more malignant tumours early treatment is of great importance." But here again he gives no data. In sharp conflict as it is with Bloom's findings,[6] this statement, too, must be set aside until proof is provided. Further, unless we are wrong in supposing that the development of metastases, after their spread, is independent of any specific influence of the primary lesion, there is no logical basis for assuming that treatment achieves material postponement of death.

BREAST CANCER IN FEMALES: ESTIMATED ANNUAL DEA
RATES PER MILLION IN ENGLAND AND WALES

Year	Age (years)					
	0–34	35–	45–	55–	65–	75 a ove
1911–20	6	176	474	696	946	150
1921–30	7	187	508	782	1052	174
1931–35	8	189	529	839	1098	184
1936–39	8	184	516	830	1132	188
1940–44	9	201	533	823	1114	161
1945	9	198	500	784	1067	159
1946	9	211	531	834	1122	162
1947	9	224	520	785	1092	171
1948	9	211	514	804	1082	171
1949	10	206	493	763	1112	175

"In this table the rates for 1936–39 are derived from the d tabulation for those years, and those of earlier periods have b adjusted by the appropriate conversion ratios obtained from t tabulation, making each series of rates comparable with those 1940–44 and 1945" [7] and later.

Professor Smithers himself has eliminated or expos the dubious or fallacious quality of all other eviden (e.g., higher survivals in some series than others) usual advanced to support his contention that changes time and type of treatment over the years have achiev a large increase in survivals. Thus his contention left without any basis of fact, and, in view of the consiste evidence to the contrary, must be rejected.

Certainly it is necessary, as he says, that the clinici warm his facts with compassion when dealing wi patients. That is often thoroughly good medicin But it is just as necessary that he keep them cold wh dealing with himself. Facts must have the same mea ing to the clinician as to that motley group of "path logists, hygienists, biometricians, and statisticians, t pyrrhonists of medicine" for whom presumably special warming of the facts is required.

Department of Epidemiology
and Biometrics,
School of Hygiene,
University of Toronto.
N. E. McKINNON.

Public Health

The M.O.H. and the Hospital Service

Dr. E. C. Downer, medical officer of health for Middle brough, says, in his report for 1951, that contact wi the hospital service is still embarrassed by his having connection with any of the three hospital manageme committees in the area or with the committee of a hospital. Dr. Downer suggests that the M.O.H. shou not be a member of any hospital management co mittee, for he cannot have two allegiances: but might attend committee meetings as an observer a have access to agendas and minutes. "The Medic Officer of Health should know what is going on in t Hospital Service and what developments are taking plac just as the Hospital Management Committees, throu their representatives on the Health Committee, ha constant and regular access to what is the mind an policy of the Local Health Authority."

Plantar Warts in School-children

In his report for 1951, Dr. Reginald Leader, medic officer of health for Ipswich, describes an investigatio into the prevalence of plantar warts in school-childre Of 664 girls in secondary schools, 2·1% were affected.

Use of Mass Radiography

In a report to the Liverpool Regional Hospital Boar the senior administrative medical officer suggests th mobile mass-radiography units would be better employe in examining general practitioners' patients than confining their attention entirely to industrial survey "Since 95% of notifications of pulmonary tuberculos

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3. McKinnon, N. E. *Canad. J. publ. Hlth*, 1950, 41, 230.
4. Registrar-General's Statistical Review, 1940–45. Part I; p. 172. Registrar-General's Statistical Review, 1946–47. Part I; p. 160.
5. McKinnon, N. E. *Canad. J. publ. Hlth*, 1951, 42, 218.
6. Bloom, H. J. G. *Brit. J. Cancer*, 1950, 4, 347.
7. Registrar-General's Statistical Review, 1940–45. Part I; p. 14

originate with general practitioners, it would only seem right that they should have the facilities of miniature radiography at their disposal at every opportunity. Such a service would not only discover a number of early cases, but also many unrecognised cases, which have been estimated at as many as 4 per 1,000 of the population."

World Statistics of Causes of Death

The World Health Organisation has published the fourth report[1] in the series dealing with the causes of death classified by country, sex, and age-group. It has been possible for the first time to give mortality statistics based on the new *International Abridged List of Diseases and Causes of Death* which was devised in 1948. Of the 54 tables in the report, 20 contain figures classified according to the new list, and other countries have since adopted this classification or will shortly do so.

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[1] *Epidem. vital Statist. Rep.* 1952, 5, 371. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 198. 5s.

Births, Marriages, and Deaths

BIRTHS

FATTI.—On Nov. 18, in Johannesburg, to Mavis, wife of Mr. Libero Fatti, F.R.C.S.—a daughter (Elisa Margherita).

SHEPHERD.—On Nov. 21, at the Middlesex Hospital, London, to Audrey (née Arnott), wife of Dr. Peter Shepherd—a son.

MARRIAGES

MACDOUGALL—HANNA.—On Nov. 15, at Las Vegas, Nevada, U.S.A., John Alvah MacDougall, O.B.E., M.D., F.R.C.S., to Beulah Elizabeth Hanna.

DEATHS

ARTHUR.—On Nov. 21, the Rev. John William Arthur, O.B.E., M.D. Glasg., D.D. St. And., late of Kikuyu, Kenya, and Woodburn Terrace, Edinburgh.

WILSON.—On Nov. 18, James Dunlop Octavus Wilson, M.D. Glasg. of Drumsheugh Place, Edinburgh, formerly of Endrick, Alloa.

WILSON CLYNE.—On Nov. 18, James Wilson Clyne, M.B. Aberd.

Appointments

DOUGLAS, MARY, M.D. Edin., D.M.R.T.: radiotherapist (consultant), Royal Infirmary of Edinburgh.

HILL, R. L. T., M.B. Glasg., D.M.R.D.: part-time consultant in radiology, Bradford Royal Infirmary, St. Luke's Hospital and other hospitals in the Bingley, Keighley, Skipton, and Settle H.M.C. group.

ROSIE, J. M., M.D. Glasg., D.P.M.: consultant psychiatrist and deputy medical superintendent, Craig Dunain Hospital, Inverness.

TLUSTY, K. H., M.D., D.C.H. Rome, C.P.H.: asst. M.O., maternity and child-welfare department, Sheffield.

WATSON, J. A. G., M.B. Lond.: asst. M.O., maternity and child-welfare department, Sheffield.

YOUNG, AUSTEN, M.B. Edin., F.R.C.S.: part-time consultant E.N.T surgeon, Royal Infirmary, Sheffield.

Liverpool Regional Hospital Board:

BAUER, FRANCIS, M.D. Prague, F.R.C.S.E., D.L.O.: consultant otorhinolaryngologist, hospitals in the North Liverpool area.

MCFARLAND, J. C., M.D. Lpool, F.R.C.S.E., D.P.H., D.L.O.: part-time consultant otorhinolaryngologist, Southport Promenade Hospital.

MARTIN, DOREEN, M.B. Lpool, M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, Wallasey Hospital for Women.

TURNER, D. P. B., F.R.C.S.: part-time consultant general surgeon, East Liverpool group of hospitals.

South-East Metropolitan Regional Hospital Board:

HAFNER, R. H. V., F.R.C.S.: consultant orthopædic surgeon, Camberwell group of hospitals.

HINDS, S. J., M.R.C.S., D.M.R.: consultant radiologist, Dartford, Medway, Gravesend and Mid-Kent group of hospitals.

MCDOUGALL, BERTHA, M.B. St. And., D.A.: consultant anæsthetist, Brighton and Lewes group of hospitals.

SAMMAN, P. D., M.A., M.D. Camb., M.R.C.P.: consultant dermatologist, Orpington and Sevenoaks group of hospitals.

SAMRAH, M. E., M.B. Lond., D.A.: consultant anæsthetist, Brighton and Lewes group of hospitals.

SPACEK, M. R. W., B.A., M.B. Dubl., D.A.: consultant anæsthetist Brighton and Lewes group of hospitals.

WOOD, P. H., F.R.C.S., D.L.O.: consultant in E.N.T. surgery, Medway and Gravesend group of hospitals.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

STANDSTILL ON PROGRESS

IN their report for 1950–52 the Luton and Hitchin Group Hospital Management Committee record with pleasure considerable progress in upgrading their hospital facilities and accommodation. But they remind us that this general improvement has been bought at a price. All over the country levelling up has been achieved only by enforcing a standstill order on the more progressive hospitals. As the administrative body closest to the hospital, staff, and patients, the committee claim to see at first-hand the effects of this policy. The limited capital resources made available by Parliament have done little more than provide for alterations and improvements to existing buildings, and no large hospital building scheme has been undertaken for the past decade. The committee fear that there is a real danger " that these factors will have the effect of losing in frustration the vitality which has always distinguished the best of our hospitals."

POSTGRADUATE AWARDS

THE association of Universities of the British Commonwealth (5, Gordon Square, London, W.C.1) have published a list of awards for advanced study and research including fellowships, scholarships, and grants. The list is divided into two parts: the first describes awards tenable in the United Kingdom with an indication of whether they are open to *graduates from this country and/or overseas*; the second sets out the more important awards tenable overseas by British graduates but does not claim to be comprehensive. The list will appear as appendices II and III of the *Commonwealth Universities Yearbook 1953.*

EXTRACURRICULAR READING FOR THE D.T.M. & H.

DISASTER came upon Govind, the Indian tailor, in the midst of his modest, contented, and busy life when he realised that he had contracted leprosy. His way of life and his illness are unfamiliar to most of us; but in the *Mask of the Lion*[1] Dr. A. T. W. Simeons succeeds in making them real. By describing Govind supervising his shop, bathing, eating the meals his wife has cooked, and setting out for a railway journey at an hour selected by an astrologer, Dr. Simeons teaches us a set of conventions as rigid and well-mannered as those that governed Cranford. His experience as director of the medical health services of an Indian State enables him to show us equally vividly Govind's life as a leper and the varying standards of medical care offered to him. Guided by Dr. Simeons's sympathy and tolerance we come to understand how the hardships and excitements of the wandering life of a band of beggars may be preferable to the restrictions and monotony of even a well-run leprosarium. It is a pity that the last chapters, describing Govind's cure by an unnamed drug, are the least satisfying part of the book.

In *White People Smile at Me*[2] Mrs. Christine Garnier deals less successfully with another problem and another culture. Doéllé, the missionary-educated African midwife, is not wholly accepted by the white community at Manoho. Nor is she wholly free of the fetishism which rules the life of the village where her mother still takes offerings to the Temple of Pythons. The descriptions of African traditions and ceremonies in this over-intense and uneasy book are effective. But where Dr. Simeons is content to interpret the unfamiliar, Mrs. Garnier seems to prefer to shock with the strange.

PLURAL BIRTHS

Dr. C. F. Mayor, late editor of the *Index Catalogue* of the U.S. Surgeon-General's Library, apparently does not share the intense interest that is usually aroused by the arrival of quads or quins, for he has excluded such events from his engaging paper[3] on plural births. He has made a critical and systematic review of the 95 historically authenticated or legendary cases of births in which the mother has been delivered of six or more children from a single pregnancy. Each instance is described briefly and the original source of the report indicated or assessed. A few hoaxes have been included; indeed, it is unlikely that many of the births were as spectacular as history relates, but this in no way lessens their interest. Barbara

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[1] London: Gollancz. 1952. Pp. 240. 12s. 6d.

[2] London: Putnam. 1952. Pp. 218. 10s. 6d.

[3] Mayer, C. F. *Acta genet. med. gemellol., Rome*, May, 1952.

Stratzmann of Würtemberg, for example, was an exceptionally fertile woman. Among her 53 children born in the 15th century, were five sets of twins, four of triplets, one of sextuplets, and one of septuplets. A 16th-century woodcut portrays the whole family grown up and apparently healthy, although only 34 were born alive. A more convincing lady is the Roman mother who in 1811 gave birth to thirteen children, six boys and seven girls, within an hour. The attending midwife, not unnaturally, obtained the help of an obstetrician. All the children were born alive and well-formed, but none of them survived for long. The incident caused some stir and was reported in print within the month. Then there is the story of a serving-maid who gave birth to triplets. She was accused of promiscuity by her mistress, who held that it was impossible to conceive three children from the semen of one man, twins being the maximum, one from each testis. The lady herself then became pregnant and gave birth to nine children! The interesting illustrations to Dr. Mayer's paper include a reproduction of a bas relief on the house where the Römer septuplets of Hamelin were born in 1600. The two boys and five girls lived long enough to be baptised, but none survived longer than a fortnight. The carving was made in the same century and local opinion has no doubts about the truth of its story.

BIBLICAL FLORA

AN up-to-date flora of Palestine would be far more welcome to botanists than a new attempt,[1] by Mr. Harold Moldenke, PH.D., curator of the herbarium at the New York Botanical Garden, to identify the flora (including bacteria and *Treponema pallidum*) either mentioned or indirectly alluded to in the Bible, in an age when scientific botany was totally unknown. A few choice errors in other matters in the Bible are listed in the initial historical sketch, thus emphasising the fact that the translators were apt to slip up badly in naming plants which they did not know (witness the muddle over the bulrush). In fact nearly every item in the present work is, as an identification, a sheer guess or a bundle of suppositions. Under each heading are grouped all the conceivable plants that have been, or might be, suggested as the correct translation of the original Hebrew. Nevertheless the contents are extremely interesting both to botanists and to Biblical students. For instance, the burning bush is identified with a crimson-flowered mistletoe; the antiquity of favism is possibly to be deduced from the information given under *Faba vulgaris*; and a host of Biblical references are adduced to support the claim that syphilis goes back not to Columban America but to Sinai about 1490 B.C. (according to Archbishop Ussher's long-obsolete chronology, which is followed by the authors). The illustrations are, on the whole, lavish and excellent except for the inclusion of worn-out Victorian woodcuts (from C. W. Wilson's *Picturesque Palestine* published in 1883) used to illustrate trees which can barely be recognised.

University of Birmingham

Dr. A. B. MacGregor has been appointed to the chair of dental surgery, which has been given the title of the John Humphreys chair of dental surgery.

Dr. MacGregor, who is 43 years of age, was educated at Marlborough College and Trinity Hall, Cambridge. He entered St. Mary's Hospital with the senior scholarship of the year, and after graduating M.B. Camb. in 1933 he held house-appointments there in the E.N.T. department and as house-physician and obstetric officer. He entered the Royal Dental Hospital, and while working on dental research for the Medical Research Council took the L.D.S. in 1936. At the Royal Dental Hospital he won the Saunders and Woodhouse scholarships and the Storer-Bennett research prize. During the late war he served for six years in the R.A.F.V.R. Medical Service as a maxillofacial specialist. In 1944 he took his M.D. and four years later was elected F.D.S. R.C.S. For his work in dental surgery he was awarded the Colyer prize of the Royal Society of Medicine in 1937 and the Howard Mummery prize, British Dental Association, in 1948. He holds appointments as dental consultant to the Royal Navy, St. Bartholomew's Hospital, Royal Dental Hospital of London, Plastic and Jaw Centre, Hill End Hospital, St. Albans, and as maxillofacial consultant at Amersham Hospital. He is an examiner for the L.D.S. R.C.S. and a member of the board of the Faculty of Dental Surgery of the Royal College of Surgeons. He has published papers on research in oral and dental surgery and the treatment of jaw injuries.

Dr. J. L. Hardwick is to be acting head of the department of dental surgery for the current session.

University of London

At recent examinations the following were successful:

Final examination for M.B., B.S.—Vincent Ainsworth, A. J. Bowdler (university medal), J. J. Brown, John Ernsting, Kathleen M. Huntington, W. J. Jones, Violet H. Meyerstein, Doreen M. Nutbourne, J. I. S. Robertson, R. J. Shephard, R. P. Wise (with honours); Lilian E. Ackermann, E. D. B. Allen, L. G. Andrews, J. M. Armitt, J. A. Armstrong, K. M. Backhouse, A. H. W. Bain, D. T. C. Barber, Joyce L. Barber, N. H. Barley, D. W. Barnes, I. R. Beale, Anthony Betts, J. F. Bird, Joan M. Bishop, S. W. Bissell, Joy S. Blight, Richard Blight, Maurice Bloch, E. A. Boulter, Stanford Bourne, J. G. Bradford, R. F. Braithwaite, Louise A. Brandram, J. H. Breed, E. W. Brentnall, C. P. B. Brook, M. D. Brydson, Mavis Buck, Jeffery Caplan, Margaret S. Cavendish, E. J. Chalker, P. J. C. Chapman, H. P. Charles, Lisbeth S. Chazan, D. A. Chiswell, R. H. Clark, L. J. Clark-Wilson, Elizabeth P. Cloake, T. J. Clyne, Evelyn Coates, P. J. Cook, C. W. Coole, A. F. C. Coppin, M. P. M. Coupland, J. C. Coury, B. J. Cremin, P. N. Cretney, D. M. Cuthbert, Pauline M. Daniels, Alan Davies, P. E. Davies, L. M. Davis, E. C. Dawson, V. E. Dean, W. M. A. Depla, P. A. de Raeve, Margaret M. Derrington, J. E. Dessart, Ronald Dewar, Sheila Dewhurst, D. M. Digues La Touche, Peter Dilnot, T. L. Dormandy, A. E. Dossetor, R. E. Dreaper, Sylvia I. Duckworth, Thomas Duffy, C. J. E. Dusseau, J. J. H. Eastwood, C. J. R. Elliott, Isabel K. M. Elmslie, L. L. Emery, C. A. S. Emmett, Anne C. Evans, Gwenda W. Evans, M. D. C. Evans, F. W. Fairhead, Michael Fanning, P. M. Forster, A. I. Fram, J. L. Fraser, A. G. E. Fung-a-Fatt, D. R. Gamble, Frank Gaskell, H. R. George, P. R. Gilbert, G. A. L. G. Glazebrook, G. D. Glennie, R. M. H. Gompertz, Stephanie J. Goodin, A. W. G. Goolden, D. E. Granger, C. M. Grant, G. C. Grassby, D. K. Gray, D. J. Green, Elizabeth A. Grimditch, M. J. Gryspeerdt, P. J. Guly, Christine E. E. Hammond, E. H. L. Harries, Joyce Harrison, K. A. Harwood, J. R. K. Henry, E. R. Herst, J. P. N. Hicks, F. A. Hill, William Hindle, Julian Hirsh, C. B. Hodes, David Hooker, C. J. Hopkins, B. J. Houghton, C. K. Hudson, K. R. Hughes, J. P. Hurrell, V. H. Hutchinson, C. F. Hutchison, P. L. Huxley-Williams, Anne L. Jacobs, W. H. James, D. G. W. Jenkins, P. B. Jensen, Gwyneth M. V. Johns, H. S. Jones, H. D. Jones, E. E. F. Keal, R. J. Kennedy, Patricia M. Kenney, D. J. Kidd, D. W. King, D. W. G. King, J. F. King, Iris M. Krass, Margaret A. Lakeman, A. N. Lamplugh, S. P. Lapage, A. V. Large, J. D. Le Bouvier, M. J. F. Lee, Monica C. Lewin, Rachel B. J. Lewis, A. B. Lodge, E. C. Long, E. E. Low, J. G. Lymbery, Judith Lyne, Kathleen E. Mackinnon, Diana O. McKnight, Padraic MacMahon, W. E. H. Maeckelberghe, Nancy S. Maguire, R. D. Mann, Stella M. Manners, John Manuel, Philippa M. Martin, J. F. A. Maskell, R. A. Matthews, T. J. K. Merritt, Isahek Mohammed, E. T. Mold, Ann G. Morgan, D. C. Morrell, B. A. Morrison, I. G. Mowat, E. A. Murray, R. G. Newberry, E. W. P. Noall, P. R. Norris, M. D. O'Riordan, W. G. Owen, F. M. Owers, A. R. W. Page, J. R. Palmer, F. I. Partington, P. F. Peeks, Naomi I. Penfold, R. J. V. Peter, G. I. Phillips, R. V. Pierson, A. J. Platts, A. P. Pritchard, D. S. Ractliffe, F. C. Ramsey, James Randall, H. F. Reichenfeld, C. E. Rhodes, Dorothy M. Roberts, J. K. Roberts, T. E. Roberts, M. P. Robinson, Barbara E. C. Robson, R. S. B. Rogers, S. K. Rogers, Jean L. Romanes, M. E. Rope, E. M. Rosser, P. E. H. Rutter, Elizabeth A. Ryan, J. F. Ryan, D. H. Ryde, M. G. Selson, J. E. Shahmoon, F. M. Shattock, D. B. Shaw, B. J. Sheerin, Mary S. Shenai, Elizabeth L. Siddle, G. E. Singer, F. B. Singleton, June T. Slatter, W. D. A. Smith, Arthur Spencer, S. P. Spiers, T. J. Stanton, J. L. Stevenson, Kathleen M. Stevenson, M. F. Sturridge, R. V. Sutton, D. A. Symers, Elizabeth J. Taylor, M. G. Taylor, A. J. Third, Patricia M. Thompson, Lorna G. Tolchard, Maureen A. Tudor, P. J. van den Brul, A. A. A. C. G. van der Bracht, A. G. Villeneau, David Watkins, G. C. Watson, Joyce D. Waye, R. A. J. Webb, J. S. Wesson, Janet M. White, J. H. White, Gladys M. H. Williams, J. H. Williams, Eileen M. Williamson, J. B. Williamson, Roy Wilton, Mary A. Winser, Sylvia H. Wollner, A. R. Worters, A. P. Wright, D. A. Wright, D. E. Wright, F. A. Yates.

D.P.M.—E. F. Carr.

University of Leeds

Dr. R. G. Paley has been appointed research fellow in medicine for 1952–54.

Royal College of Surgeons of England

Prof. George Perkins will deliver the Robert Jones lecture at 5 P.M. on Thursday, Dec. 11, at the college, Lincoln's Inn Fields, London, W.C.2. His subject will be Rest and Movement.

Royal College of Surgeons in Ireland

On Nov. 21 the fellowship was conferred on the following:

J. T. Carroll, D. L. T. G. Finn, S. J. Heffernan, I. C. Modebe, J. P. McMullin, O. M. O'Malley, R. D. H. Parker.

Kettle Lecture

Dr. C. V. Harrison will deliver this lecture on Thursday, Dec. 4, at 5 P.M., at the Wright-Fleming Institute of Microbiology, St. Mary's Hospital Medical School, London, W.2. He will speak on Pulmonary Vessels in Mitral Stenosis.

Harben Lectures

Lord Horder will deliver the Harben lectures at the Royal Institute of Public Health and Hygiene, 28 Portland Place, London, W.1, on Tuesday, Wednesday, and Thursday, Dec. 9, 10, and 11, at 4.30 P.M. His subject is to be Fifty Years of Medicine.

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[1] Plants of the Bible. Waltham, Mass.: Chronica Botanica. Pp. xx + 364. $7.50. Obtainable in Great Britain from Messrs. Wm. Dawson & Sons Ltd. 60s.

The International Hæmophilia Society

A meeting of this society will be held at the Seymour Hall, Seymour Place, London, W.1, on Sunday, Nov. 30, at 2 P.M.

Illuminating Engineering Society

At a meeting of this society to be held on Tuesday, Dec. 9, at the Lighting Service Bureau, 2, Savoy Hill, London, W.C.2, at 6 P.M., Mr. H. C. Weston, F.I.E.S., will present a paper on Visual Fatigue with Special Reference to Lighting.

Health Education in the Secondary School

The Ling Physical Education Association is holding a course on this subject at the Victoria Hall, Bloomsbury Square, London, W.C.1, from Jan. 5 to 7. Sir John Charles will give the opening address and speakers will include Dr. Melville Mackenzie and Dr. A. G. Mearns. Further particulars may be had from the secretary of the association, Hamilton House, Bidborough Street, W.C.1.

Hearing-aids

The number of patients waiting for National Health Service hearing-aids at the end of last August stood at 66,000 compared with 110,000 in August, 1951. In the six months ending in August, each week 1800 patients were supplied with aids and nearly 800 new patients were added to the lists. Since the beginning of the National Health Service up to the end of last August, over 230,000 patients have been fitted with hearing-aids.

Manchester Bequest

Dr. Catherine Chisholm has left half the residue of he estate to establish a trust fund for the promotion of researc into the health and diseases of infants to be known as "Th Alice Chisholm Fund," and the other half to the Victori University of Manchester to be applied in, or towards, th endowment of the school of child health.

Kingston and Malden Victoria Medical Foundation

This foundation was formed last year by a group of doctors and laymen who plan to start a new voluntary hospital to take the place of the former Victoria Hospital, Kingston, which was taken over as a gynæcological unit by the South-west Metropolitan Regional Hospital Board (see *Lancet*, 1951, ii, 644). In an appeal to general practitioners for subscriptions Dr. F. B. Lake, the foundation's chairman, says that the aim is to acquire a large house and convert it into a small hospital; and "we are about half way to the minimum sum we think it prudent to collect before we can acquire property and start conversion." "We believe," says Dr. Lake, "that in creating a new independent local hospital we will do much to demonstrate the value of such institutions and eventually help to establish the just place of the general practitioner in the Service." Cheques, payable to the Kingston Victoria Fund, should be sent to the hon. treasurer, 9, Coombe Rise, Kingston Hill, Surrey.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 1108. The proportion admitted was 91·24%.

Diary of the Week

NOV. 30 TO DEC. 6

Monday, 1st

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Dr. H. Grüneberg: Animal Genetics and Diseases in Children.

BRITISH PSYCHO-ANALYTICAL SOCIETY
8.15 P.M. (1, Wimpole Street, W.1.) Prof. R. W. Russell, PH.D.: Behaviour Under Stress. (Ernest Jones lecture.)

Tuesday, 2nd

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. P. R. Peacock: Carcinogenesis.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. S. C. Gold: Lupus Erythematosus.

UNIVERSITY OF BRISTOL, Bristol, 8
8.30 P.M. Prof. Geoffrey Hadfield: Bacterial Hypersensitivity and Rheumatic Carditis. (Carey Coombs lecture.)

Wednesday, 3rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of History of Medicine.* Mr. R. C. Brock: Sir Astley Cooper.
5 P.M. *Section of Surgery.* Dr. E. E. Pochin, Dr. F. T. Farmer, Mr. D. M. Wallace, Mr. Selwyn Taylor, Mr. T. P. Morley: Use of Radio-isotopes in Surgery.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Mr. A. Dickson Wright: A Historical Review—Royal Illnesses.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Hargraves Cell and L. E. Phenomenon.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. Ettore Bocca (Milan): Laryngectomy with Block Dissection of the Neck—Unilateral and Bilateral.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2
5 P.M. Mr. J. F. Barrington: Indications for Treatment in Enlarged Prostate.

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. C. H. Andrewes, F.R.S.: Recent Work on the Common Cold.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION
8.15 P.M. (Royal Free Hospital School of Medicine, 8, Hunter Street, W.C.1.) Mr. Charles Evans: Explorations in Solu Khumbu, Nepal.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (University of Manchester.) *Section of Medicine.* Sir Geoffrey Jefferson, F.R.S.: Varying Behaviour of Pituitary Adenomas.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons of Edinburgh, 18, Nicolson Street.) Dr. Douglas Kerr: Health, Physical Standards and Training of Motor Drivers, in Relation to Road Accidents.

Thursday, 4th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5.30 P.M. Dr. C. H. Andrewes, F.R.S.: Common Cold.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. Wilson Smith, F.R.S.: Virus Adaptability in Relation to Human Disease.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of United Services.* Surgeon Lieut.-Commander W. H. B. Ellis: Human Factor in Naval Aviation, with Particular Reference to Deck Landings.
8.15 P.M. *Section of Neurology.* Dr. F. M. R. Walshe, F.R.S.: Thoughts on the Equation of Mind with Brain. (Hughlings Jackson lecture.)

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. J. Hamilton Paterson: Neurological lecture-demonstration.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Dr. C. V. Harrison: Pulmonary Vessels in Mitral Stenosis. (Kettle lecture.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Haber: Cellular Nævi and Melanomas.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
3 P.M. Dr. Graham Weddell: Cutaneous Sensibility.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Mr. W. Selby Tulloch: Surgery of the Prostate.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. F. A. E. Crew, F.R.S.: Medicine as an Instrument of Social Policy.

Friday, 5th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Section of Otology.* Mr. J. Angell James, Mr. Gavin Livingstone, M[illegible] [illegible] nic Otitis Media.
2.30 P.M. *Section of* [illegible] Collins, Mr. D. S. Middleton, Mr. [illegible] of Nose and Upper Jaw.
5.30 P.M. *Section of Anæsthetics.* Dr. E. H. Rink, Dr. A. M. Hutton, Dr. D. M. Carnegie: Anæsthesia in Cardiac Disease.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Sir Ernest Finch: Romance of Surgery. (*Lees* lecture.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Gold: Lupus Erythematosus.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, E.11
8.30 P.M. Dr. W. J. O'Donovan, Mr. A. E. Mortimer Woolf: Should the Doctor Tell?

Saturday, 6th

MIDLAND TUBERCULOSIS SOCIETY
3 P.M. (Chest Clinic, 151, Great Charles Street, Birmingham, 3.) Dr. V. H. Springett: Fates of Some Minimal Lesions.

ŒSOPHAGEAL CONTRACTION AND CARDIAC PAIN*

WILLIAM EVANS
M.D., D.Sc. Lond., F.R.C.P.
PHYSICIAN TO THE CARDIAC DEPARTMENT OF THE LONDON OSPITAL AND TO THE NATIONAL HEART HOSPITAL; CONSULTING CARDIOLOGIST TO THE ROYAL NAVY

DURING twenty-five years when the clinical recognition f cardiac infarction has become commonplace, and nowledge of its cardiographic design has grown, our wareness of the frequency with which coronary disease rovides the cause of chest pain has increased. The elation of cardiac-like pain to disease of the coronary rteries when the electrocardiogram is strictly normal ontinues to be ill-understood. It was while searching or a solution to this problem that I found help from vatching during cardioscopy the progress of a barium neal along the œsophagus.

A moderately thick paste, when swallowed, quickly eaches the level of the aortic arch, whence it progresses nore slowly, with an awl-like head, over the arch, and in urn over the left bronchus, the left auricle, and the lescending aorta, until it passes through the diaphragmatic opening into the stomach. In some cases the propulsion of the meal is very rapid and in others it is tardy. Such progress depends on œsophageal contraction more than on gravity, because the barium reaches the stomach just as quickly when it is swallowed while the subject is in the inverted position. Allison (1942) has pointed out that the act of swallowing increases the intra-œsophageal pressure, causing food to enter the stomach irrespective of peristalsis and of gravity.

The Abnormal Radiological Sign

At times the customary rhythmical progression of the meal along the œsophagus gives way to irregular movements. In this event the first portion of the meal halts, often momentarily, at the diaphragmatic opening, and some or much of it may pass into the stomach. When the next portion of the meal arrives, it is again held up, and each additional supply of barium distends the lower end of the œsophagus. As the act of swallowing proceeds, the air above presses on the column of barium below and causes the tube to swell still more, but the œsophageal trap holds firm, and the bulk of the meal fails to enter the stomach. The next notable event is a sharp recoil of the meal so that it is suddenly jettisoned upwards in the gullet, whose lumen resumes its customary narrow-calibre for a brief period. This sequence of events may be re-enacted several times before the barium is ultimately discharged piecemeal into the stomach. If the trap at the diaphragmatic opening remains closed, the œsophagus may hold a tall column of barium and may not display its spectacular movements until it is partly emptied; this phase differs from the naturally sluggish œsophagus where the meal passes slowly but without noticeable impediment and without recoil.

Since these irregular movements represent a departure from the normal rhythmical progression of the barium swallow, I have named the condition *œsophageal arrhythmia.* It is not to be confused with cardiospasm or achalasia, nor with the effects of carcinomatous obstruction at the lower end of the œsophagus, where the barium might be held at the seat of the block, causing the gullet above to widen as it fills and the meal to recoil; this more ominous lesion is told by inspecting the head and particularly the neck of the column, for its outline is never smooth and is irregular on one or both sides.

Although œsophageal arrhythmia is easily recognised during cardioscopy and best when the patient is in the right oblique position, its graphic registration is difficult. A kymographic examination of the barium swallow can demonstrate a change in the direction of the meal, and McLaren (1943) has devised a method which traces graphically the progress of the œsophageal movements, but the analysis is confined to the brief period during which the kymogram is recorded (fig. 1). Cineradiography, too, cannot display satisfactorily the sequence of events, because of the short duration of the observation period. A diagrammatic representation is not wholly satisfactory either (fig. 2). Nonetheless, once œsophageal arrhythmia has become familiar to the observer, no examination beyond cardioscopy is necessary to discover it.

The Investigation Described

When œsophageal arrhythmia first came to my notice in a patient with cardiac-like pain in whom the electrocardiogram had proved to be physiological, I decided to seek this radiological sign in other patients in like circumstances. Although this investigation was started casually some fifteen years ago, when the importance of the sign was less clearly appreciated, the majority of the patients in the series have been assembled during the last ten years. This has supplied the opportunity to observe the subsequent progress of the patients, and especially of those in whom œsophageal arrhythmia was the only abnormal sign.

A detailed history was taken in each case and a routine physical examination made. An electrocardiogram included the three orthodox limb leads, lead IIIR (III during deep inspiration), and the three chest leads, CR_1, CR_4, and CR_7; occasionally other leads were recorded as well. The cardiogram was often repeated after strenuous physical exercise. The progress of a barium swallow was watched during cardioscopy in every instance.

Results

The patients were allocated to two main groups, one consisting of control cases and the other, which comprises the test series, of patients in whom cardiac-like pain was associated with a normal electrocardiogram.

CONTROL SERIES

To test the specificity of the œsophageal sign the results have been controlled by seeking it in 700 healthy

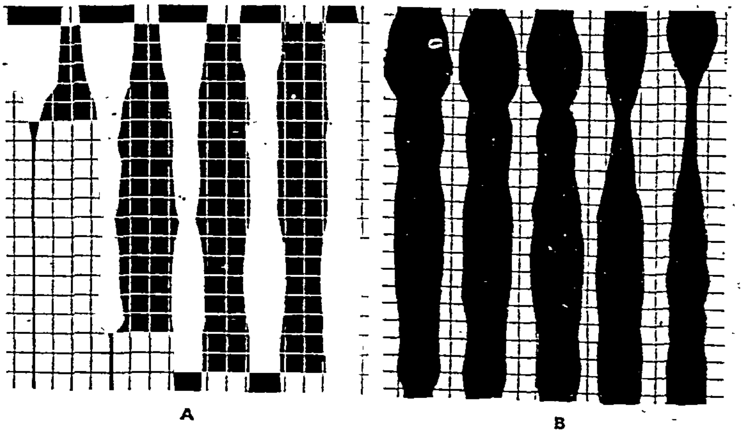

Fig. 1—Kymographic appearances of progress of œsophageal contraction in a patient with œsophageal arrhythmia. Black columns depict outline of œsophagus at intervals of two-fifths of a second. In A the band of contraction is progressing downwards; in B, recorded soon afterwards, it is moving upwards.

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* St. Cyres lecture, 1952.

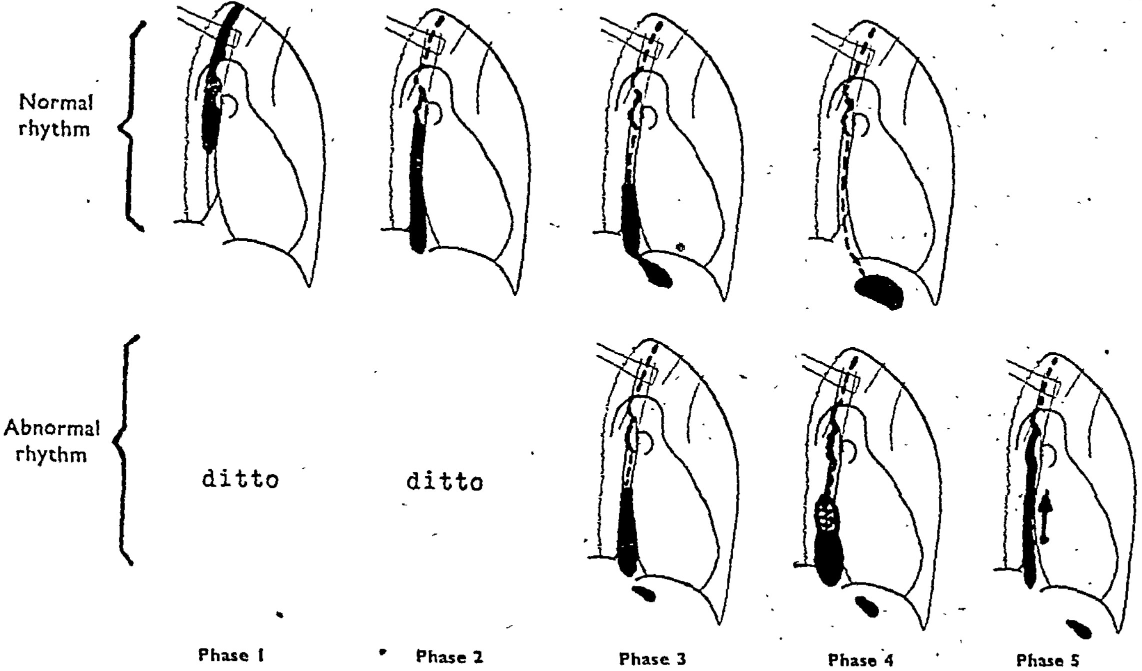

Fig. 2—Normal and abnormal movements of œsophagus observed in right oblique position during progress of barium swallow.

subjects, in 200 patients with painless heart disease, and in 500 patients with cardiac infarction. Thus, in 1400 cases œsophageal arrhythmia, if present, would have been a fortuitous finding and not part of any painful syndrome, for pain of any kind was absent in 900 and had a cardiac source in 500 where the electrocardiogram had shown the presence of cardiac infarction. The results will now be considered for each of the three groups.

Healthy subjects.—In order to annul the age factor from the analysis of the comparative results, 200 of the 700 healthy subjects were young people (average age 27), and 500 were adults over 45 (average age 57). Care was taken to exclude organic heart disease in all, and in none was there chest pain. Œsophageal arrhythmia was found once in the younger and smaller group and six times in the older and larger group.

Patients with painless heart disease.—In this group 200 patients were examined and their age was 45 or more. They included 137 patients with hypertensive heart disease, 49 with valvular heart disease, 9 with thyrogenic auricular fibrillation, and 5 with heart block and failure. Their symptoms, if any, consisted of palpitation and breathlessness for the most part. None had chest pain. Clinical examination elicited physical signs characteristic of the heart condition which happened to be present. Similarly the electrocardiogram varied in accordance with the nature of the heart condition and sometimes it did not deviate greatly from the normal. Cardioscopy usually revealed some cardiac enlargement. The impression was sometimes gained that, when there was great enlargement of the heart, the progress of the barium swallow was sluggish, but there were too many exceptions to regard this as a significant finding. Œsophageal arrhythmia was observed in 5 (2·5%) of the 200 patients.

Patients with cardiac pain.—This third control group was made up of 500 patients with an abnormal electrocardiogram from cardiac infarction. In 409 the pain had appeared at one time or another while they were at rest, or had lasted a long time and for periods exceeding half an hour, so that a clinical diagnosis of cardiac infarction was likely on this account. In 91 (18%) the pain had been caused by exertion only and had quickly yielded to rest, suggesting the syndrome of cardiac ischæmia or angina pectoris of effort, but in thes patients as in the former ones the electrocardiogram ha proved the presence of cardiac infarction. Althoug patients of every age were admitted into this group, there were only 31 under the age of 45 years. The number showing œsophageal arrhythmia was 25 (5%). The slightly higher incidence of the radiological sign in this group might be explained by dyspepsia causing a share of the pain in that this was more frequent and more severe at rest in 5 patients than was expected from coronary arterial disease alone, although this was known to be present in each and the cause of the pain at the start of the illness if not subsequently.

All three groups.—When these three groups were considered together, œsophageal arrhythmia was present in 37 out of 1400 cases (2·6%). The sign occurred in 12 (1·3%) of the 900 cases without chest pain, and in 25 (5%) of the 500 cases of cardiac infarction whose pain presumably was the direct outcome of coronary arterial disease. From these data it will be seen that although œsophageal arrhythmia is found in health *it is uncommon*, and when met with it can have little significance in a person free from symptoms. In only 3 subjects in the control series was the sign prominent, and these were patients with cardiac infarction who were subject to frequent painful attacks at rest. It has not yet happened that one of the 7 healthy subjects showing this radiological sign has returned with chest pain, but the number is small, and no attempt has been made to recall these cases for re-examination lest they should develop unjustifiable invalidism from such medical inquisitiveness.

TEST SERIES

The patients in this class complained of chest pain which subjectively was characteristic of cardiac pain, but the electrocardiogram had failed to confirm the presence of coronary arterial disease. The clinical history had suggested this ætiology in each instance because the pain, usually in the centre of the chest, was described as gripping, constricting, a tightness, a sense of pressure, a dull ache, or like indigestion; never once was it lancing. It often radiated to the jaw, the shoulder, or the left arm, and sometimes it spread into the right arm as well. There were 332 patients in this group, and in 114 the pain was brought on by exertion only and quickly yielded to rest. In the remaining 218 cases the pain had occasionally set in at rest, and/or had lasted an hour or more, suggesting cardiac infarction. Very often episodes of pain had been severe while the patient was at rest and had awakened him from sleep, necessitating the urgent attendance of a doctor, who had invariably diagnosed coronary thrombosis and administered morphine for the relief of the pain. In none was there pain on swallowing, for this symptom would have excluded them from the series. Thus, the history of the illness in each patient differed in no particular way from that obtained in a patient where a subsequent electrocardiogram had proved the presence of cardiac infarction, except in the higher incidence of pain precipitated by effort alone. Indeed, a diagnosis of cardiac pain had been made by a general practitioner, and often by more than one, in every instance; often a consulting physician had added his opinion. Long periods of rest in bed had been enforced in some cases, and for the relief of short painful attacks glyceryl trinitrate had been prescribed, often with benefit. Clinical examination had discovered no abnormal physical signs in this group: the blood-pressure was natural, cardiac enlargement was absent even on radiological examination, and there was neither triple heart rhythm nor evidence of valvular disease.

The electrocardiogram was carefully examined to discover any signs which might suggest coronary arterial disease. After such scrutiny the tracing was judged to be normal in all the cases. When the patients were recalled for examination after two years, the same competent electrocardiogram was repeated and the test of induced cardiac anoxæmia was often added. The incidence of œsophageal arrhythmia in this group was impressive, for the sign was present in 133 (40%) of the 332 cases (table I).

TABLE I—ŒSOPHAGEAL CONTRACTION IN PATIENTS WITH CARDIAC-LIKE PAIN IN WHOM THE ELECTROCARDIOGRAM WAS NORMAL AND IN PATIENTS ASSEMBLED FOR CONTROL

Description	No. of cases	Initial electrocardiogram		Œsophageal contraction	
		Normal	Abnormal	Normal	Abnormal
Patients with cardiac-like pain ..	332	332*	0	199	133 (*40*%)
Control series:					
Healthy subjects under 45 ..	200	200	0	199	1 } (*1*%)
Healthy subjects over 45 ..	500	500	0	494	6 }
Patients with painless heart disease	200	Variable		195	5 (*2·5*%)
Patients with cardiac pain..	500	0	500	475	25 (*5*%)

* In 5 patients the electrocardiogram later showed changes (see text).

I have accepted this finding as meaning that, when a patient with cardiac-like pain presents a physiological electrocardiogram, even after exercise, and at the same time shows œsophageal arrhythmia, the pain has a dyspeptic source. Even in those without this radiological sign it is likely that dyspepsia is the commonest cause of the pain, though occasionally other external influences, such as excessive smoking, play a part.

Naturally, this assumption demands that the electrocardiogram is strictly normal, and it also tests the view that a normal electrocardiogram excludes the presence of coronary arterial disease as the source of the chest pain. Decision on this cannot come easily, and the contribution which the sign of œsophageal arrhythmia makes to this problem had to be examined. It meant, therefore, that the patients with cardiac-like pain and a physiological electrocardiogram had to be watched for years lest in time any should give the abnormal tracing belonging to coronary arterial disease or unexpectedly die from cardiac infarction without any cardiographic warning. The patients belonged to a precarious age-group in that cardiac infarction might happen fortuitously in them, and this would delay final opinion on this issue. Such incidental deaths, if they took place, must necessarily be few if it is possible to predict an absence of a special susceptibility to the effects of coronary arterial disease in this class of patients. on the other hand, should the casualties prove light, we may conclude that in such patients the source of the chest pain is unlikely to reside in coronary arteries affected by an unusual degree of atheroma. The progress of these patients was therefore watched. Their ages varied from 37 to 85 and the average age was 55 years. The period of observation has been less than two years in 93, over two years in 239, over four years in 158, over six years in 87, and over ten years in 15 (table II).

TABLE II—LENGTH OF OBSERVATION PERIOD IN 332 PATIENTS WITH CARDIAC-LIKE PAIN COMPARED WITH THAT IN 332 WITH TRUE CARDIAC PAIN

Description	Period of observation in years since start of pain.				
	Less than 2	More than 2	More than 4	More than 6	More than 10
True cardiac pain ..	143	189	111	52	10
Cardiac-like pain ..	93	239	158	87	15

It was not easy to keep in touch with so many patients and to observe their progress three times in six years. There were delinquents, but special care was taken in such instances to ascertain the cause of absenteeism and in this way to avoid upsetting the statistical analysis.

The subsequent progress of these patients with cardiac-like pain will now be considered in relation to the persistence and the severity of the painful attacks, to any change in the erstwhile normal electrocardiogram, and to the incidence of death from cardiac infarction.

Change in Character or Incidence of Pain

Mention has already been made of the higher incidence in this group of pain which was induced by exertion alone and which quickly disappeared when the effort causing it was discontinued. This was true of 34% of the patients; but when the same information was sought in a like number of patients with true cardiac pain it was found in only 18%. When patients in the first group, however, were re-examined, many of them in the meantime had experienced occasional attacks while at rest, and/or these had lasted a longer time. It also came to light that in some instances the pain had left them after a time, and this applied particularly to those cases where the painful attacks had been long ones or had appeared at rest. This remission from pain was a feature in 83 patients; in 34 the pain had been absent for periods up to two years, in 49 for two years or more, and in 16 for more than four years. This freedom from pain was in obvious contrast with the findings in the same number of patients with true cardiac pain. In this second group such remission from pain was present in only 22 patients (table III).

TABLE III—INCIDENCE OF REMISSION FROM PAIN IN 332 PATIENTS WITH CARDIAC-LIKE PAIN COMPARED WITH THAT IN 332 WITH TRUE CARDIAC PAIN

Description	Remission from pain			
	Total	Less than 2 years	More than 2 years	More than 4 years
True cardiac pain	22	4	18	2
Cardiac-like pain..	83	34	49	16

This knowledge cannot prove useful in diagnosis nor help to allocate a patient to either group when he first presents for examination, but it does emphasise the difference in prognosis between the two groups, and in turn it suggests for each a different ætiology.

Subsequent Electrocardiogram

The initial physiological electrocardiogram in 5 of the 332 patients gave way to an abnormal tracing. In one, however, it was because of the development of aortic stenosis; later the changes suggested a myocardial injury from coronary arterial disease, and at necropsy there was considerable coronary atheroma, although frank cardiac infarction was absent. This is the only instance in the series where death resulted from heart disease, and the case is described in greater detail below.

In the remaining 4 patients the electrocardiogram recorded at their first attendance was judged to be faultless. These cases could not be regarded as examples of cardiac infarction taking place fortuitously in an ageing patient, because each complained of chest pain at the time when the normal tracing was obtained; and, in view of the subsequent abnormal electrocardiogram, the pain must have been the outcome of coronary arterial disease at the start.

During this investigation 4 other patients came to my notice whose chest pain was caused by coronary arterial disease and whose electrocardiogram for that reason showed changes due to cardiac infarction, but whose tracing on a subsequent occasion proved to be normal. It is necessary to include these 4 along with the other 4 patients in any discussion on the infallibility of the electrocardiogram to tell true cardiac pain; for, had they been seen for the first time when the electrocardiogram had recovered, they would have been regarded as cases of cardiac-like pain. None of the patients had symptoms or signs which suggested auricular tachycardia or pericarditis as causes of temporary cardiographic changes, and none showed œsophageal arrhythmia. Thus in only 8 patients out of 332 would a wrong diagnosis have been made if it had rested on the premise that chest pain arising from coronary arterial disease is associated with changes in the electrocardiogram. Of these 8, 4 were the only exceptions among the 332 patients considered to have cardiac-like pain, and the other 4 were the only exceptions among 1000 consecutive patients with true cardiac pain in that their abnormal cardiogram appeared to have recovered. It needs emphasis, however, that in none of the 8 patients was the electrocardiogram repeated after exercise, and critical re-examination of the tracing accepted as physiological in the first place either showed suspicious changes or found it to be an inadequate electrocardiogram in 6 out of the 8.

Incidence of Deaths

The mortality-rate among the 332 patients with cardiac-like pain was compared with that in 1000 patients with true cardiac pain examined during the same observation period. In the first group there were only 14 deaths compared with 190 in the second group, a mortality-rate of 4·4% against 19%. Of greater significance, however, is the result of an analysis of the cause of death in the two series. Among the 190 patients with true cardiac pain death was due to cardiac infarction in 184, renal failure in 3, carcinomatosis in 2, and rupture of the abdominal aorta in 1. In 13 of the 14 patients with cardiac-like pain and a normal resting electrocardiogram death was due to causes outside the heart (table IV). In 3 death followed an operation for gastric ulcer, in 2 it resulted from carcinoma of stomach, in 2 from carcinoma of pancreas, in 2 from carcinoma of lung, in 1 from carcinoma of uterus, in 1 from carcinomatosis, in 1 from pulmonary embolism following systemic venous thrombosis, and in 1 with scleroderma from pulmonary hypertension. Of these patients who died, 7 belonged to the group showing œsophageal arrhythmia and 7 to the group where this radiological sign was absent. In 6 out of 7 cases examined at necropsy, there was no excessive coronary atheroma nor an unhealthy myocardium. The remaining patient was aged 72 when she died.

TABLE IV—CAUSES OF DEATH IN 190 PATIENTS FROM AMONG 1000 WITH TRUE CARDIAC PAIN AND IN 14 FROM AMONG 332 WITH CARDIAC-LIKE PAIN OBSERVED DURING THE SAME PERIOD

True cardiac pain		Cardiac-like pain	
Cause of death	No. of cases	Cause of death	No. of cases
Cardiac infarction ..	184	Heart failure; aortic stenosis	1
Renal failure.. ..	3	Gastrectomy for ulceration..	3
Carcinomatosis ..	2	Carcinoma of stomach ..	2
Rupture of abdominal aorta	1	Carcinoma of pancreas ..	2
		Carcinoma of lung	2
		Carcinoma of uterus	1
		Carcinomatosis	1
		Pulmonary embolism ..	1
		Pulmonary hypertension and scleroderma	1

She was first examined because of cardiac-like pain at the age of 50. The pain had started twelve years before, when she was 38. It was described as 'gripping' and as a tightness in the chest, with pain spreading into both arms. Exertion, especially walking in cold weather immediately after a meal readily brought on the pain, which quickly subsided on resting. She continued to attend the cardiac department of the London Hospital for twenty-two years, and in all she had been subject to painful attacks for thirty-three years, apart from a period of a year, when she had been free from them. During the last few years the pain had set in when at rest.

Clinical examination found no abnormal signs, and during the earlier years the limb-lead electrocardiogram was normal, and so also were the chest-lead tracings when these were added. At the age of 62 signs of aortic stenosis appeared, and in time this affected the cardiogram. In her last year the tracing showed signs of coronary arterial disease as well. Œsophageal arrhythmia was always a prominent sign. Through the years she had obtained great benefit from glyceryl trinitrate, and had ingested some 45,000 tablets; but latterly they had proved less effective. Subjectively the severe paroxysms of pain resembled those from coronary arterial disease, but I always regarded them as arising from a dyspeptic source. An œsophageal mercurial bougie introduced three times a day for a week had no effect on the œsophageal arrhythmia, nor had the removal of the myenteric plexus at the lower end of the œsophagus.

In further support of the thesis that the pain had a dyspeptic rather than a cardiac source were the following facts: in spite of daily attacks of strong chest pain over twenty-four years the electrocardiogram had remained strictly normal, and only when aortic stenosis set in did it show left ventricular preponderance and, in the last year of life, the effects of coronary arterial disease.

Constipation was a life-long complaint, and so also was flatulence; hence a carminative mixture gave relief always comparable with glyceryl trinitrate, and latterly it gave greater relief. During her stay in hospital on one occasion the surgeon considered that air-swallowing caused the painful attacks, and instructed that a cork should be kept between her teeth, but this procedure did not abate the attacks; belladonna improved her symptom for a time.

At her last admission to hospital she was found to have heart failure with bilateral hydrothorax and she died. At necropsy there was severe aortic stenosis and atheroma of the coronary arteries, which had caused narrowing without occlusion, and subendocardial ischæmic fibrosis; frank or salient infarction was absent. There was no obvious abnormality of the œsophagus.

It is likely that this patient's painful attacks during at least twenty-three years were unrelated to the heart. The onset of aortic stenosis and the presence of severe coronary atheroma could have induced cardiac pain latterly, but the absence of cardiac infarction at the last was a notable finding.

Lerche (1950) has described the case of a woman, aged 26 who had experienced cardiac-like pain for ten years. Repeated radiological examination of a barium swallow had shown œsophageal spasm at its lower end. She was taken ill with pneumonia and died. No gross abnormality of the œsophagus was found at necropsy; the coronary arteries were not examined.

Discussion

MECHANISM OF ŒSOPHAGEAL ARRHYTHMIA

The *first phase* of œsophageal arrhythmia is characterised by a spasm which affects the lower third of the gullet as a rule and usually its lower end. This spasm may come into being as the meal reaches the affected part, with the result that nothing proceeds beyond the impasse at the start, but it is commoner for this sphincter-like action to begin after part of the meal has entered the stomach unimpeded, and then only the last part of the meal is halted abruptly.

Moersch and Camp (1934) described three kinds of spasm at the lower end of the œsophagus: (1) the diffuse irregular spasm which was the commonest form; (2) diffuse narrowing which suggests tetanic spasm; and (3) segmental spasm producing concentric narrowing at different levels.

A study of the myenteric nerve plexus at the lower end of the gullet allowed Lendrum (1937) to say that there was loss of ganglia cells with advancing years, and from the examination of 12 cases of achalasia, where spasm is associated with failure to relax, he concluded that a fault in the myenteric plexus had caused the spasm.

My series of healthy subjects, made up of a younger and an older group, did not show decisively that age influenced the incidence of œsophageal arrhythmia, while the patients with both the radiological sign and chest pain belonged only to a slightly older age-group. Thus, the average age of 199 patients with cardiac-like pain and no œsophageal arrhythmia was 53 compared with 60 years for 133 patients with œsophageal arrhythmia. Removal of the myenteric plexus round the lower end of the œsophagus in one patient did not, however, affect the radiological sign, which was seen after the operation as clearly as before.

There is no general agreement on the presence of a sphincter muscle at the lower end of the œsophagus. Those who have asserted that an anatomical sphincter exists at the cardia include Cannon (1911), Todd (1915), Thieding (1921), Bennett (1925), Hurst (1925), and Lerche (1950), while Fleiner (1900), Zaaijer (1923), Jackson (1927), Abel (1929), and Lendrum (1937) have stated that there is no sphincter. Whether there is an anatomical sphincter or not, there is no denying that this localised purse-string appearance of the barium-filled œsophagus is an affair of the gullet, which is not merely pinched at the diaphragmatic opening, because the constriction is often situated above this.

The *second phase*, characterised by a sharp recoil of the meal up the gullet, is more difficult to explain. Is it a relaxation of the œsophagus after the downward peristaltic wave has ended, allowing the compressed meal below to regurgitate and the gullet to collapse and assume its customary size with a narrow lumen, or is the action caused by an active retroperistaltic movement? The latter appears to be the explanation, for in some cases the spasm appears to be a minimal effect, and repeated recoil of the meal a spectacular feature.

Moersch and Camp (1934) considered that with the spasm of the lower end of the œsophagus the barium moved up and down with peristaltic activity, and that such rapid changes in the size of the lumen distinguished the deformity from the fixed defect of cardiospasm. Dahm (1931) used the kymograph to record these antiperistaltic movements which take place in œsophageal stenosis from various causes. Even such methods of recording, however, can hardly distinguish unerringly between the two mechanisms which might be causing the recoil of the meal. If the spasm is situated high in the œsophagus and then usually associated with an œsophageal pouch, recoil of the meal is not seen.

SIGNIFICANCE OF ŒSOPHAGEAL ARRHYTHMIA

The association of chest pain and œsophageal spasm has been reported by others.

Moersch and Camp (1934), describing 8 cases of diffuse spasm of the lower part of the œsophagus, found that the pain in some of them was experienced during swallowing, but in 2 the pain was characteristic of angina pectoris, and this clinical diagnosis had been applied to them in the past.

Wolferth and Edeiken (1942) regarded œsophageal spasm as the most important of all extracardiac causes of angina pectoris, although they had often observed spasm without symptoms. They said they had excellent reasons for believing that many of the seizures thought to be angina pectoris among highly strung nervous people, heavy smokers, and patients with gall-bladder disease, were really due to œsophageal spasm; the electrocardiogram in such cases remained normal even during the painful attack.

Harrison (1945) reported 35 cases with chest pain which in respect of its location and severity resembled angina pectoris, where œsophageal disease was responsible for the pain in 11 and gastric disorders in the remaining 24. In 8 of the 11 cases with an œsophageal fault there was spasm. Harrison opined, however, that neither in œsophageal nor in gastric disorders was the pain ordinarily related to physical exertion. His patients, therefore, showed pain which resembled cardiac pain from infarction rather than one readily induced by exertion and quickly yielding to rest.

MECHANISM OF THE PAIN

It has been held for some time (Schrager and Ivy 1928) that reflexes arising from diaphragm, œsophagus, stomach, or gall-bladder, in health or in disease, may affect the coronary circulation and produce cardiac symptoms. The thoracic, phrenic, vagus, and spinal nerve pathways are much the same for the diaphragm, lower end of the œsophagus, and the stomach, and Miller (1939, 1942) has described these nerve pathways and explained the radiation of the pain to the sternum, præcordium, and left arm in hiatus hernia as well as in other thoracic and abdominal visceral disease. Afferent pathways from the stomach, diaphragm, and œsophagus may enter practically all the dorsal spinal roots and even overflow into the brachial and cervical plexuses.

Gilbert et al. (1940) observed diminution of the coronary blood-flow in dogs when the stomach was distended, a vagal reflex which could not be abolished by vagotomy or by injection of atropine. These experiments confirmed earlier ones made by Anrep and Segall (1926) on the regulation of the coronary circulation which allowed them to conclude that it was possible for stimuli in the vagal or sympathetic nerve-endings in the lower end of the œsophagus or stomach to produce vasomotor changes in the coronary arteries initiating cardiac ischæmia or its equivalent effect and giving rise to the characteristic pain of angina pectoris.

From these physiological experiments some clinicians have assumed, perhaps too readily, that hiatus hernia can produce pain in the chest through reflex vasoconstriction of the coronary arteries. Indeed, many workers have held that hiatus hernia can produce pain in the chest identical with angina pectoris from coronary arterial disease (Jackson and Jackson 1936, Jones 1941, Herman and Singer 1946), and Jones and Chapman (1942) reported disappearance of the pain after successful surgical treatment of the hernia. Master et al. (1949), however, from their experience with the anoxæmia test in 57 cases of hiatus hernia, stated that this condition, with few exceptions, did not produce typical angina of effort unless it was associated with coronary arterial disease; they added that the œsophageal lesion might act as a trigger mechanism in precipitating angina pectoris when the coronary arteries are sclerotic.

Paul White (1937) pointed out that in Liddell and Scotts' Greek Lexicon καρδία was translated as heart or stomach and καρδιακος as pertaining to the heart or stomach; dyspeptic. It was no wonder, he added, that we had remained confused on differential diagnosis!

RESPONSE TO TREATMENT

Now that emphasis has been given to the dyspeptic origin of this cardiac-like pain, we may examine its response to treatment.

Morrison and Swalm (1940) stated that several of their patients with angina pectoris responded indifferently to glyceryl trinitrate, and that therapy directed to the gastro-intestinal tract gave much better results and reduced the number of the painful attacks.

Wolferth and Edeiken (1942) also found that in such patients the pain as a rule was not relieved by glyceryl trinitrate in a degree comparable with the effect gained in patients with cardiac pain from coronary arterial disease, and that the pain yielded in time to treatment with antispasmodics, sedatives, and psychotherapy.

Douthwaite (1943) found that belladonna and 'Eumydrin' had no effect on achalasia, but that amyl nitrite produced full, though temporary, relaxation; glyceryl trinitrate had the same action, more lasting though less complete.

In 4 children with achalasia Field (1944) found that octyl nitrite relaxed the cardia and produced clinical improvement greater than amyl nitrite or glyceryl trinitrate.

The painful attacks which physical exercise produced in my patients have yielded to chewing tablets of glyceryl trinitrate, and as readily as in those of cardiac origin, but not with the same success when used as a preventive, nor in the attacks which set in spontaneously at rest and which last some time in the face of all remedies other than morphine.

It was difficult to tell whether glyceryl trinitrate relieved the pain in virtue of its action on the coronary circulation or on the intestinal tract. Breaking wind was a common sequel, but this follows ingestion of trinitrin both in patients with cardiac-like pain and in those with true cardiac pain.

Reassurance on the more innocent nature of the pain, together with sedation for a time, has given the most consistent benefit. In those with obstinate constipation needing the habitual and daily use of a saline laxative, a tablet containing nux vomica, belladonna, and aloes has often reduced the susceptibility to pain; so also has a weight-reducing diet in the obese. Discontinuance of smoking has reduced or even annulled the painful paroxysms in a few cases. Cajaput oil and brandy are two carminatives that have sometimes helped.

It will be seen, therefore, that response to a particular form of treatment does not tell the nature of the pain, but on the whole the patients in this group have responded to remedies intended to relieve gastro-intestinal rather than cardiac symptoms.

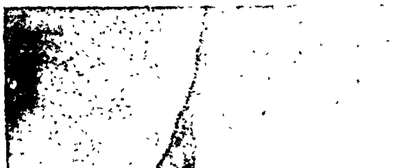

Fig. 3—Right oblique teleradiogram of intrathoracic stomach showing deviation of œsophagus to right (1) by stomach (2) which has herniated through diaphragm on left side, in a woman, aged 57, with cardiac-like pain.

THE SPASM AND PAIN

I cannot agree with the view that chest pain is the direct outcome of œsophageal spasm, except in the case of segmental spasm. Œsophageal spasm was met with in people who did not complain of symptoms, and, even when it was a prominent feature in a patient with cardiac-like pain, the pain never set in during radiological examination, which showed the presence of both œsophageal spasm and recoil of the meal.

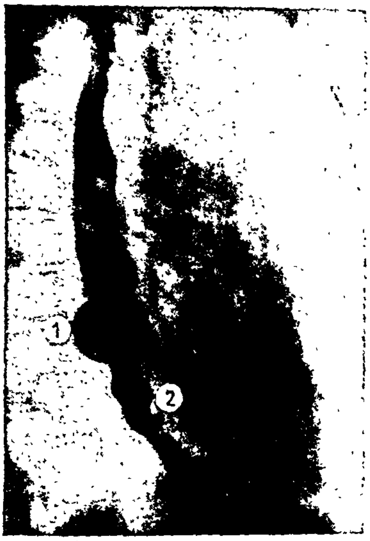

Fig. 4—Right oblique œsophogram showing œsophageal pouch (1) in middle third of gullet and segmentation (2) of its lower third, in a woman, aged 56, with cardiac-like pain. In a search for this condition patient should be examined in both oblique positions.

The protean symptoms identified with achalasia, œsophageal ulceration, pouch or hernia, gall-bladder disease, and gastro-intestinal upsets provide a common playground for the sport of many departmental specialists, but to be drawn into a discussion of the differential diagnosis of these several ailments is unprofitable, and I am concerned here only to find whether any of these conditions came to light in those patients with cardiac-like pain in whom the electrocardiogram proved to be strictly normal during the time they were being watched.

In the patients forming my series, however, gastro-intestinal lesions were not deliberately sought by special tests unless symptoms and signs pointed suspiciously to their presence, and this did not happen in any of the cases when they first presented with cardiac-like pain. The presence of hiatus hernia, for instance, was never tested by special radiological investigation unless it was seen while watching the progress of a barium swallow.

Not once did achalasia or œsophageal ulceration explain the pain, but a definite lesion of the intestinal tract apart from œsophageal arrhythmia appeared during a period of observation in 18 patients. Thus, gastro-duodenal ulceration was eventually found in 4, intrathoracic stomach (fig. 3) in 4, œsophageal pouch (fig. 4) in 3, cholecystitis in 3, carcinoma of stomach in 2, carcinoma of pancreas in 2, and segmental spasm of the œsophagus in 2; the last 2 patients are not included among the 133 cases which showed œsophageal arrhythmia.

Alongside the symptom of cardiac-like pain, others which appeared included flatulence, abdominal pain or discomfort, and obstinate constipation needing a daily aperient. Although such symptoms were also present in patients with true cardiac pain they were far more common in the series with cardiac-like pain, but they have not been regarded here as giving proof by themselves that the chest pain had a dyspeptic source.

* * *

At the turn of the century windy dyspepsia was a common bedside diagnosis in a patient bent by chest pain and trying to break wind, assisted by a host of carminative mixtures which remain in our pharmacopœia to remind us of the determined attempts once made to ease this symptom which was thought to be caused by gastro-intestinal ballooning. When it was shown that cardiac infarction could be the cause of such painful episodes, its recognition soon became commonplace, and windy dyspepsia was henceforth to recede as an inelegant diagnosis. In this the older clinicians have been shown to be wrong. It is likely that they were wrong many times, but were they wrong all the time, and today are we not wrong sometimes? It is my thesis that we are.

If we rely on a characteristic history for the positive diagnosis of cardiac pain there is a 3 to 1 chance that we are right, but it would be well to express this differently and to emphasise that there is 1 chance in 3 that we are wrong.

Enforced unwarranted invalidism is a cruel imposition at any age. It is most cruel when the autumn of life is clouded by unjustified restrictions which not only deny hobbies anticipated pleasurably during years of hard work but also indelibly remind the sufferer that he harbours a mortal illness within his breast. For the doctor to miss a step here is to commit a mistake from which there is no clear retreat; even when the diagnosis is eventually withdrawn, harm has been done and the mental injury lasts. Failure to recognise the marks of coronary arterial disease is of equal moment; hence at this cross-roads the doctor must read the signs clearly when the patient awaits to know which road he is to take and in what manner he must travel.

Osler once reminded us that the diagnosis of pain was made from a regard of the patient's statement, that its severity was judged by observation, and that the recognition of its cause demanded a thorough study. This applies specially to cardiac pain, where the scarcity of physical signs has driven us to rely on the electrocardiogram. It is the theme of this communication that, when the electrocardiogram is strictly normal in a patient with cardiac-like pain, as it often is, we shall gain help in our search for the cause of the pain if we look for the radiological sign of œsophageal arrhythmia.

I wish to thank Dr. Russell Reynolds for recording the œsophageal movements by cineradiography in five, and Dr. J. W. McLaren by kymography in two, of my patients.

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A TEASPOONFUL OF BAKING-SODA

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> "Once I had a pain when my stomach was empty. Now I get a pain when it's full."
>
> (A patient, after his partial gastrectomy.)

IN these days of gels and resins it is unfashionable to prescribe sodium bicarbonate for dyspepsia. We point to its undesirable property of stimulating acid secretion in the stomach and to the dangers of alkalosis. Yet some patients remain irritatingly unconvinced by these disadvantages and may even assert that baking-soda gives them more relief than does anything else. Perhaps more of it is used in medical wards than we know of or suspect.

There seems to be some doubt about whether either rebound or direct stimulation of gastric secretion takes place after the administration of bicarbonate, and the dangers of alkalosis have possibly been overemphasised, but a whittling down of the side-effects does not fully explain a dyspeptic's preferences.

The ability of sodium bicarbonate to neutralise hydrochloric acid is not outstanding, being only about a quarter of that of magnesium oxide weight for weight, and little more than half of that of magnesium carbonate or of calcium carbonate. It has been tacitly assumed that it relieves pain so well because of the rapidity with which it buffers gastric acidity. This explanation may serve for patients with hyperchlorhydria but hardly for those who have little or no acid in their stomachs, some of whom dislike acid hydrochlor. dil. and flourish on sodii bic. Latterly the numbers of this group have been increased by the accession of those with post-gastrectomy syndromes.

There is a further class of patients who perform, as it were, a physiological gastrectomy on themselves. They present with symptoms of a duodenal ulcer, and a test-meal may show hyperacidity. A deformed duodenal cap is seen on X-ray examination, and it is assumed that the diagnosis of duodenal ulcer has been established. The years roll on, the episodes of dyspepsia persist, but the gastric acidity diminishes and may eventually disappear; and yet they continue to gain relief from alkalis, particularly sodium bicarbonate, and it is as easy to explain to them why this should be as it is to dissuade them from demanding to undergo partial gastrectomy.

A colleague, challenged by the unwillingness of some patients with "dumping" syndromes to continue taking the acid hydrochlor dil. he had prescribed for them, after they had submitted to partial gastrectomy operations designed to reduce their gastric acidity, advanced an ingenious hypothesis. He thought that a sort of conditioned reflex had become established after many years of food→pain→alkali relief, and that alkali had become part of a ritual and an essential support for the psyche during digestion. It seemed to us, however, that, since sodium bicarbonate is a major constituent of both bile and pancreatic secretions, adequate amounts of it were probably essential for the proper functioning of the digestive mechanisms of the small bowel. We therefore thought it more likely that the therapeutic efficacy of bicarbonate lay in its power to make good a deficiency when taken by mouth. An attempt was made to test this idea.

METHODS

Eighteen patients who had been admitted to hospital for the treatment of post-gastrectomy syndrome were examined by the dextrose-barium-meal technique (Glazebrook 1952, Glazebrook and Welbourn 1952). In this examination 230 ml. of a 50% solution of dextrose in water is added to 230 g. of barium, and the patient is asked to swallow the mixture, the motility of the small gut being observed by screening, and the appearances being recorded by fifteen-minute and hour films.

Nine of the cases were thought to be motility disturbances, as judged from the clinical history and examination and the results of radiography and balloon kymography. Three were diagnosed as afferent-loop-distension syndrome because pure bile unmixed with food was vomited after meals. In two cases stomal ulcers had been seen on gastroscopy.

The examination was also done with the same dextrose-barium mixture combined with 4 g. of sodium bicarbonate.

Six patients were given the unmodified dextrose-barium mixture soon after admission to hospital, and the bicarbonate-modified mixture seven days later. Afterwards, to minimise influences due to the hospital régime of rest and dietary control, the remaining twelve patients were given the bicarbonate-dextrose mixture first and the unmodified dextrose-barium meal a week later.

The X-ray appearances, particularly within the first fifteen minutes of the examination, and the symptoms produced by the dextrose were compared in each case on the two occasions. Some had a third examination in which the effects of atropine and of a synthetic spasmolytic, 'Ro 2-3773,' given by injection, were compared with those produced by bicarbonate.

RESULTS

The results are given in the accompanying table.

The sodium bicarbonate quietened the rush and spasm of the small gut produced by the sugar of the barium meal in each of the twelve cases of motility disturbances and, in addition, abolished or ameliorated the unpleasant symptoms brought on by the examination.

The bicarbonate relaxed the small bowel in each of the three cases of afferent-loop-distension syndrome but did not relieve the symptoms in one of them in spite of the X-ray appearances, which suggested an easement of the tension.

Not one of the three patients with stomal ulceration noticed any change in their sensations as between the two barium meals; in one some relaxation of the small bowel was seen on X-ray screening. In these three cases very little barium entered the small bowel during the first fifteen minutes, in contradistinction to the fifteen cases mentioned above, owing to stomal spasm, and this spasm was not much affected by bicarbonate.

ILLUSTRATIVE CASES

Intestinal Hurry

Case 1.—A man, aged 45, had undergone partial gastrectomy for chronic duodenal ulcer in 1950. Severe postprandial symptoms led to a second laparotomy in 1951, but nothing abnormal was found, and the abdomen was closed after appendicectomy. When the patient came under our observation his symptoms were characteristic of intestinal hurry—weakness, distension, and sweating after meals, with loose light-coloured bulky motions, and an inability to maintain his weight. The fifteen-minute film after a dextrose-barium meal shows the rapid rate of travel of the meal through the small bowel (fig. 1); the man had all of his postprandial symptoms during this time. A second dextrose meal, with sodium bicarbonate 4 g. mixed with it, showed quite different appearances at fifteen minutes (fig. 2), and the man had no symptoms save slight distension.

EFFECTS OF BICARBONATE

Syndrome	No. of cases	Effect on symptoms	Effect on radiograph
Postprandial "dumping": Intestinal hurry	2	Relieved in both cases	Rate of passage of meal slowed in both cases
Intestinal spasm	3	Relieved in all cases	Spasm relaxed in all cases
Mixed types	4	Relieved in all cases	Spasm relaxed in all cases; rate of passage slowed in 1 as well
Afferent-loop distension	3	Relieved in 2 cases; unchanged in 1	Bowel relaxed in all cases
Stomal ulcer	3	No change in symptoms	No change in 2 cases; bowel relaxed in 1

Intestinal Spasm

Case 2.—A man, aged 31, had a duodenal ulcer which perforated twice before he underwent partial gastrectomy in 1950. After this operation he never felt well. He had exactly the same sort of epigastric pain after meals, its severity being equal to that of the original ulcer pain at its worst just before his second perforation, and he still had to diet himself and take alkalis for its relief. His bowels were very costive and his motions small and dark; he felt generally weak but had not lost any weight. Although he felt like lying down after meals, there were no vasomotor symptoms, such as sweating, palpitations, and pallor. The pain had changed its time of onset in relation to meals, coming on fifteen minutes after eating instead of two to three hours, and an intense feeling of distension was prominent. A dextrose-barium meal brought on all of his symptoms, with severe pain and feeling of distension, and severe spasm was seen at fifteen minutes (fig. 3). The patient's conception of being "blown out with the wind" should be compared with the radiograph of his small bowel, which appears to be tied up into knots. The same examination, repeated with sodium bicarbonate 4 g., led to less spasm at fifteen minutes (fig. 4) and less intense symptoms, although he still had a good deal of discomfort.

Afferent-loop-distension Syndrome

Case 3.—A man, aged 27, had a bad family history, his father having died of a perforated gastric ulcer and two of his brothers having had peptic ulcers. The patient had undergone partial gastrectomy in 1950, after a radiological report of a deformed duodenal cap. During the operation he had severe laryngospasm. No definite evidence of either gastric or duodenal ulcer was obtained, but nevertheless four-fifths of his stomach was amputated. Severe post-

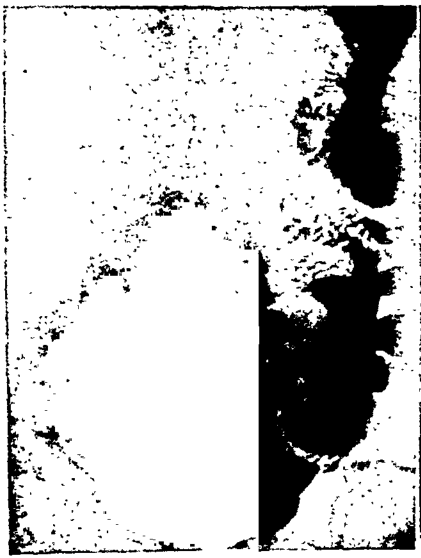

Fig. 1—Fifteen minutes after dextrose-barium meal in case 1, showing rapid rate of travel of meal through small bowel.

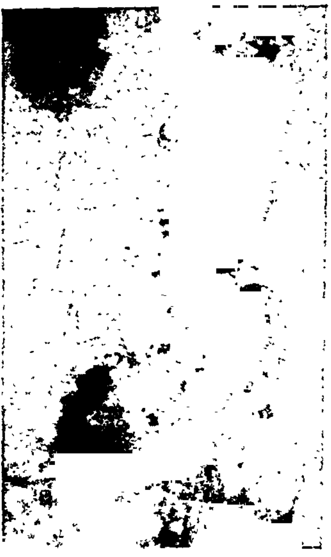

Fig. 2—Fifteen minutes after bicarbonate-dextrose-barium meal in case 1 (cf fig. 1).

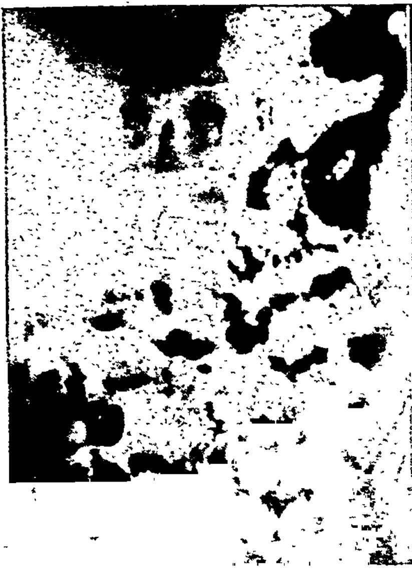

Fig. 3—Fifteen minutes after dextrose-barium meal in case 2, showing intestinal spasm.

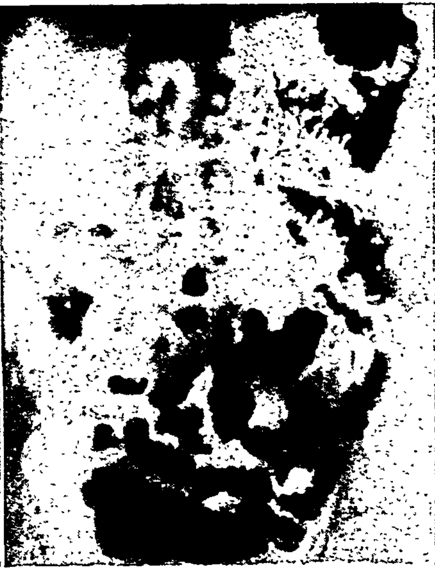

Fig. 4—Fifteen minutes after bicarbonate-dextrose-barium meal in case 2 (cf. fig. 3).

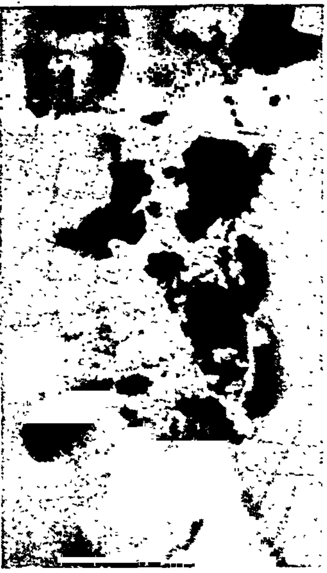

Fig. 5—Fifteen minutes after dextrose-barium meal and injection of Ro 2-3773 in case 2 (cf. figs. 3 and 4).

prandial distress, relieved by vomiting large amounts of pure bile, was noticed as soon as he had got over the immediate postoperative phase. The bile was unmixed with food, even although he had just eaten. Once the bile had come up, he might be free from distress for some hours and get through the next meal without trouble. Certain foods —e.g., eggs—invariably brought on the symptoms, and he had got into the habit of refusing most things offered to him, preferring to live on a diet of dry bread and 'Bovril.' On this régime he lost weight slowly, became too weak for his employment, and was troubled with obstinate constipation. Fig. 6 is the fifteen-minute film after a dextrose-barium meal, and fig. 7 the fifteen-minute film when 4 g. of bicarbonate had been added to the dextrose-barium mixture. On both occasions the patient felt nausea and distension, but the symptoms were milder when bicarbonate was used. The degree of relaxation seen in fig. 7 is remarkable, but a similar degree of relaxation was seen in four other patients.

Flatulent Distension

This common symptom of the dyspeptic, which is so amenable to sodium bicarbonate, is associated, in our experience, more often with bowel spasm than with gaseous distension, although it is difficult to convince the patients of this fact, so certain are they that they are being blown out with wind.

Case 4.—A man, aged 40, underwent partial gastrectomy in 1950, an active duodenal ulcer being found. Afterwards he had one main symptom—flatulent distension ten minutes after food. He had maintained his weight but, like so many patients after partial gastrectomy, he never felt as strong as he did before operation. A dextrose-barium meal showed most of the meal at fifteen minutes to be in the small gut (fig. 9), which responded by initial localised spasm followed by hurry, the barium being evacuated within one and a half hours. Intense flatulent distension with nausea was complained of for the first twenty minutes after the meal. When the examination was repeated with the addition of sodium bicarbonate 4 g., the bowel relaxed and became full of gas at fifteen minutes (fig. 10), yet the symptom of "flatulent distension" was relieved.

Gas was noticed in the bowel of one other patient after the bicarbonate-dextrose-barium mixture.

COMPARISON OF SPASMOLYTIC EFFECTS OF SODIUM BICARBONATE AND OF VAGUS-BLOCKING COMPOUNDS

Atropine gr. $^1/_{100}$, injected subcutaneously just before the barium meal was swallowed, led to similar changes, relieving spasm and slowing hurry, the effects observed being comparable to those seen after giving sodium bicarbonate by mouth. In some cases atropine seemed

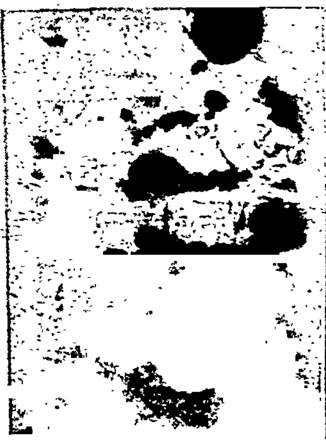

Fig. 6—Fifteen minutes after dextrose-barium meal in case 3 with afferent-loop-distension syndrome.

Fig. 7—Fifteen minutes after bicarbonate-dextrose-barium meal in case 3 (cf. fig. 6).

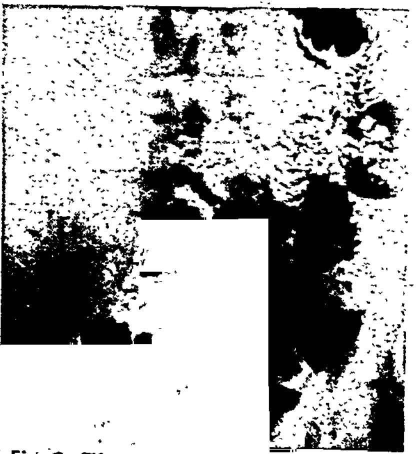

Fig. 8—Fifteen minutes after dextrose-barium meal and injection of Ro 2-3773 in case 3 (cf. figs. 6 and 7).

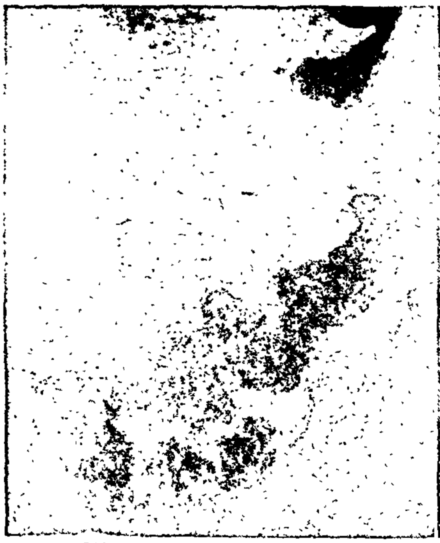

Fig. 9—Fifteen minutes after dextrose-barium meal in case 4 with "flatulent distension."

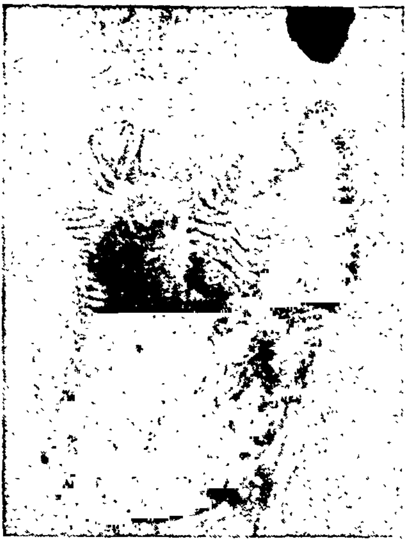

Fig. 10—Fifteen minutes after bicarbonate-dextrose-barium meal in case 4 (cf. fig. 9).

to have a relaxant action rather superior to that of bicarbonate ; in others it was not quite so effective.

Ro 2-3773 is a vagus-blocking agent which also has about the same activity as tetraethylammonium bromide as a ganglion-blocking agent (Randall et al. 1952) Balloon kymography had shown in man that its action on the small bowel, and the nature and extent of its side-effects, were similar to those of atropine.

Fig. 5 shows the fifteen-minute film of case 2. Ro 2-3773 10 mg. had been given immediately before he took the dextrose-barium meal. More relaxation was obtained, compared with the bicarbonate picture (fig. 4), and the patient felt even less distressed during the X-ray examination after Ro 2-3773 than after the two other barium meals.

In case 3, however, 10 mg. of Ro 2-3773 did not relax the bowel to the same extent that bicarbonate did at fifteen minutes (fig. 8). On the other hand, although most relaxation was seen with the bicarbonate, Ro 2-3773 afforded greater relief from symptoms.

DISCUSSION

One of the attractions of gastro-enterology is that the commonplace so often stimulates. One sometimes wonders, for instance, whence cometh the wind that distresses our chronic dyspeptics so woefully, and it certainly seems odd that a man should find he still has to take his alkali and his spasmolytic after partial gastrectomy.

The experimental work described here and elsewhere (Glazebrook 1952, Glazebrook and Welbourn 1952) suggests that small-gut spasm and hurry play their part in the production of post-gastrectomy syndromes. It must be admitted that the mixing of dextrose with barium is an artificial way of inducing disorders of motility, and other workers (Frazer et al. 1949, Ardran et al. 1950) state that the appearance of clumping of the barium, which we believe is largely due to spasm, is caused by the flocculating action of mucus. However, we are satisfied that both vagus-blocking agents and sodium bicarbonate can modify the X-ray appearances and the symptoms induced by the sugar.

The action of atropine and related compounds is expected ; that of bicarbonate is interesting, and the results encourage thought and speculation.

So far as the problems of partial gastrectomy are concerned, perhaps motility disorders of the small bowel are in some cases due to minor forms of the afferent-loop-distension syndrome, the bile following the meal down the alimentary canal instead of being mixed with it. In other cases possibly the food is dumped into the small gut so rapidly that it is denied the buffering actions and digestive ferments of the pancreatic juice.

There may be a type of dyspepsia related to deficiencies in the production of bile and pancreatic juice rather than to excess production of acid ; in some people the risks of alkalosis may prove a lesser evil than the long-term effects of diminishing pancreatic output by powerful vagus-blocking agents. Certainly after partial gastrectomy, where so much of the glandular apparatus of digestion has been abolished, further loss of digestive power by pancreatic depression should be avoided if possible.

Some of the most severe cases of post-gastrectomy syndromes are met with in patients who, so far as can be made out, have never had a duodenal ulcer at all, the X-ray sign of a deformed duodenal cap being taken as sufficient evidence to justify partial gastrectomy. Perhaps a primary disorder of intestinal motility, due to instability of the neuromuscular apparatus of the gut which makes it more sensitive to pH changes, is at fault. The man quoted at the head of this paper underwent partial gastrectomy at the age of 22. No evidence of a peptic ulcer, or of the scar of one, was seen either at operation or by the pathologist who reported on the removed tissues. The man, who found his pain was relieved by bicarbonate after the operation just as well as before, misinterpreted his visceral sensations. His gastric stump was empty at the time that he had his pain.

SUMMARY

Peristaltic rushes and spasms caused by giving sugar to eighteen patients with post-gastrectomy syndromes were, in fourteen cases, quietened by a teaspoonful of baking-soda.

The spasmolytic effect of the baking-soda was similar to that obtained by injecting either 0·6 mg. of atropine or 10 mg. of the spasmolytic substance Ro 2-3773 (1-methyl-3-benziloyloxy-quinuclidinium bromide).

We are grateful to Prof. J. le F. C. Burrow and Mr. George Armitage for their help and encouragement. We wish to thank the Director-General of Medical Services, Ministry of Pensions, for permission to publish, and Messrs. Roche Products Ltd. for supplies of Ro 2-3773.

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"... It will be a great day for the mental hospitals when the physicians, surgeons and practitioners of the impersonal specialities enter the wards.... There is only one place to learn clinical psychiatry, and that is in the mental hospitals. . . . And then I see a large parcel of students straining to hear whether the cardiac murmur is in systole or diastole, whereas their first night in general practice might bring them a schizophrenic, an alcoholic and young married people in sexual difficulties—the happy inertia of academic learning. What Galen said went on for centuries."—Dr. BARRY MULVANY, *Med. J. Aust.* Nov. 29, 1952, p. 761.

PROGRESSIVE ORAL GANGRENE ROBABLY DUE TO LACK OF CATALASE IN THE BLOOD (ACATALASÆMIA)

REPORT OF NINE CASES

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An enzyme which generates oxygen in all animal nd plant cells by decomposing hydrogen peroxide has ong been known. Loew in 1901 named it catalase, nd it has been the subject of considerable biological nd chemical research; its rôle has hitherto remained bscure because of the difficulty of excluding catalase xperimentally from the tissues.

About five years ago I found a girl who had no atalase in her blood. She presented at hospital with painful mouth, and oral gangrene was found which had started at the margin of her gums. It was not until after considerable investigation that I found she had no catalase in her blood, and then I suspected a close connection between her lack of catalase and her symptoms.

After that I found five more cases of this rare condition, four of them being in siblings (see figure). These cases have already been published (Takahara and Miyamoto 1949); but I am still studying this subject and have discovered several new facts (Takahara 1951).

CASE-RECORDS

Case 1—On Dec. 25, 1946, a girl, aged 11 years, complained of pain in her mouth. Small ulcers had begun to appear on her gums when she was 8 years old. Some of them disappeared spontaneously, but were very soon succeeded by others which encroached upon the gums and dental alveoli, thus loosening the teeth. When these teeth dropped out spontaneously or were pulled out, the affected parts healed. After a tooth had been extracted in November, 1946, a sequestrum appeared at the site of the tooth, and gangrene followed. Various medical treatments were given unsuccessfully; in fact, the condition became worse. About Dec. 15, 1946, the right cheek began to swell, causing keen pain, and the patient's temperature rose to 101°F.

On examination her cheeks were greatly swollen and slightly reddened, and she was pale. She had lost several teeth, and almost all the remaining teeth were affected by gangrene. The most conspicuous symptom was caries in the right maxilla, extending as far as the maxillary sinus and nasal cavity and giving forth a nauseating smell. The patient's temperature was 99·5°F, and pulse-rate 85. Her liver and spleen could not be felt. Examination of her blood showed erythrocyte-sedimentation rate 35 mm. in one hour, 54 mm. in two hours; red cells 3,450,000 per c.mm.; leucocytes 9400 per c.mm.; Hb 65%; bleeding-time and coagulation time normal; and serum negative for syphilis. Nothing abnormal was detected in the fæces and urine. On rhinoscopy I found, in the right nasal cavity, a tumour covered with putrid granulations, which bled easily on being touched. A biopsy specimen revealed chronic inflammation.

Operation.—The tumour was radically removed and the area curetted. I washed the operation wound with hydrogen peroxide as usual, whereupon the cavity in the maxilla and the blood oozing from the wound immediately became brownish black, just as if silver nitrate had been applied by mistake. Thinking this was so, I frantically poured on saline solution to neutralise the silver nitrate. Next, I washed the wound with hydrogen peroxide from a new bottle, and the same thing happened again. Finally I noticed that the black colour was caused by the blood oozing out of the wound, and that there were very few bubbles.

Postoperative Course.—The diseased part in the upper right jaw took a turn for the worse three times after the operation. Sequestra formed three times, necessitating curettage each time; but the affected part was completely cured in about two months. In January, 1948, the site of the extracted teeth became ulcerated; so it was curetted, and sulphanilamide was given. In spite of this, gangrene developed spread rapidly toward the root of the tongue. So I made a small opening from the diseased part to the submental part and inserted a drainage tube. By repeatedly washing out with 'Rivanol' solution through the opening for about a month the pus was cleared away and the disease checked. In October, 1948, another tooth was pulled out. Gangrene rapidly developed from the site of the tooth, and the cheek became much swollen, causing great pain. The patient's temperature rose to 101·3°F, and other constitutional symptoms developed. After a course of intramuscular penicillin G 400,000 units, a sequestrum came away spontaneously, and the part was cured. After that, teeth were pulled out one after the other whenever ulcers appeared in her gums. Now, at the age of 15, she is in full development and in good health but has not a tooth left. She recently had her first menses.

Her mother told me she had five children besides this girl, and that two of them, a boy and a girl, had the same disease. I got them to come to the hospital for a blood examination. I dropped hydrogen peroxide into the blood taken from their ear lobes. As I expected, the blood turned brownish black instantly and no bubbles were generated. By the same method I found that another sister, aged 8 years, had the same kind of blood. In other words, four children out of six born of the same parents (see figure) had no catalase; and only these four children showed similar symptoms in their gums.

Case 2.—A boy, aged 13, older brother of case 1, also had sporadic ulcers of the gums from the age of 8 years, and the diseased teeth dropped or were pulled out. When he was aged 12, a tooth became loose and was extracted by a dentist. Later an ulcer formed at the site. It did not heal readily and part of the jaw became very painful, swollen, and slightly inflamed. The diseased part of the lower jaw was resected, and the disease was checked. A year later the defect in the jaw was made good with part of one of his ribs. Half a year or so later another tooth in the maxilla was extracted, and afterwards an ulcer developed from the socket of the extracted tooth and advanced to the maxillary sinus. I curetted the affected part by Luc's method, and it soon healed.

In June, 1949, when he was 14, a boil appeared on his right cheek and suppurated. Two or three days later the right submaxillary gland became swollen, causing a dull pain, and was massaged at home. Next, his neck began to swell and the pain became unbearable; his temperature rose to 101°F. At midnight he complained of a difficulty in breathing and appeared to have Ludwig's angina. As soon as day broke he was brought to our hospital. Tracheotomy was done immediately, and the swollen part was incised just below the right jaw. A drainage tube was inserted to enable the incised wound to be washed out every day with rivanol solution, and intramuscular penicillin G 1,000,000 units was given. The boy recovered and was completely healed within ten days.

Case 3.—A girl, aged 4 years, sister of cases 1 and 2, was attacked by the disease at an earlier age than her sister and her brother. When she was aged only 2 years, gangrene started at the gums of her lower front teeth. After five teeth had been pulled out, the ulcers healed. When she was aged 4 years, her upper teeth became affected likewise.

On examination she was a little pale but she was otherwise in good health, and her liver and spleen were impalpable. A blood-count showed red cells 5,030,000 per c.mm; leucocytes 8500 per c.mm., Hb 74%.

Treatment and Progress.—By pulling out all the affected teeth, the patient was soon cured. Two or three new permanent teeth have begun to appear since then, and nothing unusual is noticeable about them.

Case 4.—A girl, aged 9, sister of cases 1–3, showed nothing abnormal in her mouth when I first examined her with the other siblings of case 1 and found that her blood was blackened by hydrogen peroxide. Later, however, she began to complain of dull pains round some of her upper teeth at night. Next, the gums between the teeth became slightly shrunken and a small ulcer appeared there. The same happened to other upper teeth in the next two months; but the disease disappeared spontaneously without any medical treatment.

Case 5.—A boy, aged 13, had had similar trouble for ten years. When he was aged about 3 ye a small ulcer w far as the buccal mucosa and an œdematous swelling appeared on the cheek, resembling noma. This was checked by medical treatment, but ulcers recurred in other parts of the gum. Although various treatments had little effect, the disease did not progress rapidly. The boy's teeth were removed only after the alveoli had been destroyed and the teeth became loose. When he was aged 11 years, he was sent to hospital with ulcers over a wider area of the gums. That is when I first saw him. The condition improved temporarily, but by the next year gangrene developed, reaching the left maxilla. A sequestrum was removed, and a fistula appeared on the site, extending as far as the left maxillary sinus. The pus had a very bad smell, severe pain was felt at the diseased part, and the boy's temperature rose to 101·4°F. Temporary improvement was brought about by curettage of the diseased part followed by penicillin injections.

Towards the end of 1948 ulcers reappeared at the same place and his cheek was swollen. From that time on he began to complain of a dull pain in the right lower jaw and the *fetor ex ore* became more intense. So in February, 1949, he called at our clinic. When I added hydrogen peroxide to his blood, it blackened immediately, just as in cases 1–4. After a while it began to fade, finally becoming completely discoloured. This colourless liquid showed the pentdyopent reaction (see below). The fact that catalase was completely lacking in his blood was also shown by quantitative examination. The diseased part in the upper left jaw was removed by Luc's method, and the wound was washed with rivanol solution. At the same time intramuscular penicillin 600,000 units was given. By these treatments the diseased part was completely healed.

Later, in April, 1949, a deep ulcer, which was similar to Vincent's angina, appeared (having no connection with the teeth) on the left tonsil. Although such an ulcer was not seen in cases 1–4, I think it must be an important symptom of this same disease. Since many organisms usually live in the crypts of the tonsils, hydrogen peroxide is produced continuously by bacteria (see below). Consequently necrosis begins in the crypts of the tonsils as it does in the gums. In April, 1950, the patient had necrosis of the tongue on the left side, caused by extension of an ulcer connected with one of his lower teeth.

Besides cases 1–5 four others were found in ten siblings of the Abe family (see *figure*) in a different prefecture. They showed a lack of catalase in the blood and two of them also had the same symptoms, though slight, at the gums in their childhood.

EXPERIMENTAL STUDIES

If hydrogen peroxide solution is dropped into normal human blood, gas is evolved and the colour of the blood remains unchanged. This is because the H_2O_2 is decomposed by the action of the catalase in the blood:

$$2\,H_2O_2 \xrightarrow[\text{(catalase)}]{} 2\,H_2O + \underset{\text{(bubbles)}}{O_2}$$

TABLE I—QCAT OF BLOOD AND ORAL AND NASAL TISSUE I ACATALASÆMIC AND IN NORMAL PERSONS. ESTIMATED B WARBURG'S MANOMETRIC METHOD (FUJITA AND KODAM 1931)

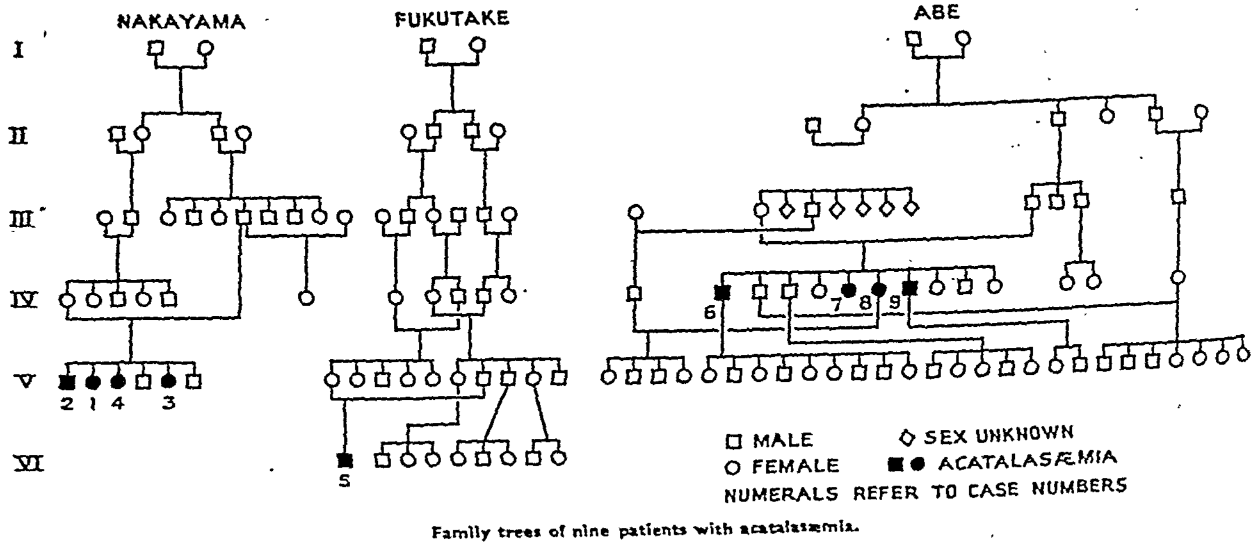
Acatalasæmia					Normal persons
Case no.	Sex	Age (yr.)	Material examined	Qcat	Qcat
1	♀	16	Blood from earlobe	7	4500
2	♂	18	Venous blood	5	About 4500
			Blood from earlobe	6	4500
3	♀	8	Blood from earlobe	10	4500
			Normal oral tissue	0	250
4	♀	14	Blood from earlobe	10	4500
5	♂	17	Venous blood	9	About 4500
			Erythrocytes of venous blood	8	12,000
			Normal oral tissue	0	250
			Marginal tissue of oral ulcer	0	..
			Tissue of oral ulcer	0	..
			Tissue of ethmoidal sinus	0	450
			Nasal polyp	0	200

Qcat (quotient of catalase) is calculated according to the following formula:

$$\text{Qcat} = \frac{\text{Quantity of } O_2 \text{ generated in 30 min. at 38°C (c.mm.)}}{\text{Weight of dried substance of examined material (mg.)}}$$

When, however, hydrogen peroxide was dropped into the blood of cases 1–5, the blood blackened immediately and gas did not appear; after a while only a few little bubbles were seen. I therefore estimated the amount of catalase in their blood (table I).

From table I it will be seen that the Qcat of every tissue taken from the nose and mouth in acatalasæmia was 0 and the Qcat of the blood of these patients was 5–10. Since this number for the Qcat of blood was a little more than that of an average observational error, it seemed that the acatalasæmic patients might have an extremely small amount of catalase in their *blood*. The Qcat of a normal person's blood is about *4500*, and the ratio between the Qcat for normal and acatalasæmic blood is about 450/1 to 900/1. Since the Qcat of the tissues of the acatalasæmic patients was always 0, it seemed possible that the number (5–10) for the Qcat of their blood had almost no meaning, in so far as it



Family trees of nine patients with acatalasæmia.

concerned the function of catalase. Such conclusions were further justified by the results, obtained during the past five years, of catalase estimations made by Inoue's permanganate method. Catalase in the blood of healthy persons and of inpatients of our clinic has been estimated by this method, and the results are shown in table II.

Table II shows that most persons whose blood was normal as regards catalase had an index number of about 5·0–10·0 (3·3–10·9). It is also clear that, except in acatalasæmia, the index numbers had no relation to disease. The index numbers of the blood in acatalasæmia were 0·0–0·1, and I have not noticed any significant change in the quantity of blood-catalase in five years.

I have thus confirmed that the quantity of catalase in the blood in acatalasæmia was about $^1/_{1000}$ of normal. If our acatalasæmic patients had had any catalase in their blood, it must have been an extremely small amount in comparison with that of normal persons. Peroxidase was found in normal amounts in the blood of all our patients.

The reason why the acatalasæmic blood was blackened by adding hydrogen peroxide may be as follows. Hydrogen peroxide poured into acatalasæmic blood is not decomposed as usual by catalase. As a result, the hydrogen peroxide changes the oxyhæmoglobin into methæmoglobin by oxidation; accordingly the blood is blackened in an instant.

TABLE II—QCAT OF BLOOD IN ACATALASÆMIC AND IN NORMAL PERSONS ESTIMATED BY METHOD OF INOUE 1920 AND INOUE ET AL. 1925 (STERN 1927, 1932)

Cases	No. of persons	Catalase index		
		Average	Min.	Max.
From families with acatalasæmia :				
With acatalasæmia	9	0·0	0·0	0·1
Without acatalasæmia	45	5·5	3·4	7·2
Normal healthy persons	20	7·4	4·3	9·5
100 inpatients of the clinic :				
Maxillary sinusitis	19	7·6	5·2	10·2
Tonsillitis	17	7·8	5·5	9·5
Suppurative otitis media ..	12	7·7	6·9	9·2
Carcinoma of larynx	12	8·9	6·8	10·9
Carcinoma of maxillary sinus ..	10	7·4	3·3	10·5
Tumour of nasopharynx ..	3	7·7	7·5	7·9
Carcinoma of œsophagus ..	3	6·9	4·9	8·0
Epistaxis	3	6·2	4·1	7·3
Diphtheria..	2	7·5	7·3	7·7
Carcinoma of tongue	2	7·6	7·1	8·1

Miscellaneous diseases :
Brain abscess, 10·9; glioma of temporal lobe, 8·6; cyst of cerebellum, 9·2; Ménière's disease, 6·3; tumour of cheek, 8·8; perforation of nasal septum, 6·2; spontaneous gangrene of nose, 7·6; sarcoma of maxillary sinus, 7·2; cystoma of dental root, 9·6; ranula, 8·9; lymphosarcoma of tonsil, 7·5; carcinoma of pharynx, 8·7; paralysis of larynx, 7·8; Mikulicz's disease, 6·9; nocturnal laryngeal dyspnœa, 4·4; carcinoma of thyroid gland, 8·2; struma cystica, 8·7.

This oxidation can be observed in a test-tube. When a small quantity of hydrogen peroxide is poured into acatalasæmic blood in a test-tube, the blood remains black for a long time. However, if an excess of hydrogen peroxide is added, oxidation continues and the blood begins to lose its dark colour within about 20–30 minutes and becomes light-reddish brown, then lemon-yellow, and finally colourless and transparent. This liquid contains propentdyopent, a final decomposition product of hæmoglobin (see below).

Previous research concerning this chemical process was carried out by Bingold (1935, 1936), Fischer and Müller (1937) and Fischer and von Dobeneck (1940). Bingold, studying the destruction of hæmoglobin by hydrogen peroxide, noticed the formation of a colourless substance, the final breakdown product of hæmoglobin. If a small amount of a solution of potassium hydroxide is added to this colourless substance, and the mixture is heated for a little while and then reduced with sodium dithionite ($Na_2S_2O_4$), a beautiful rose colour is seen. Bingold (1935) named this rose-coloured substance "pentdyopent," and the reaction the "pentdyopent reaction." The name "propentdyopent" was given by Fischer et. al. to the substance which is the foundation of the "pentdyopent reaction"—i.e., the precursor of pentdyopent. This reaction was positive with the blood of all my acatalasæmia cases.

The question arises why a particular oral disease is caused when catalase is lacking in the blood. To study this question, I made a blood-agar plate with blood from one patient and another plate with blood from a normal person. I then planted hæmolytic streptococci or pneumococci type I, taken from the affected parts of the oral cavity of patients, on to these blood-agar plates. Since hæmolytic streptococci or pneumococci type I were the predominating organisms in the affected parts, we can suppose that these bacteria were the main organisms causing the ulceration. On the blood-agar plates there was no conspicuous difference between the development of the colonies; but on the plate made from the acatalasæmic blood wide transparent rings instead of hæmolytic rings appeared round the colony after 24 hours' incubation, whether it was aerobic or anaerobic. After 48 hours these discoloured rings became wider. My explanation of this is as follows.

It is well known that hydrogen peroxide is generated when hæmolytic streptococci or pneumococci grow. When the hydrogen peroxide generated from the colony on the acatalasæmic blood-agar plate reaches the surrounding medium it oxidises the oxyhæmoglobin to methæmoglobin. As the oxidation goes on, the media round the colony gradually fades and is finally turned into transparent propentdyopent. Needless to say, the ring-shaped colourless zone round the colony showed the pentdyopent reaction.

In this rare disease, thought to be due to a lack of catalase in the blood, one would expect special histological features of the affected parts. In preliminary histological examinations I have observed the following special features: despite a striking tendency to necrosis, inflammation was only rarely seen; the capillary vascular wall was much destroyed, and it seemed that an affected part had formed round the destroyed blood-vessel.

DISCUSSION AND CONCLUSIONS

From the above-mentioned experimental research I conclude as follows. Gums are apt to be injured by mastication. Wounds in gums are suitable media for oral and other bacteria. Hæmolytic streptococci are most commonly found among oral bacteria. As already mentioned, the hæmolytic streptococcus generates hydrogen peroxide. In normal persons hydrogen peroxide thus generated is easily neutralised by the catalase, and no trouble is caused. But in people who lack catalase in their blood the consequences would be serious. In them the hydrogen peroxide produced by the bacteria would oxidise blood reaching the lesion, thus depriving the infected area of oxygen and causing necrosis. This would favour multiplication of the bacteria and thus increase the amount of hydrogen peroxide being generated and lead to further oxidation of oxyhæmoglobin. In this way a small ulcer might gradually develop into a very large one with much necrosis but not much inflammation.

The acatalasæmia in at least two of these three families is probably hereditary. The family relationships are shown in the accompanying figure. In the Nakayama family four out of six children have acatalasæmia, and their parents are consanguineous, being second cousins. In the Fukutake family the patient has no brothers or sisters; but not only are his parents first cousins but also both his father and his mother are the children of two pairs of cousins. In the Abe family four out of ten children have acatalasæmia, and their parents are also first cousins. It therefore looks as if acatalasæmia is hereditary and facilitated by consanguineous marriages.

As regards the dental disease, in the Nakayama family the father, two aunts, and a grandfather all have severe alveolar pyorrhœa. The father's teeth were all gone before he was 30, owing to alveolar pyorrhœa. In the Fukutake family the patient's father also had this disease. Thus, although the main cause of the oral gangrene described above is the lack of catalase in the blood, it is also probable that its occurrence might be promoted by factors transmitted from the paternal side.

SUMMARY

Nine cases, in three families, of complete lack of catalase in the blood (acatalasæmia) are reported.

Seven of the nine patients had progressive oral gangrene which was probably due to the lack of catalase.

The most prominent characteristic is that the blood blackens instantly when hydrogen peroxide is added to it.

The condition is probably inherited.

I wish to thank my colleagues Dr. H. Miyamoto, Dr. H. Sato, Dr. H. Matsumura, Dr. S. Inoue, Dr. K. Tsugawa, Dr. M. Doi, Dr. S. Mihara, and Dr. Y. Ogura, whose coöperation was a great help to me in this research.

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CONGENITAL VACCINIA AND VACCINIA GRAVIDARUM

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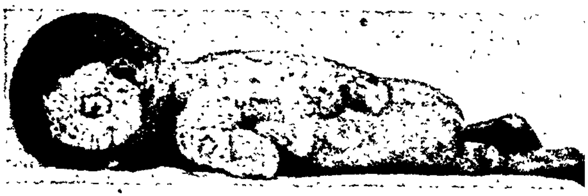
IN 1950 there was an outbreak of smallpox in the West of Scotland (Laidlaw and Horne 1950) and many people came for vaccination in the first week of April that year. Among them was a young woman about three months pregnant who had never before been vaccinated. She developed a severe primary reaction, and three months later she was spontaneously delivered of a feeble hydropic premature infant covered with a very severe generalised vaccinia (see figure). The child died 18 hours after birth and necropsy was performed. The detailed clinical and pathological features on which the diagnosis of fœtal vaccinia was established, including nuclear inclusion bodies similar to those described in vaccinia, have been recorded elsewhere (Macdonald and MacArthur 1952).

Considering the countless millions of vaccinations that have been done, it is remarkable that congenital vaccinia has been described only once before (Lynch 1932). The recognition of this case prompted further investigations to determine the frequency with which vaccination during pregnancy has a harmful effect on the fœtus.

PRESENT INQUIRY

As a very large number of persons had been vaccinated during the West of Scotland outbreak of smallpox it was thought that valuable information might be obtained from a follow-up of a series of women who were pregnant at the time of vaccination.



Premature infant with severe generalised vaccinia.

A sheet of paper bore on one side a letter from th Medical Officer of Health reminding the recipient of h interest in her health and welfare, and exhorting her t answer the list of questions on the other-side of th paper and to return it to him. The questions wer designed to discover whether the woman had bee successfully vaccinated, whether she was pregnant a the time of vaccination and, if so, the result of he pregnancy, with dates, birth weight, place of confinement and other information. In only 3 cases was it necessar to correspond further with a woman to clarify he statements.

In all, 5059 of these questionnaires were posted t women under the age of 45 years who had given the titl "Mrs." before their name at the time of vaccination No other selection was made, and the names were take consecutively from the vaccination returns until about 5000 had been obtained. The Post Office delivered 482 of these 5059 questionnaires, and 3408 (71%) replies were received. At any given time there will be an approximately equal number of women in each trimester of pregnancy ; and therefore, if chance alone determined the incidence of reply, we should expect about an equal number of returns in each trimester. Table I shows that similar numbers were in fact received. The first trimester has, however, been extended by two weeks to include women who became pregnant within two weeks of vaccination ; and therefore this group should have been somewhat larger than the other two. Since this expectation is not fulfilled, it is possible that a somewhat larger proportion of the women who did not reply may have been in this group. This hypothesis is further supported by the fact that a woman is less likely to remember the exact date of an early abortion than the date of her child's birth, and if she receives an inquiry more than a year later she may not remember whether she aborted shortly before or shortly after her vaccination. If she aborted during the second month she may not even be sure that she was pregnant. Being in doubt she would probably leave the inquiry unanswered.

It is believed, therefore, that the 29% of women who did not reply may have had no influence on the results obtained ; or, if they did influence the figures, it is most probable that they did so by diminishing the number of abortions in early pregnancy. If these women had replied they would thus have been more likely to reinforce the argument than to weaken it.

Of the replies, 259 were from women who had been pregnant about the time of vaccination, but 45 of these women did not develop a vaccination reaction leaving a scar, and a further 11 became pregnant more than tw weeks after the day of vaccination. When these 56 ar eliminated, there remain 203 women who developed vaccination reaction and were pregnant at the time o vaccination or became pregnant within two weeks of the day of vaccination.

These 203 pregnancies were classified according to the stage of pregnancy at the time of vaccination (table I). There were 67 in the first trimester, 69 in the second, and 67 in the third. The first trimester was further subdivided into (1) women who were pregnant for less than four weeks before vaccination or became pregnant within two weeks after vaccination, and (2) women whose pregnancy lasted from four to twelve weeks when they were vaccinated.

The results of each of these 203 pregnancies has been determined (table I), and it is at once obvious that only in the first trimester, particularly in the second and third months of pregnancy, could there be any question of vaccination having a harmful influence on the pregnancy. No less than 47% of women vaccinated in the second or third month of pregnancy failed to give birth to a healthy child; or, if the whole of the first trimester is taken together, the proportion is 24%.

It was impossible to devise a suitable local control series with which to compare the results obtained in this inquiry; so a review of recent literature on the incidence of unintentional abortion was undertaken to obtain a basis for comparison. The senior consultant obstetrician in the area in which the inquiry was made (Dr. R. A. Tennant) is confident that the incidence of unintentional abortion in the area is comparable to modern experience in other centres and is far less than was encountered in this inquiry. The incidence of stillbirths is known to be less than 3% of all births. There is a considerable measure of agreement among recent workers on the frequency of unintentional abortion, and Randall et al. (1950), after reviewing the subject and presenting their own series of 2050 women with 5·5% abortions, conclude that "recent literature indicates that the overall incidence of abortion in any sizeable series of cases should approximate 5–7 per cent and should never exceed 10 per cent." For statistical comparison, if these estimates are correct and the mortality has been the worst possible—i.e., 10% abortions and 3% stillbirths—the total fœtal loss would be 13%. In the vaccinated series only women in the first trimester have been included, because the great majority of abortions occur during this stage of pregnancy, and almost all the women who became pregnant at the same time as those in the second and third trimesters (table I) but aborted did so before they were vaccinated and therefore do not appear in this inquiry at all. A statistical test shows that there is a significant increased mortality (on the 5% level of significance) among the fœtuses of women who were vaccinated during the first trimester of pregnancy (table II).

TABLE I—ANALYSIS OF REPLIES TO QUESTIONNAIRE

Stage of pregnancy	No. of women	Result of pregnancy	Percentage of abnormals	
Less than 4 weeks ÷ Women who became pregnant within 2 weeks after vaccination	33	32 Normals 1 Miscarriage	3	24
4–12 weeks	34	17 Normals 1 Normal premature 10 Miscarriages 5 Stillborn 1 Congenital abnormality	47	
2nd trimester ..	69	66 Normals 1 Normal premature 1 Stillborn 1 Neonatal death	3	
3rd trimester ..	67	63 Normals 3 Normal prematures 1 Cerebral birth trauma	2	

TABLE II—FŒTAL LOSSES

Series	Fœtal deaths	Total number of pregnancies	Fœtal loss (%)
Randall et al. (1950) (with highest possible mortality)	267	2050	13
Present vaccinated series (1st trimester)	16	67	24

DISCUSSION

Since the introduction of vaccination by Jenner in the 18th century there have been many reports that vaccination has no harmful effect on a pregnant woman or on the fœtus within her. Sometimes the statement has been copied word for word from one publication to another. Most of these reports come from workers who vaccinated pregnant women in a maternity hospital. Sometimes no information is given about the duration of pregnancy at the time of vaccination, but it is obvious from most reports that most of the women were at or near term when vaccinated. One example of a report that has been copied by other authors is that of Urner (1927). He vaccinated 129 pregnant women and stated that there was not a single case of threatened abortion, miscarriage, or premature labour. He concluded that vaccination in pregnancy had no deleterious effects on mothers or their infants. But he did record the stage of pregnancy at which the vaccinations were done, and we find that of the 129 women 107 were in the last trimester: indeed only 1 woman was vaccinated in the twelfth week of pregnancy, and 128 in the fourth month or later.

It is obvious that investigations of this scope do not justify the sweeping conclusions that have been drawn from them. Nearly all these studies were made before the work of Gregg (1941) and Swan et al. (1943), in Australia, established the importance of virus infection in the second and third months of pregnancy as a cause of fœtal abnormality. What they do show is that vaccination in the later months of pregnancy has no harmful effect, at any rate in the great majority of cases. On the grounds of analogy it seems probable that, even in the last weeks of pregnancy, vaccinial infection in the mother could be transmitted occasionally to the fœtus, since it is fully established that the related virus infections of variola and of chickenpox are capable of transplacental transmission (Marsden and Greenfield 1934, Shuman 1939).

There has been one study of the effect of vaccination in the first trimester. In 1947 there was an outbreak of smallpox in New York, and about five million people were vaccinated. Greenberg et al. (1949) found no significant increase in the number of malformed children, premature births, or stillbirths born to 4172 women vaccinated in the first trimester of pregnancy. But there is much to criticise in this investigation of such enormous numbers. These workers studied reports on children admitted to child-welfare centres at the appropriate time and the notifications of stillbirths and the number of babies born prematurely in the city's maternity hospitals, and then set out to discover whether or not the mothers had been vaccinated in pregnancy. The 4172 women classified as "vaccinated during the first trimester" were examined by doctors and were retained in this group although it is stated that almost half of them bore no vaccination scar. Greenberg et al. had no information about abortions. There are opportunities for cumulative statistical errors in this inquiry, and, further, this retrospective method of study has inherent fallacies which have been clearly described by Logan (1951), who asserts that the only satisfactory approach to the problem of the effects of virus infection in pregnancy is the prospective type of inquiry which begins with a series of pregnancies and studies their results. The inquiry conducted by us was of this prospective type.

It is regrettable that no suitable control series of unvaccinated women could be arranged to run concurrently with the vaccinated series, and the lack of a comparable control certainly diminishes the reliability of the findings. There is, however, so large a measure of agreement among recent investigations into the frequency of abortion that this deficiency should not invalidate my conclusions. The control that has been used is theoretical and not factual; it represents the highest incidence of fœtal loss that Randall et al. (1950) considered could occur in a series of normal pregnancies—not an average figure but nearly twice the rate of fœtal loss that Randall et al. (1950) encountered in their own practice. The figure of 2050 pregnancies is the number in Randall's own series. Although there is no control series with which to compare the pregnant and vaccinated women, some internal comparisons in the group of vaccinated women are of value.

It is very striking that only one fœtus was lost by the 33 women vaccinated within four weeks of conception, when the fœtus is much more completely separated from the mother than in the later months, when intimate placental contact between the two circulations exists. It was during the next two months that the fœtal loss was greatest, though the potential duration of exposure to damage from the virus was similar in these two groups. This virus seems to be particularly lethal to the fœtus during the second and third months of pregnancy.

Of the 24 pregnancies going to term, or nearly to term, in the second group (table I) 5 produced stillbirths, but only 1 of the 169 other such pregnancies produced a stillbirth.

We have no knowledge of the pathological changes in the fœtus which lead to death, though it would be very valuable to know what these are. Nor have we any detailed clinical information about the health of the survivors, but it is intended to pursue this later. In the absence of this information no useful statement can yet be made about vaccination as a cause of congenital abnormality in children.

CONCLUSIONS

The conclusions reached from this study are as follows:

(1) Vaccination of a pregnant woman may, though very rarely and perhaps only in special circumstances, lead to fatal generalised vaccinia of the fœtus.

(2) Vaccination of a pregnant woman during the first trimester of pregnancy, and especially during the second and third months of pregnancy, significantly increases fœtal mortality.

If these findings are confirmed by others, it will be clear that vaccination should never be done during the first trimester of pregnancy as part of routine public protection, and that it should be done at this stage of pregnancy only in women who have been in contact with smallpox. Damage to the fœtus is done, however, only during the first trimester of pregnancy, and there is virtually no risk from vaccination during the later months.

SUMMARY

A case of congenital vaccinia following vaccination of a pregnant woman at the end of the third, or beginning of the fourth, month of pregnancy is recorded.

An inquiry was made into the frequency with which vaccination during pregnancy is harmful to the fœtus. Analysis of the results in 203 pregnancies in which the woman was vaccinated immediately before or during pregnancy showed a highly significant increase in mortality among the fœtuses of women vaccinated during the first trimester of pregnancy.

I am greatly indebted to Dr. Andrew G. Reekie, medical officer of health for Lanarkshire, for generous facilities and assistance in this inquiry, and also to Mr. David Reid, of the department of public health, Lanarkshire County Council, and his assistants, who did so much extra clerical work. I am also grateful to Dr. R. A. Robb, lecturer in statistics in the University of Glasgow, for the statistical analysis; to Dr. A. M. Macdonald for the photograph; and to Prof. Stanley Graham and Dr. J. H. Hutchison for advice on the preparation of this report.

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TERRAMYCIN IN THE TREATMENT OF INFECTIVE DIARRHŒA IN INFANTS

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Terramycin, isolated from *Streptomyces rimosus* by Finlay et al. (1950), has been shown to combine low toxicity with a wide range of antibacterial action. It is effective against many gram-positive and gram-negative bacteria and against spirochætes, rickettsiæ, and some viruses. Except for the one case of Neter and Shumway (1950) we have found no reference to the use of terramycin in the treatment of non-specific diarrhœa in infants. By non-specific diarrhœa we mean cases of infective diarrhœa other than those due to infection with organisms of the salmonella or shigella groups or with *Giardia lamblia*. The small clinical trial here described was undertaken to determine the possible value of terramycin in this condition.

FORM OF TRIAL

The trial was confined to 21 infants admitted to one floor of the Leonard Parsons infants' block of the Birmingham Children's Hospital between March 31 and June 20, 1952. The ages of the infants varied from 2 weeks to 8 months; the average age of those receiving terramycin was 4½ months and of the controls 5 months. The criterion for inclusion in the trial was the presence of diarrhœa severe enough to require a period of feeding with clear fluid. Infants with gross parenteral infection were excluded, as well as any whose diarrhœa could be ascribed to overfeeding. At the time of their selection for the trial cases were classified into two groups, mild and severe; those requiring parenteral fluid was classed as severe. No reclassification was made later, whatever the course of the illness. Alternate infants in each group were given terramycin, the others serving as controls. The number and form of the stools passed each day were recorded. Fæces or rectal swabs were cultured at the time of selection for the trial and then daily for at least two weeks. The results of these bacteriological studies were not made known to those responsible for the ward work during the trial.

The first specimens were examined fully for salmonellæ, shigellæ and, when possible, *Giardia lamblia*. Specimens were plated on to desoxycholate citrate agar and into selenite F, the latter being subcultured after 1 and 5 days on to desoxycholate plates. Every specimen was plated on MacConkey's medium, and the colonies were examined by slide agglutination for the presence of 6 of the specific strains of *Bact. coli* that have been found to be associated with infantile gastro-enteritis. Positive cultures were confirmed by biochemical study and by tube agglutination against O and K specific antisera.

All the infants, terramycin-treated and controls, were fed alike. For the first twenty-four hours feeds were restricted to 5% dextrose in $N/5$ saline solution, and this was followed by the gradual reintroduction of milk feeding, the aim being to achieve full-strength feeds by the tenth day of treatment. The infants with severe diarrhœa received intravenous fluids for various lengths of time. An elixir of terramycin was given six-hourly by mouth for 7 days in a total dosage of 75 mg. per lb. of body-weight a day to infants in the treated group. No other antibiotic or chemotherapeutic agent was administered to any infant, unless there was evidence of parenteral infection, and in these only intramuscular penicillin or streptomycin was used. One terramycin-treated baby and 2 controls were so treated. For the purposes of assessment all infants receiving full-strength feeds whose diarrhœa had ceased by the tenth day of entry into the trial were regarded as having made a "satisfactory recovery." Any return or increase in severity of diarrhœa within the next three weeks requiring treatment with clear fluids orally was termed a "relapse."

RESULTS

Mild Group

Of the 8 infants *treated with terramycin* all still had diarrhœa at the end of seven days' treatment, with 5–10 loose green stools a day. When terramycin was discontinued, the stools diminished in number and became of normal consistence and colour within 3–5 days. 6 of the 8 terramycin-treated babies in this group were regarded as having made a "satisfactory recovery." Of these 6, 1 later "relapsed." Of the 2 infants whose clinical course was unsatisfactory 1 continued to pass frequent loose stools and later "relapsed," whereas the progress of the other was apparently retarded by a complicating parenteral infection. 7 out of these 8 infants had *Bact. coli* type 0·111 B.4 (Kauffmann and Dupont 1950) cultured from rectal swabs taken at the time of entry into the trial. At the end of the seven-day treatment with terramycin this organism could no longer be isolated from the fæces, but in 4 infants the organism had reappeared within five days of stopping treatment with terramycin. Only 1 of these 8 babies showed evidence of parenteral infection. This infant had an upper respiratory-tract infection which rapidly cleared on treatment with terramycin, but the character and frequency of the stools remained unaltered.

In the 7 *control cases* the diarrhœa seemed to abate rather more rapidly, but full recovery from diarrhœa in both treated infants and controls was achieved in about the same number of days. 4 infants were deemed to have made a "satisfactory recovery," and none of these 4 relapsed. 1 of the others continued to have diarrhœa and showed evidence of a parenteral infection. The clinical course was prolonged in the second. The third infant had persistence of loose stools and eventually a "relapse."

On entry to the trial 6 of the 7 control infants had *Bact. coli* type 0·111 B.4 in the fæces, and these organisms were still present in 5 at the end of a week.

Since the object of the trial was the treatment of diarrhœa, the numbers of stools passed by the terramycin-treated and control infants are shown in the accompanying table.

COMPARISON OF NUMBERS OF STOOLS OF TREATED INFANTS AND CONTROLS

Group	Average no. of stools passed daily during first 7 days' treatment	Average no. of stools passed daily during 8th to 12th days of treatment
Terramycin-treated (8 cases)	5·5	4·2
Control (7 cases)	3·8	4·0

Severe Cases

Of 6 babies with severe diarrhœa 3 were treated with terramycin. Of these 1 made a "satisfactory recovery." A second had persistent diarrhœa but was later shown to have pancreatic fibrosis. The third infant died thirty-two hours after admission to the trial with bilateral suprarenal hæmorrhages. This was the only death in the whole series. In the first and third infants *Bact. coli* type 0·111 B.4 were isolated from rectal swabs.

Among the 3 controls 2 recovered within two weeks; the third ran a more prolonged course but eventually recovered. *Bact. coli* type 0·111 B.4 were isolated from the stools of all 3 infants.

In none of the 11 terramycin-treated cases did any evidence of moniliasis appear. There was no vomiting or anorexia which could be attributed to terramycin; nor was there any increased tendency to sore buttocks.

DISCUSSION

As most of the cases included in the trial had their origin in a small institutional outbreak of infantile gastro-enteritis, probably the majority in each group were affected by the same ætiological agent. Every effort was made to ensure that both terramycin-treated and control groups were comparable. Though the results of so small a clinical trial must be examined with caution they suggest that terramycin in the dosage used is without effect in controlling diarrhœa or in preventing relapse. Terramycin produced a rapid disappearance of *Bact. coli* type 0·111 B.4 from the stools, but in many of those treated the organism reappeared within five days of stopping treatment with terramycin. These results differ from that of Neter and Shumway (1950), whose 1 infant infected with *Bact. coli* 0·111 was later treated successfully with terramycin. These workers also tested in vitro nine strains of the same organism against different antibiotics. Their results suggested that, though sensitive to terramycin, the strains studied were more sensitive to chloromycetin and polymyxin.

No definitely toxic reactions were noted. The terramycin-treated babies tended to have a greater number of loose green stools while receiving terramycin than did the controls; this may have been an effect of the terramycin, although this symptom has been reported only occasionally and was not noted by Wooding and Scott (1951) who gave doses larger than those used in the present trial.

SUMMARY AND CONCLUSIONS

A small clinical trial to assess the possible value of terramycin in the treatment of infective diarrhœa in infants is described.

No evidence is adduced to suggest that this antibiotic used alone is of any real value in this condition.

We are indebted to Dr. W. H. P. Cant for allowing us to include in the trial patients under his care; to the antibiotics trials committee of the Medical Research Council for supplying the terramycin; and to Dr. J. M. Webb, Sister E. Tanner, and Sister J. Bradley for their generous coöperation.

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ANTIDIURETIC SUBSTANCE IN HUMAN SERUM

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Birnie et al. (1949b) found an antidiuretic substance (A.D.S.) in the serum of rats, and Lloyd and Lobotsky (1950) detected A.D.S. in human serum by the same method.

Birnie et al. (1949a) consider that the A.D.S. found in rat serum is probably made in the posterior lobe of the pituitary gland. Biologically it resembles the anti-diuretic hormone (A.D.H.) in that it is antidiuretic and stimulates the renal excretion of chlorides; it is inactivated on standing and by neutralised thioglycollic acid; it is not present in the blood of hypophysectomised rats; it exerts its antidiuretic action by increasing the resorption of water through the renal tubule cells; its level alternates in rats subjected to hydration and dehydration; and "in all respects tested its actions are like those of posterior pituitary extract."

It is well known that during human pregnancy there is retention of water; in fact excessive retention of water, shown by increase in weight of the patient, is used as a sign of pre-eclampsia. I thought that the serum-A.D.S. level might throw some light on this retention and therefore determined this level in women during the normal menstrual cycle, normal pregnancy, and the early postpartum period. The results have already been reported briefly (Hawker 1952).

METHOD

The method of Birnie et al. (1949a) was followed closely.

Venous blood was collected not more than 45 minutes, and generally less than 30 minutes, before the assay. The blood was centrifuged for 10 minutes, and 1 ml. of the serum was injected intraperitoneally into virgin female Wistar rats weighing 130–200 g. each. At least three rats were included in each group of controls and of serum-injected test rats.

Two doses of distilled water, 3 ml. per 100 sq. cm. of body-surface (calculated from the formula $6{\cdot}27 \times \text{weight}^{0{\cdot}73}$), warmed to body-temperature, were administered by stomach-tube hourly to rats placed in funnels draining into 25 ml. measuring cylinders. The urine excreted was measured an hour after the second dose of water. Any rat which, during this hydration period, excreted 50% more or less urine than the mean volume excreted by the other rats was not used for the experiment.

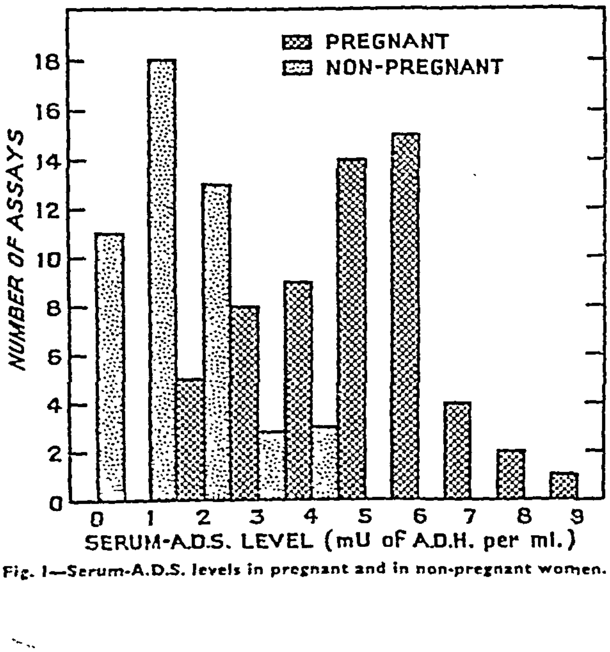

Fig. 1—Serum-A.D.S. levels in pregnant and in non-pregnant women.

A third dose of water was next administered, and serum was injected into the peritoneal cavity of the test rats. The urine excreted was measured 1½ hours after injection of the serum. Control rats were not given an intraperitoneal injection of isotonic saline (NaCl) solution, because it was previously found that this precaution had no effect on excretion values.

The serum-A.D.S. level was calculated as follows. The difference between the volume of all the water given in the three doses and the volume of urine excreted at the end of the two hours' hydration was called the "water load." The percentage of the "water load" excreted at 90 minutes after the injection of the serum was calculated. The anti-diuretic effect was expressed in units derived from the difference between the percentages of the "water load" excreted by the serum-injected rats and the controls. Rats which had received serum once were not used again, because of the possibility of protein sensitisation.

A graph was constructed correlating the A.D.S. units with concentrations of freshly prepared 'Pitressin' (Parke, Davis & Co.) 20 U per ml. by using other rats.

People coming for assay were instructed to abstain from fluids for four hours before venepuncture.

Serum-A.D.S. levels were assayed in healthy females, mostly medical students aged 17–22. Altogether 48 assays were done on 17 women at different times during the menstrual cycle. Assays were also done monthly on healthy pregnant women, usually from about the 10th or 12th week after the last menstrual period. In this group 58 assays were done on 14 women; and in 11 healthy women who had successfully passed through normal pregnancies and had been selected at random after parturition 50 assays were done in the first four or five postpartum days.

TABLE I—SERUM-A.D.S. LEVELS DURING NORMAL PREGNANCY AND FIRST DAY POST PARTUM

Time	Mean serum-A.D.S. level (mU of A.D.H. per ml.)
2nd trimester	4·27 (10 assays)
3rd trimester	4·40 (17 assays)
Last month of pregnancy ..	4·55 (8 assays)
1st day post partum	5·50 (11 assays)

RESULTS

This work shows that A.D.S. is present in the serum of the healthy cyclically menstruating female. Fig. 1 shows clearly that during the menstrual cycle the serum-A.D.S. level is most commonly 1–2 mU of A.D.H. per ml. of serum, with a fairly even distribution about the mode—i.e., between 0–1 and 2–3 mU of A.D.H. The arithmetic mean of the averages of the 17 cases examined was 1·91 mU of A.D.H. per ml. of serum.

It is impossible at this stage to show convincingly whether there are any real differences in the serum-A.D.S. level during successive weeks of the menstrual cycle, but the available figures suggest that the serum-A.D.S. level rises during the week preceding menstruation and falls during menstruation; the means of 8 assays made during the premenstrual week and of 7 menstrual assays were 2·85 and 1·60 mU of A.D.H. per ml. respectively.

During pregnancy the serum-A.D.S. level is higher than during the menstrual cycle, and the distribution is wider. Thus fig. 1 shows that the serum-A.D.S. level is most commonly 5–6 mU of A.D.H. per ml. The mean of the average serum-A.D.S. level of each of the 14 women examined was 4·53 mU of A.D.H. per ml. In about 78% of the 58 assays made on pregnant women the serum contained 3 or more mU of A.D.H. per ml., whereas during menstruation about 94% of the assays showed 3 or less mU of A.D.H. per ml. of serum.

The serum-A.D.S. level rises early in pregnancy; just how soon after conception has not been determined, but in one assay made eight weeks after the last menstrual period the serum-A.D.S. level was 4·2 mU of A.D.H. per ml. This was the earliest measurement made during the first trimester of pregnancy, and only a few have been made during this period. The level appears to remain comparatively steady throughout pregnancy, showing only slight fluctuations and perhaps a slight upward trend as pregnancy advances (see table I).

It has not been determined exactly when the serum-A.D.S. level rises during the last month of pregnancy, but it is suspected that it rises immediately before or during labour. This notion is supported by figures derived from two cases followed closely during the last week of pregnancy (table II).

During and immediately after parturition the serum-A.D.S. level is higher than in non-pregnant women. I therefore thought that this high titre might be related to some physiological phenomenon peculiar to the female after parturition and not to the cyclically menstruating female. Since lactation is a distinguishing feature between the two groups, it seemed reasonable that some relationship might exist between the high post-partum serum-A.D.S. levels and the onset of lactation.

TABLE II—SERUM-A.D.S. LEVELS BEFORE AND AFTER PARTURITION

Case no.	Time before delivery	Serum-A.D.S. level (mU of A.D.H. per ml.)
1	48 hours 2 hours	4·40 5·65
2	8 days 1st day post partum	3·25 5·95

Reference to table III will show that such a correlation appears to exist. Here there occurred an initial post-partum fall in the serum-A.D.S. level, and lactation began within a few hours after the serum-A.D.S. approached or reached its lowest recorded initial level. This was quickly followed by a rise in serum-A.D.S. level (except in case 2 in which it was not estimated), which subsequently began to fluctuate unpredictably. In no instance did lactation begin before the *initial* fall in serum-A.D.S. level. This correlation is shown in four typical cases in fig. 2.

The patients were placed on a strict fluid-balance régime. By the term "onset of lactation" is meant the subjective sensation by the mother of "milk let-down" and the clinical observation of the change from colostrum to milk.

The mean serum-A.D.S. levels in the 11 women (table III) on the first postpartum day and at the onset of lactation were 5·50 (SD ± 1·29) and 3·11 (SD ± 1·39) mU of A.D.H. per ml. respectively (first postpartum reading for case 4 excluded because lactation had already begun).

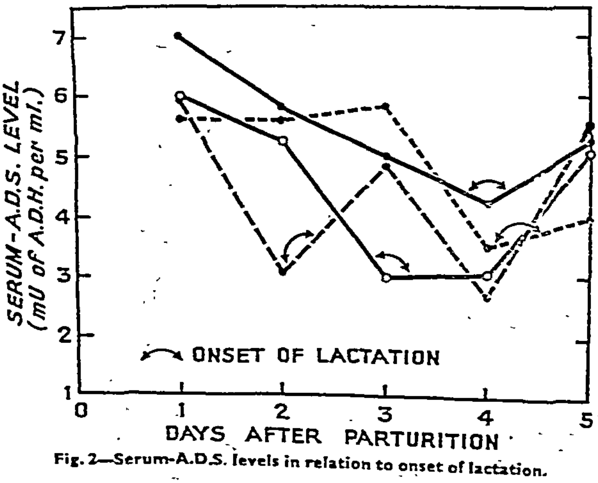

Fig. 2—Serum-A.D.S. levels in relation to onset of lactation.

TABLE III—SERUM-A.D.S. LEVELS AND ONSET OF LACTATION

Case no.	Days after parturition				
	1	2	3	4	5
	Serum-A.D.S. level (mU of A.D.H. per ml.)				
1	7·00	5·85	5·00	4·15	5·20
2	4·90	4·45	*4·00*	..	..
3	3·45	4·85	*2·35*	6·15	..
4	*2·50*	3·15	3·35	5·10	..
5	5·95	5·20	*2·90*	3·00	5·10
6	4·45	4·30	*3·35*	7·10	2·30
7	4·40	3·85	*0·00*	7·20	3·90
8	7·85	*3·30*	5·30	..	..
9	5·50	*5·15*	7·20	2·95	4·10
10	5·60	5·60	5·85	3·45	3·90
11	5·90	*3·10*	4·90	2·75	5·45

Italic figures mean that lactation began within a few hours of this point.

The results show that A.D.S. is present in the serum of women during the normal menstrual cycle, normal pregnancy, and the early postpartum period. These results are recapitulated in table IV.

DISCUSSION

Serum-A.D.S. during Pregnancy and Possible Relation to Water Retention

Water is retained during pregnancy, but evidence of this is quantitatively incomplete. Chesley (1944) has reviewed this subject and assessed the average gain in extracellular fluids as follows:

TABLE IV—SUMMARY OF SERUM-A.D.S. LEVELS DURING MENSTRUAL CYCLE, NORMAL PREGNANCY, AND POST PARTUM

—	Mean serum-A.D.S. level (mU of A.D.H. per ml.)	Remarks
Menstrual cycle:		
Whole cycle ..	1·91	Mean of all levels observed during menstrual cycle
Last week ..	2·85	Mean of all levels observed during week before menstruation
First week ..	1·60	Mean of all levels observed during week following 1st day of bleeding
Pregnancy:		
13–24 weeks ..	4·27	Mean of all observations
25–36 weeks ..	4·40	" " " "
37–40 weeks ..	4·55	" " " "
Post partum:		
First day ..	5·50	" " " "
Onset of lactation	3·11	" " " "

	Litres
Products of conception	1·5–2·0
Uterus and breasts	0·7
Blood-plasma	1·3
Extragenital interstitial fluid	2·5
	6·0–6·5

The extracellular compartment of the total body-water increases from 12 litres to 18·5 litres during pregnancy (this accounts for most of the water retained). There is a 60% increase in the plasma (1·3 litres extra) and 33% increase in the interstitial compartment (3·2 litres extra). Huggett (1950) states:

> "The mechanism of this water retention (in pregnancy) is unknown. There is an enlargement of the suprarenal cortex but no change in the size of the posterior pituitary. The rôle of desoxycorticosterone in this condition has got to be assessed accurately. Further, nothing is known of the effect of the salt changes in the diluted blood or the production of the antidiuretic hormone of the blood."

It is a universal clinical observation that the diuresis after drinking water is smaller in the pregnant than in the non-pregnant woman, and there is a pronounced post-partum diuresis accompanied by a rapid loss of weight.

A positive salt balance obtains throughout the greater part of pregnancy. About 3 g. is retained per week, and this retention would lead to a raised osmotic pressure in the extracellular fluid unless water were retained at the same time. It is not clear, however, whether the retention of salt precedes that of water or vice versa.

The total increase of blood volume is approximately 25–30% during pregnancy, and this increase is due mainly to an increase in plasma volume. The plasma-protein level is lower, despite an increase in quantity of the plasma-proteins, the plasma-albumin level being lower than the plasma-globulin level. Hence the colloid osmotic pressure is lower (by about 20%) than in the non-pregnant woman. The plasma-electrolytes level is lower, and the viscosity of the blood decreased. Calcium, potassium, magnesium, sulphur, and phosphorus are all retained in excess of the requirements of the developing fœtus.

Verney (1946) considers that changes in the osmotic pressure of the arterial blood stimulate, or inhibit, osmoreceptors in the hypothalamus (supra-optic nuclei), which in turn stimulate, or inhibit, the release of antidiuretic hormone by the pituicytes in the posterior lobe of the pituitary.

It is now becoming increasingly clear that some of the adrenal cortical steroids exert a reciprocal action on the excretion of water and salt by the kidney. Under their influence the retention of sodium and chloride is increased and the excretion of water is enhanced. Silvette and Britton (1938) suggested that there might be a reciprocal relationship between the antidiuretic hormone of the posterior lobe of the pituitary gland and the adrenal steroids regarding the excretion of water and salt by the kidney. Lloyd and Lobotsky (1950) have strengthened this hypothesis by their report of three patients with diabetes insipidus in whom the serum-A.D.S. level was low and urinary corticosteroid values ranged from normal to very high levels. They also observed in the untreated human with Addison's disease a very low excretion of corticosteroids and a very high serum-A.D.S. level.

It is felt that the antidiuretic activity of human serum (assessed by the biologic assay method described here) represents the algebraic sum of substances producing water retention and of substances causing diuresis. The former substance is assumed to be A.D.H., and the latter may be adrenal corticosteroids. If this notion proves to be correct, it becomes obvious that an increased antidiuretic effect can be due either to increased output of A.D.H. or to decreased output of adrenal steroids. Since it has been shown by many workers that the production of adrenal steroids is increased in pregnancy, there must be an absolute increase in the amount of A.D.S. present in the serum during pregnancy.

McLennan (1943) showed that pressure changes in the veins of the lower extremities during pregnancy could lead to the retention of water. On the hormonal side it has been reported that the water retention might be related to the concentration of œstrogens, progestogens, or adrenal steroids, all of which are normally increased in pregnancy.

In view of the finding that during pregnancy the serum-A.D.S. level rises roughly by 230%, it is postulated that this substance is responsible for some of the water retained during pregnancy. It may follow the retention of salt or be due to the influence of those hormones which are known to be increased during pregnancy: œstrogens, progestogens, chorionic gonadotrophin, adrenal steroids (which may account for salt retention), and thyroxine. Because of the salt retention that is known to take place in pregnancy one can perhaps reasonably postulate that, in accordance with Verney's concept, this is responsible for the raised level of serum-A.D.S. and hence for the water retention. So far as I am aware, there is no evidence that the ionic osmotic pressure is increased during pregnancy, and there is well-substantiated evidence which shows that in this state the colloid osmotic pressure is in fact lowered. It is almost certain that a complex pattern of physiological factors underlies the mechanism by which the serum-A.D.S. level is raised during pregnancy. In a preliminary attempt to elucidate this problem chorionic gonadotrophin was given to seven healthy cyclically menstruating women, and in each case the serum-A.D.S. level rose above 200%. The serum-A.D.S. level in 6 œstrogen-treated females did not alter significantly. It would be premature to draw any conclusions, however, from this aspect of the work, because it has not been carried on long enough.

Serum-A.D.S. Level after Parturition and its Possible Relation to Onset of Lactation

The hormonal background to lactation is not clearly understood. Petersen (1948) states:

> "It is well known that a completely developed mammary gland may not lactate; thus. factors other than those necessary for mammary growth must be present to stimulate and maintain milk secretion. Although the field is still far from being free from controversy and in need of more work before it is completely understood, there is sufficient evidence to show that several endocrine factors are essential for maintenance of milk secretion. A rather complex interaction of secretions from the hypophysis, thyroid, parathyroid, adrenals and pancreas is indicated."

In normal circumstances the mammary glands develop during pregnancy, and lactation (as is usually understood) starts soon after parturition. Much evidence has been presented that the production of the lactogenic hormone increases at the onset of lactation. The reasons for this are unknown, but it is thought that the release of the lactogenic hormone may be influenced by hormones from the ovary and placenta.

Extracts from the posterior lobe of the pituitary exert a rapid but fleeting effect on the mammary gland. The general consensus of opinion is that posterior-pituitary extract has no effect on the secretion of milk—i.e., the synthesis of milk and its passage into the alveolar lumen from the cytoplasm of the epithelial cells—but influences the discharge of already preformed milk from the mammary gland. This is possibly brought about by stimulation of the myo-epithelial cells in mammary tissue (however, it has not yet been shown that these cells possess contractile properties). In this respect it seems that the oxytocic principle is more effective than the vasopressor factor, which is probably the antidiuretic factor (A.D.H.) in posterior-pituitary extract.

In a limited number of cases it is here reported that lactation always began soon after the serum-A.D.S. level reached or approached its lowest initial level. The assays were made at 24-hour intervals, and so it is entirely possible that fluctuations in serum-A.D.S. level were missed, and that larger falls than were recorded may have preceded the onset of lactation. This difficulty is being overcome by making more frequent assays. It is tempting at this stage to suggest that a lack of onset of lactation may be associated with a steady serum-A.D.S. level—i.e., where this level does not fall—and that the onset of lactation could be inhibited by any procedure preventing a fall in this level. A time-honoured method of stimulating lacation is by hydration. Verney (1946) has shown that hydration, by lowering the osmotic pressure in the serum, inhibits the production of A.D.H. This then may be the mechanism by which water can stimulate lactation.

The results of the present work suggest that a fall in the serum-A.D.S. level is associated with the onset of lactation, and not with the continuance of lactation, because this, once started, continues, despite wide variations in the serum-A.D.S. level, provided the stimulus of suckling is present. Although it can be shown experimentally that pitressin will stimulate the discharge of already formed milk from the lactating gland, it is not likely that this procedure would provoke lactation in the non-lactating gland immediately after parturition. To my knowledge it has not been shown that it possesses this property. This conjecture is supported by the finding that the serum-A.D.S. level is high during the period when lactation is either inhibited or unstimulated.

Stilbœstrol and œstrogens are freely used to suppress lactation; but, although the production of milk is generally stopped, it is doubtful whether these hormones alone are responsible. Stilbœstrol given by me to normally menstruating women in this department, and by Cross (1951) to female rats, caused no demonstrable difference in serum-A.D.S. levels.

SUMMARY AND CONCLUSIONS

A substance possessing antidiuretic properties (A.D.S) is present in the freshly drawn serum of women during the normal menstrual cycle, normal pregnancy, and early postpartum period.

The serum-A.D.S. level is higher during pregnancy than during the menstrual cycle.

It is postulated that this high level during pregnancy accounts for some of the water retention of pregnancy.

A correlation appears to exist between the level of serum-A.D.S. after parturition and the onset of lactation. In each of eleven cases examined lactation always began after an initial fall in the serum-A.D.S. level.

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POLYCYTHÆMIA IN ASSOCIATION WITH HYDROCEPHALUS

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THE association of polycythæmia with lesions of the central nervous system is well known, especially in pituitary basophilism (Cushing 1932), encephalitis lethargica, and Huntington's chorea (Schulhof and Matthies 1927), narcolepsy (Gunther 1930), and lesions of the hypothalamus and pituitary gland (Guillain et al. 1932, Moehlig and Bates 1933, Haynal et al. 1949). Polycythæmia is common in carbon monoxide poisoning and may then be associated with damage to the basal ganglia (Dittmar 1939). It has been reported in concussion (Hecht and Weil 1929), and Drew and Grant (1945) collected ten published cases in which an expanding intracranial lesion other than of the diencephalic area was associated with polycythæmia; these cases included such diverse lesions as a subdural hæmatoma with papillœdema, and cerebellar tumours. Polycythæmia hypertonica has been attributed by Castex (1929) to a diencephalic lesion.

No case, however, of polycythæmia in association with hydrocephalus seems to have been published in the last thirty years.

CASE-RECORD

Mrs. A. is a childless widow, aged 49, who was working as a waitress until the onset of her present illness. In September, 1949, while in a general hospital in Glasgow for the removal of gall-stones, she had a blood-pressure of 180/110 mm. Hg and hæmoglobin 70%. A month later the hæmoglobin had fallen to 52%, probably because of post-operative complications and infection. She made a good recovery from the cholecystostomy, returned to work, and remained in good health until Nov. 6, 1951, when the present illness began.

Onset of Illness

The first symptoms were headache and vomiting accompanied by moderate pyrexia and mental confusion. Her condition deteriorated, and on Nov. 18 she was admitted to the neurosurgical unit of Killearn Hospital with delirium, nuchal rigidity, a positive Kernig's sign, papillœdema, left hemiparesis, and inverted respiratory rhythm. Her temperature was 101·6°F and pulse-rate 90. Her blood-pressure was 130/80 mm. Hg. Next day radiography of the chest showed no abnormality other than prominence of the aortic knuckle.

Treatment and Investigation

Penicillin 500,000 units six-hourly was given from Nov. 18 to Dec. 2. The patient became afebrile by Nov. 28, and her general condition steadily improved. On Dec. 4 she was eating well and spoke occasionally. Within the following two weeks, however, her condition again deteriorated and paralysis developed in all four limbs. There was incontinence of urine and fæces. She rarely spoke.

Ventriculography was performed on several occasions. On Nov. 21 it showed a mild hydrocephalus involving the lateral and third ventricles, the fourth ventricle being normal. On Dec. 10 the hydrocephalus began to increase rapidly until by Jan. 5, 1952, it was gross, involving the fourth ventricle, the cisterna magna, and the basal cisterns. As no air entered the subarachnoid space, it was suggested that meningeal adhesions were the cause of the hydrocephalus.

Examination of the optic fundi on Dec. 12 showed hæmorrhages but no papillœdema, and gave the general appearance of a sudden rise of intracranial pressure, which was subsiding. Ocular movements and ocular reflexes were normal.

The cerebrospinal fluid was normal throughout. For example, on Nov. 23 it was clear and under normal pressure, and contained 4 lymphocytes per c.mm., protein 20 mg. per 100 ml., chlorides 724 mg., and sugar 80 mg. The Wassermann reaction was negative and the colloidal gold curve 0,000,000,000.

Further Observations

In this state of hydrocephalus, quadriplegia, aphasia, and incontinence the patient was transferred to a general medical ward in Stobhill General Hospital on March 5.

On admission her complexion was pale and her tongue clean and moist: she had no œdema and no palpable lymph-nodes. Her radial pulse was regular, her heart sounds pure and of good quality, and her heart not enlarged. Cheyne-Stokes breathing was present from time to time, and other respiratory irregularities also occurred. Nothing abnormal was detected in chest or abdomen. The spleen was not palpable. There was arteriosclerosis of the retinal vessels, but no papillœdema or retinal hæmorrhage. The urine was infected with *Bacterium coli* and proteus, but after treatment to clear the infection it contained no albumin, sugar, blood, or casts. The blood-pressure varied from 180/135 to 215/160 mm. Hg. The erythrocyte-sedimentation rate was 6 mm. in 1 hour (Westergren).

Until June 3 there was quadriplegia in flexion with cog-wheel rigidity of all four limbs. On that day a jacksonian fit started in the right hand, and generalised convulsions shortly supervened and continued for three hours until morphine gr. $^{1}/_{4}$ was given. They then gradually diminished, but limb and facial twitchings persisted until June 12. Since June 4 the left arm and lower limbs have been flaccid, but the right arm, after being flaccid during the convulsions, is again rigid. The deep tendon-reflexes, including the jaw-jerk, have remained normal. The plantar reflexes were flexor until June 4, when they became extensor. Clonus was not present. Apart from the convulsion and subsequent flaccidity the general condition has remained similar to what it was on admission.

The hæmatological findings are shown in the accompanying table.

Date (1952)	Hb (g. per 100 ml.)	R.B.C. (million per c.mm.)	W.B.C. (per c.mm.)	P.C.V. (ml. per 100 ml.)	Eosinophils (per c.mm.)	Platelets (per c.mm.)
March 5	15·1	5·83	11,200	—	—	—
March 17	18·1	6·82	16,000	64·0	—	—
March 20	18·1	6·91	9600	63·0	50	272,000
March 31	16·1	5·57	9200	52·0	50	110,000
May 26	13·9	4·94	10,000	48·5	300	267,000
June 3*	15·2	5·40	23,600	53·0	0	—
June 12	13·2	4·82	8200	46·0	110	244,000

* 15 mins. after start of convulsions. Plasma chloride 126 m.eq. per litre (444 mg. per 100 ml.); alkali reserve 60 vol. CO_2%. *Blood films and differential white counts were normal.*

DISCUSSION

The nature of the original neurological lesion is obscure, but it seems to have caused meningeal adhesions at the base of the brain, leading to hydrocephalus. Either the original lesion or the subsequent gross hydrocephalus has produced both pyramidal and extrapyramidal lesions, and there has been a temporary erythrocytosis.

The diagnosis of polycythæmia hypertonica was suggested by the blood picture, the presence of arterial hypertension, and the absence of splenomegaly. This diagnosis proved to be untenable, however, when the blood picture reverted to normal. The same objection applies to a diagnosis of erythræmia, and in addition the blood-platelet count was normal on repeated examinations.

It has been reported in several cases of polycythæmia that, after removal of an associated intracranial lesion, the blood-count returned to normal values (Dittmar 1939, Drew and Grant 1945). In the present case the reduced eosinophil-count at the time of the maximum red-cell count may suggest that there was intracranial stress causing both phenomena, and that adjustment to it had taken place when the counts became normal. The return to normal blood values, and the disappearance of circulating eosinophils during the fit, make it unlikely that the polycythæmia was due to a destructive lesion of the basal ganglia or of the pituitary-hypothalamic system.

SUMMARY

Polycythæmia is sometimes associated with various lesions of the central nervous system.

No case of polycythæmia in association with hydrocephalus seems to have been published in the last thirty years.

Such a case, in which the polycythæmia was transient, is described. The patient also had hypertension.

ADDENDUM

The patient has since died from intercurrent infection. Gross pathology confirmed the hydrocephalus and absence of splenomegaly, but showed no obvious cause for the hydrocephalus. Histological examination has not yet been completed.

I am indebted to Prof. Stanley Alstead and other members of the visiting staff of Stobhill General Hospital for helpful criticism.

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GLUTEN-FREE DIET IN IDIOPATHIC STEATORRHŒA

REPORT OF A CASE

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The case reported here is one of a series under observation in a long-term study of the pathogenesis of idiopathic steatorrhœa. It is presented separately because of the remarkable remission induced by gluten-free diet. The work of Weijers and van de Kamer (1950), Dicke (1950), and Anderson et al. (1952) on the dietary control of cœliac disease raised hopes that gluten-free diet might also succeed in sprue. In the present case the results have been most encouraging.

CASE-RECORD

Mrs. A. was born in 1907. Her only child was born in 1926. In 1927 she was jaundiced and some weeks later developed diarrhœa, which has persisted since. Her weight fell from 120 to 110 lb., and she complained of malaise, weakness, flatulence, abdominal distension, and attacks of carpal spasm, which were controlled by calcium injections. Her stools were loose, pale, bulky, and offensive, but she normally passed only one or two daily. Two further pregnancies in 1929 and 1932 miscarried between the 12th and 16th weeks.

Idiopathic steatorrhœa was first diagnosed in 1940, when the dried fæces were found to contain from 17 to 40% of fat, which was normally split. Cholecystography showed a normal gall-bladder, and no gall-stones or pancreatic calculi were seen. Barium-meal radiography showed that the small intestine was abnormal. The hæmoglobin was 9 g. per 100 ml. In 1941 thyroidectomy was performed, because the basal metabolic rate (B.M.R.) was + 27%, and a fœtal adenoma was removed. Subsequent treatment with a low-fat diet, vitamin and calcium supplements, dilute hydrochloric acid, and pancreatic extracts did not prevent gradual but progressive deterioration in the patient's condition.

In 1950 she weighed 95 lb., and balance tests showed only 40–60% absorption of fat. Her prothrombin-time was low, and she bruised easily. The hæmoglobin was 12·5 g. per 100 ml., and macrocytosis (+ 2) was reported. The serum-calcium level was 8·1–8·5 mg. per 100 ml.

In September, 1951, she was admitted to hospital for eight weeks' treatment with oral cortisone, which produced great improvement. She remained well without further treatment until January, 1952, when she had recurrence of diarrhœa (from two to four pale loose offensive stools daily), malaise, lassitude, œdema, and tetany.

She was readmitted on Feb. 25, 1952, when examination showed pallor, œdema, hypotension, generalised brownish skin pigmentation, pathological bruising, and a positive Trousseau's sign. Her body was thin and her abdomen distended by flatus.

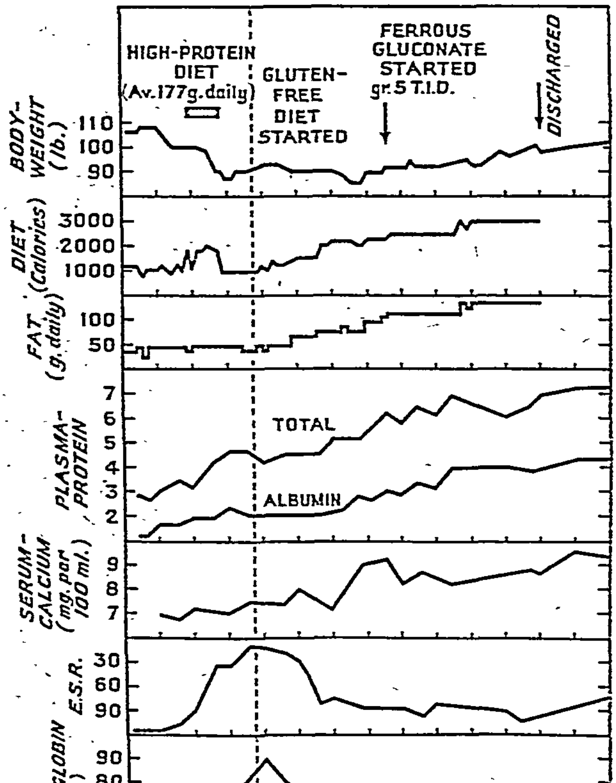
Laboratory examinations showed Hb 11 g. per 100 ml., colour-index 1·1, macrocytosis (+ 2), serum-calcium level 7·2 mg. per 100 ml., plasma-protein level 3·6 g. per 100 ml. (albumin 1·6 g.), and prothrombin-time 40% of normal. Fæcal fats were 95% split, but fat-absorption was only 60% of the 70 g. daily intake. Radiography of the small intestine showed an abnormal pattern and flocculation of barium.

Hypoprothrombinæmia was corrected by the parenteral administration of vitamin K, but no other specific treatment was given. The patient was offered a normal diet containing 70 g. fat daily, with supplements of 100 mg. of ascorbic acid, 1 tablet of 'Multivite,' and gr. 10 of calcium lactate t.i.d. She was not anxious to have adrenocorticotropic hormone (A.C.T.H.) or more cortisone, but on March 7, 1952, A.C.T.H. therapy was begun because she was now seriously ill. Her appetite was poor and her food intake inadequate; she had developed gross dependent œdema, ascites, and small bilateral pleural effusions.

A.C.T.H. 10 mg. given daily by slow intravenous infusion in 5% dextrose between March 7 and 23, produced rapid symptomatic and clinical improvement. Treatment with folic acid 15 mg. t.i.d. was started on March 24, but within two weeks diarrhœa recurred, and within four weeks the patient's condition was as bad as it had been before A.C.T.H. treatment, and diarrhœa was more troublesome.

She refused further A.C.T.H. or cortisone, and her condition rapidly worsened. Between May 12 and 15, 1680 ml. of dextran was infused intravenously to relieve œdema. With much persuasion the protein intake was raised to an average of 177 g. daily between May 29 and June 5, but although this raised the plasma-protein level and reduced the body-weight by 10 lb. it was stopped because of increasing diarrhœa, flatulence, and abdominal cramps. On June 6, there was pulmonary embolism, with evidence of phlebothrombosis in the left calf. The leg was supported by a crêpe bandage, and the patient was encouraged to walk. No further embolism took place.

On June 11 gluten-free diet was started. Bread and all foods containing wheat and rye flour were omitted, muffins made from corn and soya flour being substituted for bread.



Significant changes since the start of gluten-free diet on June 11, 1952 (indicated by vertical line). There has been gradual rise of weight representing a proportionately greater gain of tissue owing to simultaneous loss of œdema. Calorie and fat intake has risen. Plasma-protein and serum-calcium levels have risen to normal. Hb has decreased. Colour-index has fallen from 1·1 to 1·0, and progressive decrease in macrocytosis is reported on examination of blood films. E.S.R. is high at start of chart because dextran had been given intravenously a few days previously; it was a month before E.S.R. returned to normal. It rose sharply after diet was started, as it had done in previous remissions induced by A.C.T.H. and cortisone.

At this time the patient was in severe relapse. There was pronounced anorexia, malaise, weakness, œdema, and profuse diarrhœa. Within a week there was obvious improvement: appetite increased after a few days, the patient began to take more interest in her surroundings and looked better, and diarrhœa was succeeded by obstinate constipation requiring digital evacuation on three consecutive days. Since then the bowels have been open once daily, and the stools, although not normal, have become more formed, coloured, and less malodorous. 'Neptal' 1·5 ml. given intravenously on June 16, produced a good diuresis, and œdema and ascites have continued to clear as the plasma-protein level has risen, but there is still slight pitting at the ankle. Her weight has varied, but there is a net increase of 10 lb. If the loss of fluid is taken into consideration, this probably represents a substantial gain of tissue. The plasma-protein and serum-calcium levels are now normal. The amount of hæmoglobin has decreased, and the erythrocyte-sedimentation rate (E.S.R.) has risen (see figure).

The patient left hospital on Aug. 9. She says that she feels better than she has done for years. She does her own housework, has plenty of energy, and a large appetite, and enjoys her food. Although still pale and thin she looks vastly improved and is still making progress.

DISCUSSION

During the period of observation the E.S.R. has shown an unexpected pattern of change: in relapse it is normal but in remission it rises sharply to about 100 mm. in 1 hour (Westergren), only to fall to normal again when relapse sets in following arrest of A.C.T.H. or cortisone therapy. With the diet-induced remission the rate has risen again to high levels. The plasma-fibrinogen level is normal (two estimations) and it is possible that this change is associated with abnormality of the blood-globulin fraction. Facilities for electrophoretic study of the plasma to confirm this point are not available.

The hæmoglobin, which had been maintained at 10·5–13·0 g. per 100 ml. without iron therapy, decreased to 8·5 g. soon after the diet was started, and the morphology of the red cells changed. Macrocytosis decreased, and anisocytosis and hypochromia increased. The colour-index decreased from 1·1 or more to 1·0. Treatment with ferrous gluconate gr. 5 t.i.d. was started on July 8, 1952, but has not produced any change in the blood picture. It seems that the diet corrected the deficiency responsible for macrocytosis, which had not been affected by folic acid, but at the same time caused iron deficiency. Blood-loss is unlikely to be a factor in the development of this anæmia, because repeated tests for fæcal occult blood have been negative and amenorrhœa has persisted since 1943.

Although the patient's clinical condition has improved very greatly, tests of intestinal function other than fat-balance have shown little change. The blood-sugar curve after ingestion of dextrose 100 g. is flat. The small-intestinal pattern is still abnormal, the ileum particularly showing areas of hypotonicity and flocculation of barium. The volume of urine is still greater by night (6 P.M.–6 A.M.) than by day, although there has been some reduction in the ratio towards unity. The results of six fat-balance tests between May 11 and August 6, 1952, have been surprising. In three periods before the start of the diet the fæcal fat has been reported to be 17–21% greater than the intake (35 g.), and in three periods after the start of the diet there has been reported a progressive increase in absorption from 28 to 67% of the intake (50–130 g.). These figures, which have been checked and re-checked, are abnormally low and lower than any found in previous estimations in the present case. The only inference to be drawn from them is that fat-absorption has improved and may improve further.

Increasing appetite after the diet was started allowed the calorie intake to be progressively raised from 1000 to 3000, and the fat-intake from 35 to 130 g. daily. The patient, who had been indifferent to fat, now developed a liking for it.

Six weeks after starting the diet the patient drew attention to the regrowth of hair on her legs, which she said had been hairless for at least fifteen years. This was probably a non-specific expression of improvement in general nutrition, but it may also have been due to a change in adrenocortical function.

SUMMARY

A case of long-established steatorrhœa which has improved on gluten-free diet is reported.

Clinical and biochemical return towards normal has not been matched by improvement in tests of intestinal function.

The hæmoglobin has decreased, but macrocytosis has diminished.

The *erythrocyte-sedimentation rate* has shown an unusual rise.

I am grateful to Dr. R. A. Palmer, chairman of the Metabolic Unit, and to Dr. A. M. Johnson and the members of *the Metabolic Unit of the Vancouver General Hospital* for permission to publish.

ADDENDUM

The patient was last seen on Nov. 13, 1952. She remains much improved symptomatically, and the serum-protein and calcium levels are normal. Her weight is 105 lb. and all evidence of œdema has cleared. The E.S.R. has returned to 30 mm. in the first hour; and, following a course of intravenous iron between Oct. 6 and 13, the Hb has risen to 13·5 g. per 100 ml.

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New Inventions

A URINAL FOR THE RECUMBENT FEMALE

MOST hospital patients are embarrassed by the usual methods of collecting excreta, and the nursing of women in plaster beds presents peculiar problems. Owing to the strict recumbency of the patients and the limited abduction of the legs it is impossible for ordinary appliances to be used by the patients themselves. The usual method is to place a bedpan or a tin tray under the plaster bed. Usually, at the end of micturition the urine tends to trickle down the perineum into the seat of the plaster bed, with consequent softening and offensiveness of the plaster. This soiling often becomes troublesome, especially in warm weather.

At the suggestion of Mr. A. T. Fripp an appliance has been designed which can be manipulated by the patient and overcomes these difficulties.

Both the ‘Nylon’ receptacle (perineal cup) and ‘Polythene’ bag (capacity about $2^1/_2$ pints) can be sterilised by boiling but should be wrapped in a piece of gauze to prevent the polythene from coming into contact with the bottom of the steriliser. The appliance is light *in weight. Nylon has been used for the cup because it is a poor conductor of heat and therefore is not cold to the* touch. It is virtually unbreakable and is unaffected by urine. The rigidity of the lip of the cup ensures a satisfactory seal without discomfort.

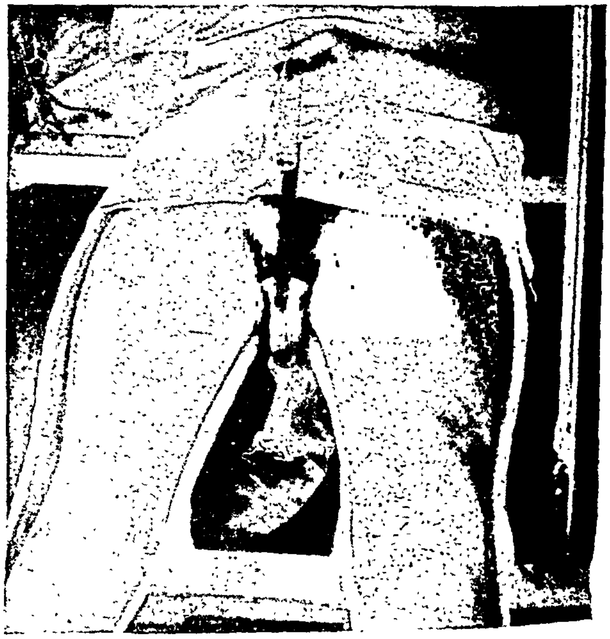

Fig. 3.

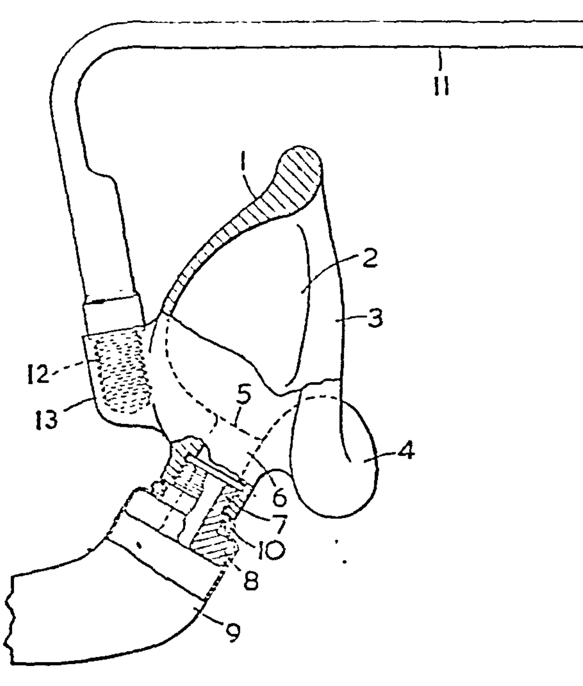

Fig. 1

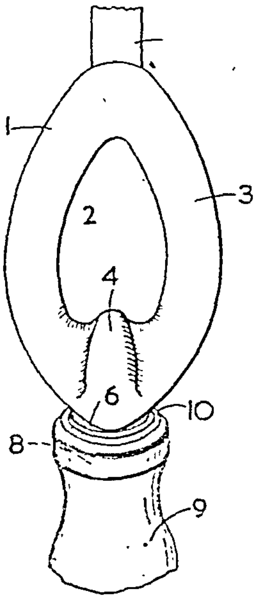

Fig. 2.

Fig. 1 shows the side elevation and fig. 2 the end elevation.

The receptacle (1) is shaped to fit between the patient's thighs. The mouth (3) of the cavity (2) is of such size as to enclose the appropriate part of the perineum. A crest (4), integral with the lower portion of the receptacle, fits between the labial lips above the posterior commissure to provide a fluid seal and prevent urine from trickling down between the receptacle and the perineum. The cavity (2) has an outlet (5) opening into a short conduit (6). This conduit is threaded to take a bush (7) having a cap or flange-like end (8) over which can be gathered the mouth of the polythene bag (9), which is retained in place with an elastic band (10). A swan-neck handle (11) is provided with a screw-threaded portion (12) which is screwed into a boss (13) moulded in the cup (1).

Although expressly designed for patients in plaster beds, the appliance has been found suitable for continent patients not in plaster beds, provided that an air-ring or pillow is placed under the buttocks. The appliance has proved popular with patients, and soiling of the plaster beds has been consistently prevented. However, the patients must first be assured that the appliance will not leak and they must be carefully instructed in how to place it against the perineum. If the appliance is held as shown in fig. 3, supination of the hand will keep the cup firmly in position. A nurse can carry four or five of these urinals compared with one tray or two bedpans. After use the polythene bag and attachment are unscrewed from the cup and washed out. The whole appliance is sterilised once daily and a new bag attached as required.

I wish to thank Sister Donnelly, of the Royal National Orthopædic Hospital, Stanmore, and Miss H. Pearn, for their invaluable help and coöperation in the design and trial of the apparatus. The photograph was taken by the medical photographic department of the Institute of Orthopædics. The appliance, which was first shown at the Congress of the Combined English-Speaking Orthopædic Associations on July 2, 1952, can be obtained from the Medical Supply Association, Park Royal Road, London, N.W.10. This device forms the subject of British Patent Application no. 16132/52, which has been assigned to the National Research Development Corporation.

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JOHN T. SCALES
M.R.C.S.

Reviews of Books

Problem Families

Five Inquiries. Editor: C. P. BLACKER, M.A., M.D., F.R.C.P., hon. secretary, Eugenics Society. London: Eugenics Society. 1952. Pp. 123. 5*s.*

THESE investigations of problem families, in North Kensington, Bristol, the West Riding, Rotherham, and Luton, "are to be regarded not as exhaustive factual reports but as experiments in method. They are, in fact, pilot inquiries." The object was to try to formulate a method of inquiry which could be applied on a national scale if at any time in the future this was thought desirable. The method employed, and the improvements which could be made in it as a result of experience, are well described.

Sponsored by the Eugenics Society, the inquiries were undertaken in 1948–49, at a time when the effects of new social legislation on local authorities made field surveys difficult. Nevertheless, valuable data have been collected and embodied in 29 tables dealing with size and composition of families; physical and mental health; occupation and income of the parents; intelligence of the children; and estimates of the incidence of illegitimacy and child loss from miscarriage, stillbirth and infant mortality, as well as of the national burden arising out of the need to care for many of these children apart from their parents. In a valuable introduction Dr. Blacker reviews the different contexts within which problem families have been considered in the last seventy years, and sets out the definitions, descriptions, characteristics, and possible causes put forward by various authors. The bibliography is comprehensive, and many detailed case-histories, chosen at random from the 379 households studied, have been included.

Child neglect, not necessarily amounting to deliberate cruelty, is one of the most disturbing features of the problem family. Local authorities took some action on receiving, in 1950, a joint circular from the Home Office and Ministries of Health and Education; but, even so, few have made any attempt to compile a register of these cases, which is a fundamental need in tackling the problem. The strength of the nation depends in the long run on the strength of its component families, and here is a study of some of the weakest links in the chain.

Medical Mycology

An Introduction to its Problems. G. C. AINSWORTH, B.SC., PH.D., F.L.S., department of botany, University College, Exeter. London: Pitman. 1952. Pp. 105. 15*s.*

ALTHOUGH Dr. Ainsworth writes as a trained mycologist, he has held a fair balance between the clinical or pathological and the essentially mycological interests. He has surveyed carefully recent papers on medical mycology and he has used current problems as the bases of discussions on groups of mycoses or of fungi.

Thus the ringworm fungi illustrate the problem of taxonomy; the mycoses of the respiratory system pose the question of the pathological significance of potentially pathogenic fungi in the sputum, which may also be common commensals in the mouth; mycetoma presents the problem of a pathological entity which can be caused by many different species of fungi; the more important systemic mycoses introduce the problem of dimorphism in pathogenic fungi and the possible influence of this phenomenon on the pathogenicity of the fungus and the epidemiology of the disease. Serological reactions and dermal-sensitivity tests help to mitigate the problem of specific diagnosis. Additional problems are found in the toxic effects of poisonous mushrooms and the allergenic properties of airborne fungal spores.

Dr. Ainsworth's lively manner of presenting his subject has made his book an effective introduction to medical mycology.

Principles and Practice of Anesthesiology

VINCENT J. COLLINS, M.D., director, department of anesthesiology, St. Vincent's Hospital, New York. London: Henry Kimpton. 1952. Pp. 528. 75*s.*

As the preface points out, the compilation of a single book covering all aspects of anæsthesia would be a monumental task. The author justifies his claim, however, to have written a textbook which is "concise, fairly comprehensive and documented from original sources."

The style is crisp, and tabulation is used to an extent to which British readers, accustomed to a more expansive literary style, may find oppressive. "Fairly comprehensive" is an understatement. The book includes, even if only briefly, every conceivable topic of clinical interest to the anæsthetist, though there is rather heavy emphasis on American sources in the extensive bibliographies. In the next edition the author might consider some rearrangement to bring related subject matter together: for example, all the complications of spinal anæsthesia might be gathered and inserted after the general account of the technique. Division of the planes of the third stage of anæsthesia into further subdivisions, all of somewhat dubious practical value, might well be given up, especially as little, if any, clear guidance is given on how to distinguish these subdivisions. He may also think of revising his good opinion of a mixture of 40% nitrous oxide in air as an obstetric analgesic, and may pause to doubt the value—even the wisdom—of smearing petroleum jelly (an ether solvent) on a patient's face to prevent the highly improbable occurrence of "ether burns."

These are but friendly criticisms of minor points. Dr. Collins has set a new standard for textbooks on his subject.

The Child's Conception of Numbers

JEAN PIAGET, professor at the University, and Institute of J. J. Rousseau, Geneva. London: Routledge & Kegan Paul. 1952. Pp. 248. 25*s.*

THIS volume, now added to the International Library of Psychology, Philosophy and Scientific Method, was published in Switzerland in 1941 under a title, *La Genèse du Nombre chez l'Enfant*, which gave a rather clearer indication of its contents.

Continuing his investigations into the growth of the child's ideas and power of thought, Professor Piaget here reports a large selection of his observations of the responses of children (aged 4–7$^1/_2$ years in the main) in situations involving the manipulation of simple apparatus—such as beads, sticks, dolls, flowers, and vases—contrived with a view to revealing the measure of their understanding of numbers. These responses are analysed with great subtlety, to make explicit the kind of thinking, in terms of classes and relations, which thinking in terms of numbers must imply. It is maintained that successful quantitative thinking is achieved, not after, but as soon as, the child can think operationally in the appropriate qualitative realm. Well-marked stages are shown to be recognisable in unreasonable to expect the railways, the owners of public buildings, and others in charge of places where accidents can happen to maintain any very considerable supplies. When it becomes clear that the casualty-list will be large, it is the custom for the ambulance control to order to the scene special bulk equipment, consisting of blankets, stretchers, hot-water bottles, morphine and other drugs, surgical instruments, and so on; and the senior ambulance officer goes in a large specially equipped ambulance which can be used as a casualty-clearing station or operating-theatre if need be. The promptitude and efficiency of this service has been demonstrated time and again. As the medical forces gather, many doctors may appear on the scene, and voluntary helpers come forward in large and heartening numbers. Indeed, Mr. N. P. JEWELL, F.R.C.S.I., in a letter to the *Daily Telegraph*,[2] said that at Harrow "most of the many doctors were wondering what to do"; and there seems little need for more than a few doctors on the spot or for a general alarm to doctors in the neighbourhood. The harnessing of the main tide of volunteers is not primarily a medical concern, but, as another correspondent in the same newspaper observed,[3] it should be included in any wider preparations for dealing with disaster. In a railway accident the director of operations, a senior member of the railway staff, takes control of rescue and clearance work; but at the moment there seems to be no clear provision for a *medical* authority—in other words, for a doctor who would be in direct charge of first-aid and other treatment, and who would decide when further help was required or when the scene was overcrowded with medical personnel. The local health authorities could, in consultation with the regional board, invite a number of doctors in each region to declare their readiness to act in this capacity; and, in the event, the regional board's emergency officer could then call on a leader for the medical advance party. Of course, in the past this responsibility has been willingly and efficiently accepted by somebody, but this is no reason for not delegating it in advance as part of the emergency plan.

Some further questions emerge. When many people have been killed, what special provision should be made for mortuary accommodation? A large building nearby could be used, and this would certainly relieve pressure on the hospitals. But there are risks and disadvantages in the suggestion, and it is probably advisable to make every effort to find space at the hospitals to which most of the injured are sent. Again, the hospitals should be relieved as far as possible of the burden of telephone inquiries, either by importing additional staff to deal with them or by setting up an inquiry bureau, as is sometimes done at present. Finally, could the medical resources of the Armed Services be brought into the plan? Recent disasters have shown how readily and effectively they can help. The routine machinery by which this aid can be quickly mobilised for civilian needs should be as simple as possible, and commanding officers should be authorised to use their discretion in bringing Service personnel and supplies into action in this way. The Royal Air Force maintains first-class mobile medical units for dealing with aeroplane crashes, and it is easy to think of occasions when such a unit might be of great value.

Our discussion of these possibilities does not imply that past experiences, at Harrow or elsewhere, have shown serious weaknesses in the present system. Indeed, both on the spot and in hospital the care of the Harrow casualties was very good. Most of them were evacuated very quickly, and no-one who was extracted alive died before reaching hospital. A few people had more than one injection of morphine, but no serious harm came of it; and this mistake (which many will think in the circumstances to be relatively trivial) could be avoided by the use of treatment labels to be filled in by the doctor giving the injection, or by some similar device. The most reassuring feature was the immediate and overwhelming surge of help from all sides. The situation was met, as others have been met in the past, by the national phenomenon of spontaneous amalgamation and teamwork, without which any plan, however careful its preparation, would remain lifeless. It does not follow, however, that the success attained at Harrow, in an area well served by roads, ambulances, hospitals, and doctors, would be attainable equally elsewhere; and we are quite sure that every region and every hospital ought to know in advance what it is going to do and how it is going to do it.

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[2] *Daily Telegraph*, Nov. 5, 1952.
[3] *Ibid*, Oct. 29, 1952.

Resection for Pulmonary Tuberculosis

IN 1945 OVERHOLT and WILSON[1] said that "pulmonary resection will find its true place as a supplementary and not a competitive form of treatment to the already established methods of rest and collapse therapy." Two years later and still before the use of chemotherapy, they and their colleagues[2] added that the rapid growth of this form of treatment for pulmonary tuberculosis was due "largely to the fact that it was needed," and that the limitations as well as the usefulness of the various kinds of collapse treatment were being appreciated more keenly. Resection had, in fact, acquired an established position, before the introduction of chemotherapy, in the treatment of certain types of lesion. It is still true that there is no real rivalry between resection and surgical collapse in the case of a destroyed lung or a fibrotic stenosis of a main bronchus with associated secondary infection. Moreover, the failures of collapse therapy, such as persistent cavitation after thoracoplasty or a dorsal-lobe cavity which has failed to respond to the simpler collapse measures and chemotherapy, are generally accepted as indications for resection where this is possible. There is also a fair measure of agreement about the advisability of resection where the inadequacy of collapse therapy can be anticipated, as, for example, with many large cavities, particularly of the tension type. The arrival of effective chemotherapy, however, has not only increased the number of patients with such lesions who can be treated by resection but, partly from a certain dissatisfaction about the value of pneumothorax, has also led to a considerable widening of the indications for excision. At this point the controversy becomes clear. There are those who are unwilling to extend the indications very far beyond

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[1] Overholt, R. H., Wilson, N. J. *J. thorac. Surg.* 1945, 14, 55.
[2] Overholt, R. H., Wilson, N. J., Szypulski, J. T., Langer, L. *Amer. Rev. Tuberc.* 1947, 55, 198.

the limits set in the era before chemotherapy; they point out that tuberculosis is not a localised disease and that thoracoplasty is a well-tried operation of proved and accepted value which it would be unwise to discard. On the other hand, the more radical view is that resection should be used for areas of localised active tuberculous disease, by which is implied not only cavitation but also caseous foci above a certain size. Such circumstances often require only a limited excision—lobectomy, segmental resection, or simple wedge excision. The mortality-rate of operation is low, complications are few, and the early results are claimed to be good.

Clearly, no conclusive verdict on the merits of excision can be reached until enough late results are available. However, the pathological evidence from resected specimens forms a useful means of assessment. Thus, NASSAU and PAGEL [3] noted that in 19 out of 26 lobectomy specimens the main lesion was "a tuberculoma of the primary complex type, either solid (12 cases) or cavitated (7 cases)": and a similar picture was seen in 4 out of 5 pneumonectomy specimens. The lung focus was recognisable as primary by its relation to a similar caseous focus in a corresponding lymph-node. Many of the solid foci not only were large and caseous but showed small areas of liquefaction on histological examination; and, as NASSAU and PAGEL pointed out, it is this type of focus which plays a decisive part in endobronchial dissemination to other parts of the lung. A lamellated structure was apparent in many of the foci, suggesting an increase in size by slow appositional growth, and the age of the lesion was also indicated by numerous calcareous nodules and particles. Indeed, obsolescent changes were often found in close proximity to fresh progressive changes, the inference being that a local recrudescence was the cause of focal extension. PAGEL [4] found that many apparently solid foci consisted of a pultaceous mass, often containing many tubercle bacilli, and, as RYAN, MEDLAR, and WELLES [5] observed, this caseous mass, even when apparently walled-off by fibrous tissue, remains in potential communication with the bronchus. Liquefaction of the focus with discharge of its contents, teeming with bacilli, into the bronchial tree is a common cause of relapse in patients who have made a good clinical recovery. It may, indeed, give rise to violent pneumonic spread, and favour the establishment of a tuberculous endobronchitis.

There is, on this evidence, a strong indictment to be made out against the caseous focus, particularly the large one, as the real culprit in clinical relapse; and the case in favour of resecting such lesions seems to be correspondingly strengthened. On the other hand, it has been shown[6] that some large foci remain unchanged for years, and collapse therapy—particularly when as permanent as a thoracoplasty—must certainly have been an effective control in many cases. Again, there are certain unfortunate consequences of resection which cannot be ignored. With upper lobectomy, overdistension of foci in the dorsal segment of the lower lobe may lead to breakdown; in many cases the ultimate effect on respiratory function must also be considered. The first difficulty can be countered to some extent by a post-resection one-stage thoracoplasty to reduce the volume of the dead space; and it is already clear that the removal of large amounts of functioning lung tissue must be avoided. There seems to be no simple answer to the question of what should and what should not be resected, but here again the pathology of the lesion can be a guide. RYAN et al. point out that there are really two types of tuberculous lesion: the pneumonic type, which does not proceed to necrosis, and the caseous type, which involves actual death of lung tissue. The former is largely reversible and heals either by resorption or by the formation of scar tissue; the latter is entirely irreversible, it cannot be absorbed, it is liable to slough (in other words, to cavitate), and it can only heal by becoming fenced-in with fibrous tissue, while liquefaction is a constant risk. RYAN et al. also think that caseous foci are more apt to form and to cavitate in the superior and posterior parts of both upper and lower lobes—i.e., in the apical and posterior segments of the upper lobe and the apical (dorsal) segment of the lower lobe. Elsewhere, they believe, even caseous foci are relatively harmless. Resection of such foci should therefore be reserved mainly for disease in the segments where cavitation is commonest, and wedge excision is, wherever possible, the method of choice. The corollary to this view is that a long preoperative preparation by bed rest and chemotherapy is essential, and all the patients described by RYAN et al. had negative sputa and gastric washings for many weeks before the operation. It was accepted as a principle that most postoperative complications are due to the presence of bacilli in the sputum at the time of operation, and these surgeons insisted on a repeatedly negative sputum. Before February, 1951, they performed 30 wedge or subsegmental resections, with bilateral resections in 3 patients (1 patient had 9 wedges removed). Pathological examination showed necrotic (caseous) lesions and the areas previously containing cavities showed filled-in cavities with *patent* bronchial communications. There was little change postoperatively in the cardiorespiratory reserve, and complications were negligible. Up to February, 1952, there was no evidence of clinical or radiological relapse in any of their patients, though 1 patient had had two positive sputum cultures.

Viewed in the perspective of a few years ago, it is rather startling to find that a consistently negative sputum has been made a strict essential for operations of this kind on patients with pulmonary tuberculosis. It is also a matter for thought that patients who have made what seems to be a good clinical recovery should be advised to undergo multiple resections of lung. But the change in outlook is backed by coherent pathological argument, as yet unrefuted, and certainly the fitter the patient the more likely he is to tolerate surgery well. Few would care to endorse without reservation the view of RYAN et al. that caseous foci, as small as 2 mm. in diameter and in certain specified situations, should be resected as a matter of course; but the plea for prolonged preparation with rest and chemotherapy, supplemented by pneumoperitoneum and postural treatment in certain cases, is entirely logical. The extended range of chemotherapy is making drug resistance less of a hazard, and the

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3. Nassau, E., Pagel, W. *Tubercle*, 1951, 32, 120.
4. Pagel, W. *Amer. Rev. Tuberc.* 1952, 65, 673.
5. Ryan, B. J., Medlar, E. M., Welles, E. S. *J. thorac. Surg.* 1952, 23, 327.
6. Moyes, E. N. *Thorax*, 1951, 6, 238.

highly desirable aim of limited resection with the greatest possible preservation of function can only be achieved with safety when all reversible lesions have been brought under control. In the final analysis only the chief foci of disease can be excised without an unwarranted sacrifice of lung tissue; and the fundamental biological processes which control the body's powers of resistance and recovery must be taken into account. Even on this point, however, it can be argued that removal of the major foci fortifies these powers and eliminates a considerable threat to the bodily economy. Here, no less than elsewhere, successful treatment depends on a careful study of the nature and behaviour of the local lesion, supplemented by an appreciation of the natural history of the disease.

Wernicke's Encephalopathy

THE main features of Wernicke's encephalopathy are loss of appetite, vomiting, nystagmus, diplopia, palsy of external ocular muscles, apathy or apprehension, loss of memory, disorientation, confabulation, and coma. Ataxia has occasionally been noted in the final stages; but its significance is doubtful since by that time the patient may be unable to coöperate.[1] The disease appears as a sequel to chronic alcoholism, long-continued vomiting of pregnancy, malignant lesions of the gastro-intestinal tract, and primary malnutrition. The pathological lesions are scattered throughout the whole brain and are localised particularly in the grey matter of the brain-stem and the structures near the third and fourth ventricles. They consist of hyperæmia, small petechial hæmorrhages, endothelial vascular proliferation, and slight nerve-cell necrosis with microglial reaction. Deficiency of vitamin B_1 is clearly responsible for much of this syndrome; but there is still doubt whether it accounts for the whole picture, and particularly the more severe mental deterioration. Most observers [1–4] agree that within a few hours of giving aneurine (*thiamine*) the vomiting and eye signs improve greatly and the emotional abnormalities lessen: "increased alertness and cheerfulness" was recorded by PHILLIPS et al.[4]; and DE WARDENER and LENNOX [2] remark that the patient may become "cheerful, coöperative, and voluble." These groups of workers also agree that if the disease has progressed to the point where loss of memory, disorientation, and confabulation are all evident, then recovery from these manifestations is slow and uncertain, however well the other features of the disease respond to aneurine. *It is this relative* unresponsiveness of these mental changes that prompts the question whether they are in fact due to vitamin-B_1 deficiency.

DE WARDENER and LENNOX [2] described 52 cases in underfed prisoners-of-war and found that "a patient with a well-established confusional state . . . was likely to take up to three months to return to normal mentality"; and one of their patients was still disorientated seven months after the onset of the disease. They pointed out that, as the whole vitamin-B complex had been given during the long recovery period, the "evidence that no vitamins other than thiamine is concerned in the profounder mental manifestations cannot be said to be complete." JOLLIFFE et al.,[1] whose patients were mainly chronic alcoholics, all of whom had advanced mental deterioration, found that among those whose life was saved by aneurine only a third made a complete mental recovery—again after protracted treatment with multiple vitamins. They concluded that confusion and confabulation in Wernicke's encephalopathy was probably due to some cause other than aneurine deficiency. PHILLIPS et al.,[4] on the other hand, who have confirmed JOLLIFFE's [1] findings in chronic alcoholics, point out that their own evidence does not exclude aneurine deficiency as the sole cause of the advanced mental deterioration.

In peace-time Wernicke's encephalopathy is found most commonly in chronic alcoholics. These patients are usually pathetic, elderly wrecks who have been adrift on a sea of alcohol for many years before they are finally shattered on the rocks of malnutrition; and their abnormal mental state is probably due to many causes. In non-alcoholics it is easier to disentangle the evidence, much of which suggests that aneurine deficiency alone can induce severe mental changes. CAMPBELL and RUSSELL [5] and CRUICKSHANK [3] each cite a case in which confusion disappeared and full mental recovery took place a few days after beginning treatment with vitamin B_1. DE WARDENER and LENNOX,[2] whose cases varied in severity when first seen, and who were thus able to observe the onset of the mental symptoms, noted that these followed the nausea, vomiting, and eye signs. Emotional changes were followed by loss of memory for recent events; then came disorientation, confabulation, and finally loss of memory for remote events. They found that if vitamin B_1 was given before the onset of disorientation, complete recovery ensued within a few days, indicating that loss of memory as well as emotional abnormalities could be caused by aneurine deficiency. They also showed that the time incidence of the classical forms of beriberi in the prisoner-of-war population coincided with the time incidence of Wernicke's encephalopathy; and they pointed out that if the other deficiencies in the diet had been concerned in the ætiology of Wernicke's encephalopathy it would have been reasonable to expect some overlap of the encephalopathy with the better-known manifestations of these deficiencies, which appeared later. WILLIAMS et al.[6] gave a diet grossly deficient in aneurine to healthy persons, who on this régime showed impaired memory and emotional balance; both these changes were corrected by aneurine.

These observations suggest that in Wernicke's encephalopathy disorientation and confabulation are the final evidence of one continuing process which, if untreated, may lead to irreversible cerebral damage. Nevertheless such patients are severely malnourished, and *treatment should include* a good mixed diet together with whole vitamin-B complex by mouth and for the first few days, aneurine and nicotinic acid (niacin) by intramuscular injection. Deficiencies of the vitamin-B group often manifest themselves *singly*; but the dietary deficiency is usually multiple.

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1. Jolliffe, N., Wortis, H., Fein, H. D. *Arch. Neurol. Psychiat.* 1941, 46, 569.
2. de Wardener, H. E., Lennox, B. *Lancet*, 1947, i, 11.
3. Cruickshank, E. K. *Quart. J. Med.* 1950, 24, 327.
4. Phillips, G. B., Victor, M., Adams, R. D., Davidson, C. S. *J. clin. Invest.* 1952, 31, 859.
5. Campbell, A. C. P., Russell, W. R. *Quart. J. Med.* 1941, 10, 41.
6. Williams, R. D., Wilder, R. M., Smith, B. F. *Arch. intern. Med.* 1940, 66, 785.

Annotations

BLOOD CATALASE AND ORAL ULCERATION

FEW disorders are more mysterious, more troublesome to the patient, and more refractory to treatment than the recurrent oral ulceration that sometimes progresses to gangrene and spreads to the nose and maxillary sinuses. Commonly this disorder seems to be exacerbated, or started on its invasive course, by removal of a tooth; and it is not controlled by local application of antibiotics. In this issue Prof. Shigeo Takahara, of Okayama, Japan, records the connection he has observed between this condition and lack of catalase in the blood and tissues.

Catalase is a specific enzyme, present in many tissues, including blood, that decomposes hydrogen peroxide; it has been known for over fifty years. When hydrogen peroxide is added to blood, oxygen is evolved, but the colour of the blood remains normal; this is because the catalase present decomposes the peroxide to water, and oxygen is released. But if catalase is not present the blood darkens in colour owing to the formation of methæmoglobin; if excess hydrogen peroxide is added the mixture eventually becomes colourless; and the addition to this colourless mixture of potassium hydroxide and then a reducing agent such as sodium dithionate gives rise to a rose-coloured substance, named by Bingold "pentdyopent."

Professor Takahara's attention was drawn to the syndrome he describes while treating a girl, aged 11, who had had recurrent ulcers of the gums for 3 years. When Professor Takahara saw her the condition had become severe, and the right nasal cavity contained a tumour formed of putrefying granulation tissue. He removed the tumour; and when he washed out the cavity with hydrogen peroxide the wound tissue turned brownish-black, and he thought that he had used silver nitrate by mistake. When fresh hydrogen peroxide was used, however, the same thing happened, and it was noticed that the black colour was due to blood in the wound mixing with the peroxide without the usual bubbling. This child had five siblings, and the mother stated that two other children also had oral ulcers. Professor Takahara found that blood from the ear in the two affected children and one unaffected child showed this same blackening when hydrogen peroxide was added, and no oxygen was evolved. He reproduced this blackening reaction with blood in the test-tube, and he also brought about the Bingold pentdyopent reaction. All this suggested that the blood might be deficient in catalase, and by the Warburg manometric method he showed that the blood and tissues of the affected children were grossly defective in this enzyme. For example: the "quotient of catalase" (the ratio of the quantity of oxygen in cubic millimetres generated in 30 minutes at 38°C to the weight of dried tissue in milligrammes) in normal persons is 4500 for ear-lobe blood, 12,000 for the red cells of venous blood, 200 for nasal polyp tissue, and 250 for oral tissue; but in these affected children the corresponding figures were 7 for ear-lobe blood, 8 for red cells of venous blood, and 0 for nasal and oral tissue.

Takahara has found, in another family of ten, four children with lack of catalase in the blood; and two of these had had mild affection of the gums. He describes one other severely affected boy, 13 years of age, in a different family; but the siblings were normal. In all three families, the affected children were the offspring of consanguinous marriages, which suggests that the condition is inherited.

The predominating organisms in the oral and nasal lesions of these patients were hæmolytic streptococci and type-I pneumococci. Hæmolytic streptococci are known to generate hydrogen peroxide. In normal persons this will be reduced by the blood catalase; but in these patients without catalase the hydrogen peroxide produced would oxidise blood reaching the lesion and deprive the tissues of available oxygen, thus leading to a vicious circle with consequent spread of the lesions.

Takahara treated his cases on conventional lines; and it would be interesting to see if local application of a catalase preparation would relieve the condition. The richest source of catalase is mammalian liver, and potent materials have been prepared by several workers—for instance, Sumner and Dounce.[1] We expect that clinicians in this country will look for similar cases, especially since the syndrome can be detected by such a simple qualitative test.

PERSISTENCE OF POLIOMYELITIS ANTIBODY

VIRUS-NEUTRALISING antibody can be demonstrated in the sera of patients with poliomyelitis before the appearance of paralysis, and the antibody titre rises during convalescence. Winsser and Sabin[2] have now investigated the level of antibody at longer intervals after infection with type-1 poliomyelitis virus. They were encouraged to find that three months and three years after infection 6 children showed very high antibody titres in their sera. Is the persistence of antibody due to repeated infection with the virus? Winsser and Sabin are disinclined to accept this explanation, and point to the fact that their patients did not develop antibody to type-2 virus during the same three-year period. It is worth recalling the interesting observations of Paul and Riordan[3] on the antibody to type-2 virus in the sera of Eskimos living on the north coast of Alaska. Practically no Eskimos under the age of 20, but 80% of those over 20, had neutralising antibody in their sera. Paul and Riordan infer from these observations that there was an epidemic of type-2 poliomyelitis among the Eskimos twenty years before, that there had been no epidemic since then (both these deductions are supported by the epidemiological records), and that demonstrable antibody had persisted for more than twenty years. The Yale workers later found[4] antibody in high titre to all three types of poliomyelitis virus in the sera of some Eskimos; and their latest work,[5] among different populations, shows a general correlation between the ages at which clinical poliomyelitis and type-2-neutralising antibody are acquired. Once present, type 2 antibody seems to persist, and it seems clear that high levels of antibody to all three types can persist in man for a long time. The success of any scheme of immunisation against poliomyelitis would depend on the production of an equally sustained antibody response, and in this respect the yellow-fever virus set a good example in the past.

PROFESSIONAL SECRECY

LAST year[6] we discussed the question of professional privilege in courts of law, and we pointed out that while in this country medical secrets are not recognised or protected in the witness-box, Continental legal systems have, under pressure from the medical profession, deliberately adopted a different attitude which gives far greater safeguards to doctors and their patients. The wider implications of the disclosure of confidential medical information were discussed at this year's German Medical Congress, held in Berlin in September, and the debate led to a number of resolutions which are, in present conditions, of great interest to doctors everywhere.

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[1] Sumner, J. B., Dounce, A. L. *J. biol. Chem.* 1937, 121, 417 Sumner, J. B., Dounce, A. L., Frampton, V. L. *Ibid*, 1940 136, 343.

[2] Winsser, J., Sabin, A. B. *J. exp. Med.* 1952, 96, 477.

[3] Paul, J. R., Riordan, J. T. *Amer. J. Hyg.* 1950, 52, 202.

[4] Paul, J. R., Riordan, J. T., Melnick, J. L. *Ibid*, 1951, 54, 275.

[5] Paul, J. R., Melnick, J. L., Riordan, J. T. *Ibid*, 1952, 56, 232.

[6] *Lancet*, 1951, i, 454.

It has been clear for some time that requests from public authorities for medical and statistical information are tending increasingly to encroach on the private and confidential relations between doctor and patient. Those who seek medical advice have a right to expect that whatever they as patients confide to their doctors will go no further, and doctors are equally anxious to respect absolutely the confidences they receive. Nevertheless, certain legislation, particularly that dealing with social insurance and health, tends to restrict, or even remove, this protection. Police regulations, notification and registration orders, tax and criminal laws, and the demands from public authorities, private concerns, and insurance companies for certificates of incapacity or health were all mentioned at the congress as causes for the gradual confounding of the patient's natural expectation that what he tells the doctor will be passed on to no-one else. The congress came to the conclusion that medical secrecy must be regarded as a fundamental human right which, for the sake of patient and doctor alike, needs far more definite protection by the law than it has hitherto received in Germany. Accordingly, a resolution was passed asking the Federal Parliament at Bonn to introduce comprehensive legislation establishing a definite medical code. This legislation is to be based on the principle that only the consent of the patient in each individual case can release the doctor from his duty, which is at the same time his right, not to divulge any knowledge gained in the consulting-room or elsewhere in the exercise of his profession. This would give him the necessary legal ground on which to resist firmly any unjustified request from whatever source.

In these discussions it was, of course, acknowledged that in certain situations a breach of secrecy may be necessary: the prevention of an epidemic or a serious crime would justify such a step; but there was unanimous agreement that the limits of such exceptions should be as narrowly drawn as possible, and that, in cases of doubt, the final decision should be left to the doctor's discretion. No doubt as a result of certain abuses in Western Germany,[7] practitioners in Germany are no longer required to report all miscarriages and abortions among their patients. The congress has gone much further in suggesting that by no means all the other notifications now demanded by law are justified, and that they are in constant danger of abuse. It was suggested that, when such returns were strictly necessary, in many cases the names of patients could be withheld without seriously interfering with the purpose of the regulations, and that, where names must be given, these should be sent in sealed envelopes to be opened only by the doctors directly concerned. One of the demands most strenuously made at the congress was that confidential medical details should not be known to non-professional civil servants or outsiders. It was proposed that, whenever a public authority or semi-official body asked for a report on a person's health or capacity for work, the information should be available only to the authority's health officer, and not to the authority at large. In these circumstances the health officer would himself be bound by professional secrecy, in the same way as the doctor acting on behalf of, for example, a private insurance company. He would pass on the result of the medical examination in the form of a definite recommendation or proposal, withholding the actual details. It was also proposed that medical certificates for employers should identify the disease by a code word, at the same time giving the seriousness and expected length of the illness.

How far these recommendations are likely to be put into practice in Germany is not yet clear. At all events, the German press and public have been strongly impressed by the practitioners' call for effective legal safeguards. Meanwhile it is interesting to note that, under an amending Bill to the German Criminal Code, which is before the Federal Parliament just now, the privilege of doctors in German courts of law is to be extended to their auxiliaries—consulting-room assistants, nurses, and midwives—and that secrecy is to cover not only what has been expressly entrusted to them by their patients, but all information which they have gained in the exercise of their profession. Past experience of overriding authority, and probably a knowledge of conditions in Eastern Germany, where all medical secrecy has been abolished and doctors have in many respects become the servants of a ministry of labour, have certainly made German doctors especially sensitive to encroachment on what they rightly regard as a fundamental principle.

THE YOUNG CHILD IN HOSPITAL

A FILM, *A Two-year-old Goes to Hospital*, has been made as part of the research work in progress at the Tavistock Clinic, and it was shown to the section of pædiatrics of the Royal Society of Medicine on Nov. 28. Opening the meeting, Dr. John Bowlby said that it might seem that the subject of a small child's stay in hospital for eight days for a minor operation, and the fact that she spent most of the time fretting for her mother, were hardly worth making a film about; but evidence was accumulating that prolonged periods of separation from the mother in early life could have serious effects on a child's mental health. He welcomed the film as a new and objective approach to the problem.

Mr. James Robertson, a psychiatric social worker at the Tavistock Clinic, who made the film, said that while he was studying the emotional reactions of children in hospitals and sanatoria he became aware of the bias both of the psychologist, who tended to identify himself with the small patient he was observing, and of the doctors and nurses, who were apt to develop a self-defensive unawareness of the child's mental suffering in order to spare their own feelings. He had therefore decided to make this film to record objectively what actually happened. Before the child went into hospital he had visited her at home, so that she was accustomed both to him and to the camera. Later, through the coöperation of the authorities of the Central Middlesex Hospital, he or a colleague was able to watch the child continuously during her waking hours. Each important event was filmed—the child's admission to hospital, the first bath, the administration of an anæsthetic by enema, and the parents' visits—and in addition films were taken each day from 11.0 to 11.40 A.M. at five-minute intervals. The only departure from routine was that a nurse was specially detailed to talk and play with the child during the morning filming. The little girl, Laura, aged 2½, had been selected at random from the waiting-list of children between 18 months and 3 years who were to come into hospital for an operation for umbilical hernia. This operation was chosen because it was minor and uncomplicated and not very painful.

The film opened with Laura playing happily with her parents in the garden of her home. Her mother had explained that she would be going into hospital and would stay there until she had had her operation and her tummy was better. On the day of her admission she was bright and interested as she sat waiting with her mother at hospital; but she was looking a bit hesitant some minutes later when the nurse took her into a strange bathroom, and she asked anxiously, "where's my Mummy?" When the nurse began to undress her she cried and struggled; but by the time she had been bathed, dried, and dressed in a nightgown she had regained her composure, showing remarkable self-control for her age. She was given a cot in a children's ward with 12 beds. She looked about her in a puzzled way, and cried when a nurse took her temperature in the axilla. But she cheered up again when her mother came to say good-bye: and she waved happily enough and watched the bus drive away. Her mother had told her she would come again tomorrow, and had left with her a teddy-bear and a piece of blanket she always cherished, her "blanket-baby." However, she spent most of the day crying and calling for her mother, and she did not take kindly to a visit from the surgeon.

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[7] *Ibid*, p. 676.

Next day she had her operation. She was given an anæsthetic by enema, an experience which terrified her and made her scream with apprehension. She was next shown when both her parents came to see her as she was recovering from the anæsthetic. She cried most of the time, and was especially distressed because her mother could not take her up in her arms. When her mother left first, she clung to her father until he, too, had to go. On the third day she seemed very sad and subdued. She was unresponsive to the nurse, and tears came easily. She called for her mother, but when her mother came she received her without enthusiasm, and it was some time before she became lively and joined in a game. From this time onwards, she became less and less responsive both to the nurses and to her mother. She spent a good deal of time watching another child who was howling lustily, and she exclaimed, "He wants his mummy." She clung to her teddy and her blanket-baby and to some books her mother had brought, but she still cried for her mother whenever some kindly grown-up came to speak to her. When her mother came to take her home, she was extremely reserved, but she brightened up considerably when her shoes were put on. She insisted on gathering up all her toys and books, and she waved good-bye as she got to the door of the ward. Then she dropped a book and for the first time showed real temper. She left rather unsteadily, but not holding her mother's hand.

In the discussion which followed, the first reaction of the audience seemed to be a frank refusal to admit that the child was distressed. However, Dr. Mildred Creak pointed out that it had taken a second showing of the film to overcome her initial resistance to the fact that most young children in hospital were unhappy. Of those who agreed that the film showed the child's distress clearly enough, many were reluctant to admit that such an experience might cause long-continued or even permanent emotional disturbances. They felt that the emotional after-effects were negligible, and depended largely on the individual child's upbringing and home life. There was a need, they thought, for control films of normal children's emotional upsets at home, and of the effects both of a longer stay in hospital and of a stay undisturbed by an alarming operation. In reply, Mr. Robertson said it was hoped that other films would eventually be made. He felt that, in spite of Laura's exceptional self-control, the film gave a fair idea of the typical reactions of a child in hospital, and he disagreed with the view that the mental suffering was negligible. Dr. Bowlby agreed that we needed detailed evidence on the effects of a period of separation from the mother, but he thought that this evidence would be of little scientific value unless it was collected and weighed by people with the necessary psychological training.

Despite daily visits by her mother, this child was shown in silent grief during most of her stay in hospital. Her self-control broke down under frankly terrifying situations. For most of the day she sat quietly clutching her treasured possessions, preoccupied with her grief. Despite this unhappy picture, the film left an excellent impression of the treatment and kindly handling of a small child in this particular hospital. However, there seemed no need for this particular operation at such a psychologically vulnerable age; and even if the operation was thought vital the child might possibly have been treated as an outpatient. If hospital is unavoidable, there are certain ways in which, on the evidence of this film, matters could be improved. Laura was kept in virtual isolation and given little physical comforting, even by her mother, who thought that it was not permitted in the ward. A strange nurse gave her a bath while her mother waited outside; and some nursing procedures were carried out without any attempt to explain them to the child. Doctors and nurses can do much to help in reducing the number of mother-child separations and to make those that are unavoidable as happy as possible. The words of one pædiatrician to his student nurses are memorable: "When you are admitting a child to hospital always try to behave as though you were welcoming a strange and nervous child who has come to spend a weekend in your home."

SISTER KENNY

Miss Elizabeth Kenny, the Australian nursing sister, died on Nov. 30. Doctors have disagreed about the value of her contribution to the treatment of poliomyelitis, but none has failed to admire the energy and perseverance with which she upheld her beliefs in the face of incredulity and discouragement. The ideas which were to cut so sharply across orthodox medical opinion were planted in her mind by her early nursing experiences in Queensland; and they grew into a system of treatment and a concept of the disease which aroused discussion and controversy all over the world. For one thing, she challenged the doctors' insistence on rest and immobilisation in the early stages of poliomyelitis, and she claimed that, given the chance of treating a patient soon enough, she could improve on the results of any other form of treatment.

Her views were at first entirely rejected, and then hesitantly acknowledged as worth investigating. The report on the year's trial at Queen Mary's Hospital, Carshalton, in 1937–38 was almost wholly discouraging, and, added to the lukewarm findings of the Royal Commission appointed by the Queensland State government in 1936, would have brought despair to the champions of most causes. But if Sister Kenny ever despaired it was certainly not for her treatment, but for the perception of the doctors who refused to see what to her was abundantly clear. She did not realise that her own enthusiasm could go against her; for the doctors thought that their treatment, energetically pursued, could achieve as much as her own, and they suggested that the benefits she brought to paralysed patients owed more to her confidence and optimism than to any originality of method.

She went to the United States in 1940, and though at first her methods gained no wider acceptance than elsewhere, things went more happily for her in the end. The Elizabeth Kenny Institute was set up in Minneapolis, and here, and in other clinics devoted to her treatment, much of her work was more favourably received than ever before. She never won for her methods or theories the unconditional approval that she and her many supporters believed them to deserve. Nevertheless, she whipped up so world-wide an interest in the treatment of poliomyelitis that, whatever the final judgment of her teaching may be, the sum of her work, in terms of suffering directly or indirectly relieved, places her among the foremost members of her profession.

Prof. R. S. AITKEN, F.R.C.P., vice-chancellor of the University of Otago, has been nominated vice-chancellor of Birmingham University.

Special Articles

GENERAL MEDICAL COUNCIL

SESSION NOV. 25–28

Prof. David Campbell's presidential address to the council was reported last week. The council appointed Dr. I. Grant to a vacancy in the Medical Disciplinary Committee.

DISCIPLINARY CASE

The council considered only one medical disciplinary case.

In November, 1950, it postponed judgment until November, 1952, after finding that *William Melrose*, registered as of 15, St. Paul's Square, Liverpool, L.R.C.P.E. (1924), had been convicted of being found drunk, for which he had been fined 10*s*. Dr. Melrose appeared and testimonials as to his conduct were read. In view of these the Registrar was not directed to erase the practitioner's name.

BRITISH PHARMACOPŒIA

Dr. H. GUY DAIN, presenting the report of the Pharmacopœia Committee, of which he is chairman, said that sales of the *British Pharmacopœia, 1948*, up to Oct. 31 totalled 48,843, and of the *Addendum, 1951*, 13,274. In preparing the new *Pharmacopœia*, which was now complete and would be published next year, care had been taken to consult other countries in the Commonwealth.

The committee had approved the issue of two further lists of approved names for various medicinal substances. Since the practice of issuing approved names was instituted in 1940, thirteen lists had been issued. Where possible, official names were given to all new substances likely to be found useful. Such substances were not necessarily entered later in the *British Pharmacopœia*.

The committee's report states that the Pharmacopœia Commission has consulted with the World Health Organisation subcommittee on international non-proprietary names, in an endeavour to achieve uniformity; but some of the names proposed by W.H.O. have had to be rejected because they conflict with trade-marks registered in this country.

The committee, on the recommendation of the commission, has arranged to publish amendments to the *British Pharmacopœia, 1948*, in relation to methods of preparation of substances which will not appear in the new *Pharmacopœia*. Dr. Dain explained that it was important that these new methods should be made statutory before the new *Pharmacopœia* came into effect.

The council approved the committee's recommendation that the British Pharmacopœia Commission, 1948–53, should end its existence on Sept. 1, 1953, when the new *Pharmacopœia* comes into effect; and that the new commission to prepare the next *Pharmacopœia* should be appointed by a selection committee consisting of four persons nominated by the council, three persons nominated by the pharmaceutical societies, and two persons nominated by the Medical Research Council.

PROVISIONAL REGISTRATION

The council considered a report by the Special Committee on Provisional and Full Registration, which made various procedural recommendations in respect of the compulsory period of service as a house-officer, which comes into operation on Jan. 1.

The PRESIDENT, who was chairman of the committee, explained the difference between the official Register and the printed Register. The council was empowered to produce a printed Register of persons provisionally registered, but such a Register would soon be out of date and nobody would want to buy it. The council authorised the amendment of standing orders to provide for the keeping of separate Registers of persons provisionally registered. It also authorised the fees which will be payable: for provisional registration the fee will be 5 guineas, and for full registration of a provisionally registered person 6 guineas; for others the fee will be 11 guineas.

The committee proposed a form of certificate for use by hospital authorities in certifying to licensing bodies that a provisionally registered practitioner had satisfactorily completed a period of employment as a house-officer. This would say that he had been employed for the period specified "and that his service while so employed has been certified by a member of the consultant or specialist staff as satisfactory." It would be signed by an officer of the board of governors, hospital management committee, or other employing body authorised to act on its behalf.

Sir RUSSELL BRAIN asked the meaning of the word "*specialist*." *If the intention* was that all house-officers provisionally registered should work under consultants, the wording should be limited to consultant. Sir HENRY COHEN, a member of the special committee, replied that the suggested wording was necessary. Most would work under consultants, but some might be under senior hospital medical officers who were not consultants under the Act but were specialists. Sir RUSSELL BRAIN agreed that in the circumstances there was no option but to have the wording as suggested, but they should "keep an eye on it."

Dr. O. C. CARTER said that there was a great deal of anxiety among students because the word "satisfactory" was not defined. Sir SYDNEY SMITH said this was a matter for individual licensing bodies. The certificate was approved for sending to licensing bodies for their observations.

The committee also recommended a form of certificate of experience to be circulated to licensing bodies, examining boards, and medical schools, for their observations.

The committee was satisfied that the compulsory internship schemes adopted in New Zealand and South Africa could be regarded as substantially equivalent to the United Kingdom scheme, and the council agreed that full registration should be accorded to practitioners who had been registered in New Zealand or in South Africa after rendering appropriate service under schemes there. In the matter of recognising hospitals in the Colonies the committee recommended, and the council agreed, that particulars furnished by the Colonial Office of recommended hospitals and posts, as revised in the light of observations received, and subject to any further adjustment which might be undertaken by the Colonial Office, be circulated to licensing bodies for their information.

A special committee was set up to consider and determine on behalf of the council applications made under Section 1 (*b*) and (*c*) or Section 4 (*c*) of the Medical Act, 1950, by persons whose applications do not fall to be determined under any *general resolution;* this concerns the registration of Commonwealth or foreign practitioners on proof of "satisfactory experience."

Medical Disciplinary Committee

The Medical Disciplinary Committee, under the chairmanship of the President, at its first sitting, on Nov. 26, heard three applications for restoration of names to the Register.

The Committee, after hearing evidence, directed the registrar to restore the names of Ralph Martin Case and Illtyd Gwyn Williams.

Stewart Quarterman Servanté applied for restoration of his name. Mr. J. B. Trier, solicitor, said that his client's name had been erased in February, 1950, following his conviction for unlawfully using an instrument to cause a miscarriage. He had made an unsuccessful application for restoration in November, 1951. In sentencing him the judge had said that there was no evidence that Dr. Servanté was a habitual abortionist. At present he was doing manual work; but he had received an offer, if he was restored to the Register, to become medical officer at a whaling station in Antarctica. The committee did not think fit to direct the registrar to restore to the Register the name of Stewart Quarterman Servanté.

FALSE ENTRY IN REGISTER

The committee heard the case of a fraudulent and incorrect entry in the Register which was made without the knowledge of the doctor concerned. The entry was that of "Joseph Claude Guyneruer Cyr," the address being recorded as "Royal Canadian Naval Hospital, Halifax, Nova Scotia, Canada," and the qualification "L.M.S. N. Scotia P.M. Bd, 1951." Mr. F. P. Winterbotham, solicitor to the committee, explained that no blame attached to Dr. Cyr, who was in no way responsible for the incorrect entry, which was made without his knowledge. Mr. Winterbotham read an affidavit from Dr. Cyr stating that the signature on the application was not his, that he had no knowledge of the application and did not authorise it, that he held medical degrees in Canada but not that of L.M.S. Nova Scotia P.M. Bd, and that his address had never been that given. The person whose name appeared on a certificate of character submitted with the application stated that the signature purporting to be his on the certificate was a forgery.

The Committee found that the entry had been made fraudulently and incorrectly and ordered its removal. The President stated: "There is not the slightest evidence that the real Dr. Joseph Claude Guyneruer Cyr had anything whatever to do with this case."

ALLEGED IMPROPER BEHAVIOUR

James Watson Richmond, registered as of Rosskeen, Kelty, Fife, M B. Glasg. (1929), appeared on having been convicted at the Sheriff Court, Fife, of offences involving improper behaviour to women, for which he was fined £25.

Mr. Gerald Howard, Q.C., M.P., stating the facts, said that the doctor had pleaded guilty and there were no notes of the evidence. Mr. Howard had obtained a newspaper cutting, and he submitted that it was proper for him to make a statement of the facts from this. The chief constable and the Lord Advocate's office had refused production of the statements taken by the police; and the chief constable had sent the officer in charge of the case, who had not been in court at all.

After legal argument as to using the newspaper cutting the Legal Assessor said that the doctor should be shown the cutting and asked if he agreed to its being read. He did not do so; and after consideration in camera the President announced that the committee had decided to proceed on the evidence produced. Mr. Howard said that, so far as he had been able to ascertain, Dr. Richmond had an excellent character. Dr. Richmond told the committee that he did not remember anything about the alleged incidents.

The President said that the committee considered the convictions disgraceful to a member of Dr. Richmond's profession; but in view of his explanation and the certificates which he produced it had postponed judgment for one year.

PAYMENT BY N.H.S. PATIENTS

William Pitt, registered as of Chatham, Sydenham Avenue, Belfast, M.B. Belf. (1942), was found to have been convicted at Birmingham Assizes of accepting payment from three National Health Service patients for treatment which should have been free. He had been fined £100 to be paid within three months, or six months' imprisonment in default. The President announced that the committee took a very serious view of the charges: but taking into consideration the assurances as to Dr. Pitt's future conduct it had decided to postpone judgment for one year.

CHARGE OF CANVASSING REFUTED

James Joseph Magill, registered as of 64, Vernon Avenue, Clontarf, Dublin, L.A.H. Dubl. (1950), was charged with infamous conduct in a professional respect. It was alleged that he had endeavoured to obtain patients of the practices of Mr. Gervase Brennan-Kelly and Mr. John Adami by means of an agent or canvasser, and by other improper means. The President announced that the committee had determined that none of the facts alleged against Dr. Magill had been proved to their satisfaction. "They have accordingly found that you are not guilty of infamous conduct in a professional respect."

UNLAWFUL REMOVAL OF A MOTOR-CAR

Jonathan Shutt, registered as of 118, Ebury Street, London, S.W.1, M.R.C.S. (1925), was charged with having been convicted at Hull of taking and driving away a motor-car without the consent of the owner or other lawful authority, in respect of which he had been sentenced to a fine of £10 or in default fifty-one days' imprisonment. The President announced that after careful consideration, and to give Dr. Shutt an opportunity to rehabilitate himself, the committee had decided to postpone judgment for one year.

IMPROPER PRESCRIPTION

Carl Xavier Rühen, registered as of Mexborough House, Market Street, Mexborough, M.B. N.Z. (1925), admitted, through his counsel, Mr. Gerald Howard, a conviction at Doncaster on May 13 of attempting to cause £1 7*s*. to be paid by the West Riding Executive Council to Boots Pure Drug Co. Ltd. by means of a false pretence. He had been fined £42 5*s*. 6*d*. The President announced that the committee took a grave view of a conviction of this nature, but in view of the testimony as to Dr. Rühen's character had directed the registrar not to erase his name from the Register.

DRUNKENNESS IN CHARGE OF A CAR

James William Hay, registered as of 51, Spencer Street, Carlisle, M.B. Aberd. (1924), had had judgment against him postponed for one year by the committee in May, 1951, in respect of convictions for driving a car whilst under the influence of drink, of driving a car without due care and attention, and of being found drunk. The committee directed the registrar not to erase Dr. Hay's name from the Register.

The registrar was directed not to erase the name of *William Allan*, registered as of 31, Hill Crest, Burnley Road, Sowerby Bridge, Yorks, M.B. Glasg. (1926), who had been convicted of driving a car whilst under the influence of drink. Judgment in this case had been postponed from the sitting in December, 1951.

The committee had similarly postponed judgment for one year in respect of *Hugh McNicholl*, registered as of Bangour Villa, High Road, Mottingham, London, S.E.9, M.B. N.U.I. (1933), who had been convicted of being in charge of a motor vehicle whilst under the influence of drink. The registrar was directed not to erase his name.

The committee postponed judgment for one year on *Archer Wilson Dunn*, registered as of 5, Airlie Place, Dundee, L.R.C.P.E. (1927), who had been fined £20 and disqualified from holding or obtaining a driving licence for six months in 1949 after being convicted of driving a car while under the influence of drink and driving without due care and attention, and in August of this year had been fined £30 and disqualified for twelve months from driving while under the influence of drink.

Gerald Francis Adye-Curran, registered as c/o Lightbounds, Jones & Co., 18, Water Street, Liverpool, L.M.R.C.P.I. (1934), was charged with having been convicted in 1947 of driving a car whilst under the influence of drugs (when he was not disqualified for the special reason that the overdose of drug was taken inadvertently, but was fined £5); in the same year of being in charge of a motor-car while under the influence of drink; and of being convicted in May last of being in charge of a motor vehicle whilst under the influence of drink and of assaulting a police constable. In the last instance he was sentenced to four months' imprisonment and disqualified for five years on the first charge, and fined £10 on the second charge. The committee postponed judgment until November, 1953.

Patrick Joseph Conlin, registered as of 1, North Terrace, Mardy, Ferndale, Glam., M.B. N.U.I. (1920), had had judgment postponed in December, 1951, to the present session after he had been found to have been convicted of being in charge of a motor-car whilst under the influence of drink. Dr. Conlin was not present but sent a telegram apologising and stating that he was on his way. After consideration in camera the President announced that the committee had decided to further postpone judgment until their session in November, 1953, when they would require testimonials as to his habits during the interval.

ABORTION

The registrar was directed to erase from the Register the name of *Archibald Miller*, registered as of 2, Douglas Drive, Ashgill, Dalserf, Lanarkshire, M.B. Glasg. (1928), who had been sentenced in June of this year to twelve months' imprisonment after being convicted in the High Court of Justiciary in Glasgow of supplying to a pregnant woman pills containing aloes and ferrous sulphate, and a liquid containing ergotamine tartrate, with intent to cause abortion. The erasure of his name is subject to appeal to the Privy Council within twenty-eight days.

HEALTH SCHEMES IN EIRE

AFTER eighteen months of comparative quiescence health schemes are once again causing controversy in Dublin. The Irish Medical Association has rejected the government's plans for improved and extended health services as outlined in the White Paper published last July. Clearly the association feels that, although the child has a different mother, the child closely resembles one which they removed from their doorstep last year.

A leading article in the association's journal[1] objects to the provision of a maternity and child-welfare scheme which would be free to all, irrespective of income. Such a development, says the article, would represent a dangerous growth of State control and a further intrusion of the civil service into one of the most intimate branches of medicine. This, it points out, is the only section of the proposals which is "free for all." While no-one would be obliged to use these free services they must, in fact, be paid for out of increased rates and taxation; and each taxpayer would naturally seek a return from this compulsory outlay. In any case the number of maternity beds is "utterly inadequate" to deal with such a scheme.

After protesting at the way in which the "so-called autonomy of our voluntary hospitals is being steadily undermined," the article goes on to say that the association is pressing strongly for an active Health Council. This would have its own secretariat, the duty of publishing an annual report, and the right of approach to the minister for health. It would advise him on health legislation and health affairs generally, and would be representative of the profession and other interested bodies.

> "... it must not be lost sight of that any Health Scheme, to operate successfully, must have the goodwill of the doctors. Is it reasonable to look for this goodwill while at the same time denying the fundamental right to representation of the very men and women in whose hands the working of the Scheme must rest?"

The article concludes that the ideal is a voluntary contributory State-aided scheme as proposed by the association over twelve months ago. Under this the local authority would pay the full premium for every poor person; for all others the State would pay one-third of the premium. A family health policy worth £200 per annum would be available in return for a weekly payment of 1*s*. 4*d*. by the head of the family. Such a scheme would be at once more comprehensive and more realistic than the government's proposals.

The reply of the minister for health, Dr. James Ryan,[2] was couched in robust terms. Referring to the association's remarks on civil service intrusion it stated:

> "The White Paper proposals involve no such intrusion and none is intended and the statement is either deliberately dishonest or arises from a confusion in the minds of the Association as to the primary function of the medical profession which is the practice of medicine and not administration."

After denying any interference, or intention of interference, with the voluntary hospitals the statement continues:

> "The Association also ignores the fact that additional maternity beds are being provided rapidly and that in this country, as in practically every country, it is not practicable to provide 100 p.c. hospitalisation."

Elsewhere the minister has given the total number of maternity beds of all kinds in local-authority and voluntary hospitals as 1503 in 1952, compared with 1215 in 1942.[3] The average number of births per year is approximately 65,000.[4] Under the terms of the White Paper, priority for admission of maternity cases to hospital will be given on medical grounds or on grounds of social need.

On the question of the Health Council, the minister stated that what the association requested was, in effect, a council that would be responsible, through him, for running the country's health services. This he rejected, but he was prepared to consider any proposals which the association might put forward for a council with advisory functions.

The minister also regards the association's insurance scheme as impracticable. Particular exception is taken to the need for a qualifying period before benefit is payable. After referring to "inconsistencies" in the I.M.A. scheme the statement refers to

> "the discrepancies between the Association's recent statement that under the scheme the full premium would be paid by the local authority and its statement in the course of a discussion with the Minister on December 20th last, that each local authority would be free to decide whether to avail itself of the scheme or not."

The minister has stated that the scheme will not be introduced without the fullest consultations with all interested parties.

PHYSIOLOGY OF THE NERVOUS SYSTEM

IN his presidential address to the Royal Society at the anniversary meeting on Dec. 1, Prof. E. D. ADRIAN, O.M., considered some of the ways in which our picture of the nervous system is changing. The work of the biophysicists, he said, was beginning to reduce the problems of cell organisation in the nervous system to the molecular level. It was likely to explain many of the characteristic properties of nervous tissue and to give a clear picture of the cell mechanism; but the cell units subserved the integrative action of the whole animal, and we had to determine how they were organised as well as how each one stored and discharged ions.

Dr. Adrian continued:

> "Since we are still searching for the physical changes which accompany learning—the changes, structural or molecular, which make the nervous system react differently after training—there is little as yet to bridge the gap between the biophysics of the nerve cell and the fully elaborated activity of the whole system. And if we could find, for instance, the cell changes which establish a conditioned reflex, we should still have only the general principles of nervous organisation. We could not forecast in detail how any particular nervous system would react unless we knew every detail of its past history. ... To understand the integrative action of the nervous system we have to relate the unit to the whole system and the system to the work it has to do. The study of the unit is advancing rapidly, though it is mostly concerned with the immediate response to stimulation and we know little about slower and more persistent effects. When we do know more, it may be that the general plan on which the units are organised will become much clearer. Perhaps a complete revision of outlook may be necessary. At all events there is no need to be pessimistic. There is a wealth of new material and new methods and a branch of natural science is in a healthy state when it has advanced to the stage where its traditional conceptions begin to look inadequate."

COMPLAINTS ABOUT A PRACTITIONER

IN connection with the case of a general practitioner in the National Health Service about whom there have been repeated complaints, the medical service committee of London Executive Council has taken the unusual course of suggesting that representatives of the council and of the local medical committee should discuss means for safeguarding the interests of the service.

The committee reported to the council on Nov. 27 a complaint by a patient and his wife that the doctor had been very rude and that he had forcibly ejected the wife rom the surgery. According to these witnesses, the onditions in his surgery virtually defied description. he place was said to be dirty and littered with old lothes, old shoes, used matchboxes, and books and apers. There was a "filthy rug" on the floor, and the esk was so littered that there was no space on which to rite; and dust and tobacco ash was all about. The espondent practitioner did not appear when the case as heard. On the ground that the doctor had failed to rovide proper surgery accommodation, as required by he Terms of Service, the committee recommended, and he council agreed, that representations should be made o the Minister of Health that £50 should be withheld rom his remuneration.

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[1] *J. Irish med. Ass.* November, 1952, p. 328.

[2] *Evening Herald*, Nov. 7, 1952.

[3] Dail Eireann Official Reports (unrevised), vol. 134, 2, columns 223–226, 229–236.

[4] *Ibid*, col. 222.

In its report the committee pointed out that this doctor had been the subject of three previous inquiries.

In March, 1951, the Minister of Health instructed that £25 should be withheld from his remuneration because of his failure to return to the council the medical records of 236 of the persons who had been removed from his list in 1949. In February, 1952, the Minister, because of the doctor's continued failure to submit the medical records of his patients, directed that the council should withhold a further £100. On Jan. 3, 1952, the council considered a report by the committee of an allegation by a patient that the doctor had struck him on the face. The doctor, who had not appeared at the committee's hearing, appealed successfully against the council's recommendation that 25 guineas should be withheld from his remuneration; but a letter from the Ministry of Health to the practitioner said that the Minister "takes a most serious view of your conduct towards the patient which he regards as highly reprehensible. Should such conduct occur again in the future, the Executive Council would no doubt need to consider whether your continued inclusion in the Medical List was consistent with the efficiency of the medical service."

The council agreed to the committee's suggestion that the case should be discussed jointly with the local medical committee. The council has power under paragraph 13 of the First Schedule to the National Health Service (General Medical and Pharmaceutical Services) Regulations, 1948, with the consent of the Minister of Health and after consulting the local medical committee to give notice to the patients on a practitioner's list that he is, in their opinion, not in a position to carry out his obligations under the Terms of Service.

Parliament

School Dental Service

IN the House of Commons on Nov. 26, Mr. JOHN BAIRD said that the school dental service had been one of the major headaches within the health service, though there had been some recent improvement. In 1938 it had 783 dental officers: on Jan. 1, 1952, the service reached its lowest ebb with 712 officers; in October, 1952, the figure had risen to 827. But the Minister of Health admitted that an efficient school dental service would need 2000–3000 full-time dental officers. Mr. Baird did not think there were any grounds for the optimistic view that more dentists would come into the service. The barrel had already been scraped. The only way to get further recruits would be to impose further charges on dentists in private practice, which would destroy the whole basis of the health service.

A short-term solution had been worked out by the British Dental Association which could be operated while a new priority dental service was being built. 1743 dentists had agreed to set aside some time each day to treat children in their own surgeries. In all over 10,000 hours would be available each week. The Ministry of Health had turned down this offer on the ground that it was better to treat children in clinics associated with schools. But the hard fact was that we did not have enough clinics. Mr. Baird admitted that he was not himself convinced that treatment in clinics was best. In the old days when working-class people could not afford to take their children to the dentist the school service was valuable. Nowadays under the N.H.S., he thought parents should be encouraged to bring their children to the family dentist. He looked forward to the time when the school dental service would inspect the children, but most treatment would be carried out in the general-practitioner dental service. The Ministry's second reason for refusal was that children could be treated more economically in clinics than on the scale of fees for the general dental service. He deplored the neglect of children's teeth while the local authorities and the Treasury struggled as to who should pay for the school dental service.

Miss PATRICIA HORNSBY-SMITH recapitulated the Ministry's reasons for believing that the best method of treating children was in school, or in local-authority clinics on a full-time or part-time basis.[1] She added that the Government intended to ensure the provision of increased facilities for the treatment of children through the local-authority clinics. Surely in the interests of the children, as well as the most efficient use of the dental skill available, dentists should be willing to give part-time service of even one session a week in the school clinics.

Hospitals in North-west Wales

In the House of Commons on Nov. 28 Mr. CLEDWYN HUGHES called attention to administrative difficulties in the hospital services in this area. In reply Miss HORNSBY-SMITH said that sparse and scattered population, poor communications, and the absence of any really large centres, had made difficult the organisation of hospital services in the rural area of Anglesey and Caernarvonshire. Despite repeated advertisements in the press for doctors to fill hospital posts, registrars did not easily go there. It was difficult to see what other steps could be taken—short of direction, which she was sure Mr. Hughes would not suggest. This difficulty was under discussion nationally by the medical profession as a matter of urgency. Demoting peripheral hospitals was no part of the policy of the Ministry of Health. But there must be a balance and a limit to which they could go in upgrading a very small unit, and the extent to which they could impose upon it all the specialties normally available in a large general hospital serving a greater area.

She realised that there was a serious tuberculosis problem in North Wales. Anglesey and Caernarvon had some of the worst figures in England and Wales. The waiting-list for T.B. hospitals in the area was 58, but the real shortage was not one of beds but of nurses, and there were 223 unstaffed T.B. beds.

The need for a new hospital for the Bangor area was acknowledged; and there was a suggestion that a hospital of 500 beds should be built there. The first priority for Wales had been allocated to the new teaching centre at Cardiff, and there were other rivals for second priority, but she had no doubt that the claims of Bangor stood high.

Beds for the Aged Sick

In the House of Commons on Nov. 19, Mr. H. HYND pointed out that, owing to the increasing proportion of old people in the country, there were 8800 chronic sick waiting for beds in the hospitals, and hospitals which took these patients had 3100 beds understaffed. It was often assumed that old people were either well or sick, but in practice many were in the borderland between health and sickness. Unfortunately neither the hospitals nor the county councils seemed to have the power to set up for the aged infirm homes linked with the geriatric service of the nearest hospital.

Miss HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, did not deny that there was a shortage of beds for the aged. Hospital authorities were responsible for the sick, and local authorities were responsible for those who were only in need of care and attention. Hospitals had been asked not to refuse borderline cases who were recommended by a general practitioner or a welfare officer. To make a new classification of a borderline section would not, she pointed out, provide more beds. The need for more accommodation was reflected in every part of the National Health Service. At present there were 57,000 chronic sick beds, and from a survey taken during the war it was believed that something like 80,000 beds were required. The waiting-list was 8800. Yet in 1951 there were 2000 more beds than in 1949 and the accommodation both in old people's homes and by adaptation of the old public-assistance institutions was being steadily increased. There were 3800 beds understaffed.

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[1] See *Lancet*, Nov. 29, 1952, p. 1076.

Geriatric services in hospitals had been greatly developed. No less than 40% of the so-called chronic sick could today be rendered fit for discharge from hospital, but there were not enough old people's homes and hostels to receive them. Progress had been made with long-stay annexes for those not fit enough to go to old people's homes, and the King Edward's Hospital Fund had provided capital for a number in the Metropolitan area which were working with great success. The proposal that the general practitioner should have greater authority to decide whether or not a patient should be admitted to a bed raised great difficulties. There might be many general practitioners in one area but only one hospital, and the only person who could decide the priority was the hospital superintendent. But Miss Hornsby-Smith assured members that a medical officer of health had the power and the responsibility to apply to the bed service to do all they could to find a bed for an acute case.

QUESTION TIME

Doctors Surcharge for N.H.S. Prescriptions

Mr. JAMES CARMICHAEL asked the Secretary of State for Scotland whether he was aware that doctors in Glasgow were having accounts submitted to them by the executive council for prescriptions issued to patients; who was responsible for this charge: and whether he realised that if this policy continued doctors would refuse to issue such prescriptions, with consequent suffering to patients, most of whom were suffering from tuberculosis.—Commander T. D. GALBRAITH replied: A doctor who writes a prescription under the National Health Service for a preparation that ranks as a food and not a drug is in breach of his terms of service, and is liable to repay to the executive council the cost of dispensing the prescription.

Mr. CARMICHAEL: I have evidence from doctors who have declared to the executive council that they gave the prescriptions as medicines.

Commander GALBRAITH: When selecting prescriptions which apparently relate to food the pricing bureau and the executive council are guided by advice from an expert committee, which is circulated to all doctors so that they know whether they are prescribing drugs or not.

Army Medical Services

Mr. FENNER BROCKWAY asked the Secretary of State for War what steps he was taking to ensure adequate supervision in the Army Medical Services.—Mr. ANTONY HEAD replied: Measures to improve the supply of experienced medical officers are under urgent consideration. The young National Service doctors have done a very good job and I would like to pay a tribute to them. I think the supervision is being carried out extremely well with the numbers available, though we are anxious to increase them.

Anthrax

Mr. A. C. BOSSOM asked the Minister of Agriculture whether he was aware that a great proportion of the cases of anthrax now occurring could be traced to imported feeding-stuffs which only had a certificate that they had been properly sterilised in their country of origin; if he would see that some more reliable arrangement was introduced to avoid continuance of this serious trouble; and if, in view of the fact that 73 outbreaks of anthrax were confirmed between Sept. 1 and 15, 96 from Sept. 16 to 30, and 52 from Oct. 1 to 9, he would call for an official investigation at the earliest possible moment as to the cause, so that a remedy might be devised.—Sir THOMAS DUGDALE replied: The requirement about the sterilisation of imported bones and bone products in their country of origin is confined to imports from Europe. The certificates that accompany such imports are signed on behalf of the government of the country of origin and I have no evidence that they are not reliable, or that imports received under these certificates have been a source of infection. My department is already conducting inquiries into the sources of infection of anthrax and the possibility of introducing further safeguards.

Crimes of Violence

In answer to a question Sir DAVID MAXWELL FYFE stated that the number of indictable offences involving violence to the person known to the police from January to June, 1952, and during the two preceding periods of six months was:

Offence	January–June, 1951	July–December, 1951	January–June, 1952
Murder	68	64	87
Attempts and threats to murder	97	75	93
Manslaughter, infanticide, child destruction	101	96	111
Felonious and malicious wounding	2608	2825	2788
Rape	180	155	147
Robbery with violence, &c. (section 23 (1) of the Larceny Act, 1916)	328	305	359
Robbery and assault with intent to rob (section 23 (2) and (3) of the Larceny Act, 1916)	101	66	116
	3573	3586	3701

Stomach Ulceration

Brigadier FRANK MEDLICOTT asked the Minister of Health if his attention had been drawn to the increase in the number of people suffering from stomach ulceration; and if he would make a statement as to what special researches were being undertaken to discover the reason for the increase.—Mr. MACLEOD replied: The evidence seems to be that the incidence of all forms of peptic ulcer has not increased recently and that of stomach ulceration is decreasing. Deaths from peptic ulceration have decreased in recent years. Research into causes and treatment is in progress in many centres.

Public Health

Coöperation in the Health Service

IN his presidential address to the 77th congress of the Royal Sanitary Association of Scotland on Oct. 21, Sir Andrew Davidson, chief medical officer of the Department of Health for Scotland, discussed some of the criticisms that have been made of the National Health Service. Apart from the cost of the service, he said, criticism tended to fasten on the tripartite administration of regional hospital boards, executive councils, and local authorities and on the overemphasis on the treatment services. He thought that the tripod structure arose from compromise rather than from tidiness of administration, and that the many appeals which had been for closer coöperation between the various bodies were not unreasonable.

But Sir Andrew's own view was that the particular need at the present time was for a proper understanding between individual workers—between the public-health staffs, hospital staffs, and general practitioners—and for more team-work and less isolationism. What is lacking, he said, is a clear understanding and appreciation of what the other fellow is trying to do. For example, domiciliary health care demands the coöperation of the family doctor and the public-health team, for social and medical needs are well-nigh inseparable. Many patients are admitted to hospital for social as well as medical reasons, or kept in hospital when they might be sent home if the home conditions were suitable, or made suitable. Expensive hospital treatment could then be reserved for people who need it from a strictly medical point of view.

In England Now

A Running Commentary by Peripatetic Correspondents

ONCE upon a time, for the advancement of Science, an experiment had to be performed on a pig.

A suitable pig was found at a neighbouring farm, and to ensure a quiet and peaceful passage to the laboratory it was thought that a draught of 'Bovril' laced with 'Nembutal' would prove suitable. A control draught of bovril was eagerly consumed by the pig; but it thought nothing of the mixture, and an impasse arose and the blandishments of scientists in white coats were of no avail.

The scene was watched with interest by a supposedly feeble-minded boy on loan from a local institution. Remarking "I'll show 'ee," he went to a manure heap and from it collected a boot, green with age. Borrowing a knife, he cut a small hole in the toe, advanced on the pig, and proceeded to belabour it on the snout with the boot. The pig resented this and seized the boot by the toe. The boy then relieved the chief scientist of his flask of bovril and barbitone and with the air of a conjuror poured it into the boot, whence it rapidly disappeared into the pig.

After a couple of fast turns round the stye, scattering the assembled scientists, who vaulted over the side with extraordinary agility, the pig lay down in a corner and sank into an untroubled sleep.

* * *

External examiners are often cynical men, who affect to be able to mark a candidate accurately from the first paragraph of his paper or from an inspection of his finger-nails. It is, however, clearly desirable that they should be versed in the theory and practice of examining in order that they may present a façade of judicious impartiality towards the candidate. The College of Medical Examiners and its affiliated body, the Chartered Society of Licensed Invigilators, have been founded to standardise the accomplishments of examiners in this respect. At present the college offers two diplomas: the membership enables its possessor to examine for the various qualifying degrees and diplomas, while the fellowship is necessary for examiners aspiring to higher things. It is intended shortly to institute a third diploma, that of tropical examining (D.T.E.), but the syllabus for this diploma has not yet been fully approved by the court.

The diploma of fellow is granted only for outstanding contributions to the science of examining, such as the raising of the failure-rate in the Conjoint to 80%, or the introduction of pin-striped trousers and a stand-up collar to a biochemistry viva.

The syllabus for the membership includes the theory of ambiguous questions, the elucidation of hieroglyphic writings and the Rorschach interpretation of ink blots, the effects of adrenaline on the speech centre, the use and abuse of sarcasm, and the care and retention of the mark sheet. Candidates are also required to undergo a practical and viva voce examination at which their reactions to bad spelling, dirty collars, and unshaven faces will be assessed. The following is a specimen paper:

COLLEGE OF MEDICAL EXAMINERS

PRIMARY EXAMINATION FOR THE DIPLOMA OF MEMBERSHIP

Human Anatomy

Time allowed: 3 hours. Not more than *six* questions to be attempted.

1. A candidate appears for his viva voce examination wearing spats. Outline the steps you would take to deal with the situation, giving your reasons.

2. Identify (*a*) the seraphic vein; (*b*) the abducter tubercal; (*c*) the vegetable pole; (*d*) the accessory do; (*e*) the antero-posterior surface of the ileum; (*f*) the uterine ossicles.

3. Enumerate the methods used to give the impression of immense knowledge frustrated by writer's cramp, other than the basic "Sorry, no time."

4. Illustrate the following situations by clearly labelled diagrams:

(*a*) "The bursar lying between the two joints is often fenestrated."

(*b*) "The kidney excretes the surplice."

5. Write a short essay on the ball-point pen.

6. What did the candidate have in mind when he wrote the following:

(*a*) "a capsular joint with an articulating capsule in the joint cavity."

(*b*) "these bones are concerned with maintaining body stature."

(*c*) "the uterus turns inside out and there you are."

* * *

May I confirm my fellow vintner's advice (Nov. 22) that bacteriological vintages should be allowed to mature. My own basic recipe is as follows:

Prepare a fermented sucrose broth by boiling 7 lb. of fruit or vegetable (even turnips will do) to a gallon of tap-water in an enamel breadbin. The water of evaporation is replaced, and sucrose (from the Food Ministry allocation for bees; 7 lb. per hive) added at the rate of 3 lb. to a gallon. This makes an approximately 30% solution, which, when fully fermented, gives a yield of 15% of alcohol. Deficiency of sugar, and therefore of alcohol content, encourages the contamination of the culture by an aerobic dishwater-producing organism, miscalled by the French *Fleur*, which floats on the surface of the mixture while it converts alcohol to water and CO_2. For removing suspended yeast cells, which give a cloudy appearance to a white wine, suction filtration through a Buchner funnel, or addition of gelatin solution which brings down the yeast when it precipitates, can be used. The usual protein precipitants are to be avoided.

For my first attempt I used a potato extract flavoured with orange juice (say, 6 to a gallon). At three months the orange flavour had vanished and had been replaced by pure pineapple (ethyl butyrate). A beaker of 100 ml. brought on in half an hour, in 100% of drinkers, a curious frontal headache, "right between the eyes." Control tap-water drinkers had no headache in 24 hours. In six months this toxic material had changed into a magnificent sauterne. The headaches were now normal in cranial distribution and did not show themselves until the morning after sampling, and then only if extensive trials were carried out. In a bad year for potato wine the product may be distilled into potato gin, after, of course, applying for an excise licence.

* * *

Ever since the age of 10, when I developed an enteric fever through eating, so my parents believed, polluted oysters in Brittany, I have been a passionate admirer of this fish, though rising costs have forced me to an increasingly platonic courtship.

Trial will show that the turbidity of an oyster's liquor is at once increased if a fork is inserted into the flesh, the assumption being that a severe wound causes evacuation of its alimentary tract. If this simple operation is performed and the liquor is not consumed, possibilities of infection should be lessened. I should add that the safety of British oysters is now such that this addition to the manuals on oystermanship will be chiefly valuable during travels abroad.

* * *

Stately teaching hospital of Rolls-rich forecourt,
World-wide reputation and the Ever Open Door,
With a cargo of therapists,
Iatrists, ologists,
Orthopods and psycho-boys, and two-three more.

County Council Temple of Preventive Hygiene,
Adding prophylaxis to the poor babe's woes,
With a cargo of home helps,
Visitors, officers,
Organisers, deputies, and keen M.O.s.

Overcrowded surgery in Back Street, Hoxton,
Coping with dyspepsias, bronchitises and croups,
With a cargo of backbones,
Spear-heads, lynch-pins,
Keystones, corner-stones, and front-line troops.

Letters to the Editor

HOSPITAL COSTS

SIR,—It seems to me that your leading article last week avoids a number of important issues arising from the reports of King Edward's Fund and the Nuffield Provincial Hospitals Trust. Apart from the two general recommendations—(1) to scrap the present system of accountancy, and (2) to install a system based on departments and services—there is little agreement between the two reports: for the methods of allocating and charging cost and sometimes the units to be used differ appreciably.

There is also disagreement between the Trust and the Fund on the immediate advantages of installing departmental costing systems. The Trust states that no dramatic economies can be effected because "there is no dramatic waste to be cured." The Fund states, on the other hand, that "handsome dividends in the way of economies and increased service may be secured by more effective control of expenditure." The conflict between these two statements points to a major weakness of the findings when taken jointly. If no great economy can be achieved, one must presume that the main reason for installing a uniform costing system would be its advantage to the "management"; and you yourself state there is "need to link executive and financial responsibility." It is not, however, clear how a uniform costing system will by itself have this effect in the hospital service. To a live management there is no mystery about the reasons for the present differences of cost between hospitals. To call for a comprehensive costing system to indicate these is like calling for a micrometer for measuring to the nearest foot. Nor can a costing system of itself, even if it forms part of a budgetary system, prevent hospital authorities scrambling to spend "balances in hand" and frittering money away on "short-term palliative maintenance work, pieces of equipment, furniture, and so on," before the end of the financial year. If this has been the case in the past, such authorities will not be prevented by a costing system from doing likewise again if tempted by underspending on their total approved expenditure.

The practicability of introducing that departmental or functional or standard costing has never been seriously doubted. The real problem is the value of the results in a milieu where the cost may be of secondary importance. It is difficult to avoid the conclusion that the enthusiasm of the Fund and Trust for their systems reflects the association of these bodies with the pre-1948 form of general administration of the voluntary hospitals, who were supplicants for grants. For better or worse there is now a new and unique form of administration where decisions are taken centrally by separate statutory bodies largely advised on hospital matters and local conditions by medical advisory committees. Local service may transcend purely monetary considerations; and the use of a big stick marked "costs" by the higher authorities might provoke local storms which would affect adversely the hitherto mainly successful, but admittedly loose, structure of the service.

There is at the moment no uniformity in hospital administration or medical organisation, and such uniformity is probably neither desirable nor even possible. In the circumstances it is doubtful whether the hospital service possesses the basic conditions for a uniform intricate system of costing of the sort that is no doubt necessary for an organisation whose policy is governed by the inescapable facts given in a balance-sheet and trading and profit-and-loss account.

This is not to deny the need for investigations locally into the "business" side of hospital administration; many anomalies in cost and comparative statistics call for investigation. It is, however, well to realise that there are limitations to the purely costing approach to analysis—and there may indeed be dangers if the final arbiter is a remote authority not concerned with day-to-day administration under local conditions.

Both the Fund and the Trust are too firmly rooted in the great tradition of social service to claim too much for costing in a public organisation dealing primarily with intangibles such as medical treatment and human needs. Yet their reports come perilously near to providing fuel for the extremists and ultimately for the centralist-minded.

In your leading article you refer to the dangers of uniformity, but dismiss the risk as slight compared with the apparent (sic) advantages. A special article in the *Times*,[1] welcoming these two costing investigations, said:

> "The Minister has in prospect through the development of departmental accounts in some of the hospitals, with the help of the King's Fund and the Nuffield Trust, a yard-stick which should enable him to say with considerable accuracy what the services provided by such and such a Regional Board ought to cost if they are efficiently managed."

If this is indeed the prospect, it implies eventual rationalisation with, inevitably, a measure of uniformity. This seems the only end that would justify at present the universal application of a full-scale comprehensive costing system.

London, S.W.6. GORDON MCLACHLAN.

THE UNIDENTIFIED DRUG

SIR,—Your annotation on Accidental Poisoning in Children (Nov. 22) draws attention to the difficulties in treatment if the nature and quantity of the poison are unknown. It is not generally realised, until the information is required in an emergency, that drugs supplied on the National Health Service prescription form E.C.10 lose their identity when they pass into the hands of the patient. In some instances, of course, a distinctive colour, shape, or smell may provide a clue to the identity of a drug; but without such a clue the rapid identification of the drug may be virtually impossible.

It is by no means rare for a supply of the offending drug to be sent with the patient admitted to hospital for suspected poisoning. The drug may be in a properly labelled container bearing the name and address of the pharmacist from whom it was obtained; but if the pharmacist is asked to identify the drug, he will be unable to do so unless he happens to remember what was dispensed for the patient in question. The pharmacist is required to record transactions of dangerous drugs, but with the N.H.S. prescriptions he is not required to keep a record of any other drug. At the end of each month the E.C.10 prescription forms (his only record) are sent in bulk to a pricing bureau.

The pricing bureau in due course, during working hours, may be able to trace a single prescription; but it is not empowered to disclose the nature of the drug without the authority of the local executive council. The unknown drug may thus be known, but not to those who need the vital information.

The Ministry of Health have been informed of this curious anomaly, and no doubt permission will be given to pricing bureaux to disclose information in such emergencies. But much more than this is required: E.C.10 forms should be issued in duplicate, like the N.H.I. prescription forms, so that a facsimile of every prescription would be retained by the pharmacist, for tracing and naming the unknown drug.

W. TRILLWOOD
Director of pharmaceutical services.

United Oxford Hospitals.

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[1] *Times*, August 23, 1950.

AGGLUTINATION TEST FOR RHEUMATOID ARTHRITIS

SIR,—In their article in your issue of Feb. 23 (p. 389) Dr. Hobson and Dr. Gorrill suggested that there is a close relation between the factor in normal serum responsible for the agglutination of sensitised red cells and the fourth component (C'4) of complement. Both are destroyed by ammonia and hydrazine, and both are increased in serum from patients with rheumatoid arthritis. However, Dr. Ball (March 22, p. 614) remarked that, provided the concentration of the ammonia is not too high, the C'4 can be destroyed, whereas the agglutinating factor remains unaffected.

We have found that the same holds good for hydrazine. We performed the reaction with human red cells (group O),[1] sensitised with rabbit amboceptor (half the minimum agglutinating dose). Using human cells has the advantage that absorption of heterophil antibody is unnecessary. Wager[2] has shown that sensitised human red cells can give positive agglutination with rheumatoid-arthritis serum, in the same way as sheep cells.

Adding 0·1 ml. of 0·16*M* solution of hydrazine to 1 ml. of serum[3] with a positive Waaler-Rose test and incubating the mixture for one hour at 37°C destroys the lytic activity, whereas the agglutinating activity of the serum is only slightly affected. It is remarkable that the influence of hydrazine on the agglutination reaction is seen only where the serum concentration, and consequently the hydrazine concentration, is greatest—in the tubes with serum-dilutions 1:4, 1:8, 1:16. In the higher dilutions of the serum the reaction is just as strong as in the control series without hydrazine. Consequently the titre of the serum is affected little or not at all. The first tubes show a somewhat weakened reaction when the serum is strongly positive; with low titres the reaction may become completely negative (see table I).

These results suggest that hydrazine may influence the sensitised red cells rather than the agglutinating factor of the serum. To verify this supposition, a negative serum of a healthy person was treated with hydrazine as described above. The Waaler-Rose test was carried out, and was, of course, negative. The cells from each tube were then centrifuged, washed, and again suspended in 0·5 ml. of saline. To each tube 0·5 ml. of a positive serum was added in a dilution which had previously produced a distinct reaction. In the tubes where the original serum concentration and consequently the hydrazine concentration had been greatest, the positive serum produced no agglutination, whereas in the originally higher dilutions positive reactions appeared (see table I).

TABLE I—AGGLUTINATION OF SENSITISED RED CELLS BY DIFFERENT DILUTIONS OF VARIOUS SERA

Serum dilutions	Agglutination of sensitised red cells						Red cells from experiment A resuspended in positive serum	Red cells from experiment B resuspended in positive serum
	Positive serum		Positive serum*		Negative serum			
	Treated with hydrazine	Untreated	Treated with hydrazine	Untreated	Treated with hydrazine (experiment A)	Untreated (experiment B)		
1 : 4	±	++	−	+	−	−	−	++
1 : 8	±	++	±?	+	−	−	−	++
1 : 16	±	+	±?	+	−	−	−?	++
1 : 32	±	±	±?	±?	−	−	±?	++
1 : 64	−	±	−	±?	−	−	±	++
1 : 128	−	−	−	−	−	−	±	++
1 : 256	−	−	−	−	−	−	+	++

*In this case the reaction was performed with sensitised sheep's red cells.

The next step was the investigation of sensitised red cells brought into contact with varying quantities of hydrazine. To tubes containing 7 ml. of a suspension of sensitised human group-O red cells 1·4, 0·7, 0·35, 0·14, 0·07, and 0·02 ml. of 0·16*M* hydrazine solution were added respectively. The tubes were incubated at 37°C for one hour. The cells in the first three tubes changed to a brown colour after a short time. The red cells were centrifuged, washed twice with saline, and added to a known-positive serum (see table II).

The sensitised human red cells pretreated with hydrazine in concentrations of 1·4, 0·7, and 0·35 ml. per 7 ml. were not agglutinated by a positive Waaler-Rose serum. As the concentration decreases, the effect of hydrazine on the red cell diminishes; and agglutination by the positive serum conforms more and more to the pattern visible in the untreated control.

TABLE II—AGGLUTINATION OF SENSITISED HUMAN RED CELLS TREATED WITH DECREASING AMOUNTS OF HYDRAZINE

Dilutions of positive serum	Agglutination of sensitised group-O red cells						
	Amount of hydrazine used (ml. of 0·16*M* solution per 7 ml. of cell suspension)						
	1·4	0·7	0·35	0·14	0·07	0·02	0
1 : 16	−	−	−?	+	++	+++	+++
1 : 32	−	−	−?	+	++	+++	+++
1 : 64	−	−	−	±?	±	+++	+++
1 : 128	−	−	−	−	−?	±?	++
1 : 256	−	−	−	−	−	−	±?
1 : 512	−	−	−	−	−	−	−

It seems probable therefore that the inhibition of agglutination by hydrazine in the Waaler-Rose test is due to an influence of this compound on the sensitised red cell.

No difference was observed in the action of guineapig-complement on untreated and hydrazine-treated sensitised red cells.

On the whole, therefore, it seems unlikely that the agglutinating factor in rheumatoid serum is identical with the fourth component of complement.

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F. WESTENDORP BOERMA
H. H. COHEN.

THE NOTIFICATION OF DISEASE

SIR,—In his article (Oct. 11) Dr. Irvine referred to the need for extending notification to include some non-infectious conditions. This is the one subject which few would deny that the medical officer of health can call his very own, and yet only one medical officer of health has written to comment on Dr. Irvine's views.

The problem of notification and prevention of disease is complicated by: (1) the difficulty of maintaining the local health authorities' interest in the prevention of disease without the stimulus of their bearing the cost of, or the satisfaction from, medical treatment; and (2) the hospital boards' inherent reluctance to be interested in prevention, which can only result in the reduction of professional and administrative empires. My only criticism, if that is the word, of Dr. Irvine's paper is that today the use of notification as an essential prelude to the control of disease should not be limited to immediate control in the form of direct action as practised by the health-department staff.

If the medical officer of health of the future is to be continuously aware of the state of the public health, he must be able to evaluate the medical, social, and economic problems of many diseases. He cannot do this without the figures. This work would not require an increase of the public-health staff, as immediate visits would not be made, but rather a study by the medical officer of health according to a well thought out plan and only giving results after some years.

In the case of cancer of the lung we are obviously in the early stages of an epidemic process of unknown duration; and, as with other diseases, the most suitable time to study cause is during an epidemic phase. As history shows, the causative factors can be postulated with some accuracy by epidemiological study, and some degree of control achieved without knowing the specific cause. There is a case for the notification of many conditions; but cancer of the lung is an urgent public-health problem, and if it were tackled in this way we would have the greatest chance of achieving some control.

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[1] The human red cells were stored in modified Alsever solution for 10 to 12 days before use.
[2] Wager, O. Thesis, University of Helsinki, 1950.
[3] Ecker, E. E., Pillemer, L., Seifter S *J. Immunol.* 1943 47 181.

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C. W. DIXON.

BOVINE TUBERCULOSIS AND HUMAN TUBERCULOSIS

SIR,—In a letter which you published a year ago [1] I expressed the opinion that eradication of tuberculosis from cattle is leading to an increased incidence of pulmonary tuberculosis in man. In support of this opinion I presented figures showing that in Scottish counties where more than 50% of the dairy herds were attested (i.e., free from reaction to tuberculin in three successive tests) the incidence of pulmonary tuberculosis had risen. By contrast, in Scottish counties where less than 16·5% of the herds were attested the incidence had fallen.

In assessing this evidence I have now had the help of the Scientific Computing Service Ltd., who have related my figures to the populations of the counties during the relevant periods and have recast my tables as shown below. It should be noted that the Attested Cattle scheme began in 1936.

Commenting on the figures, the Scientific Computing Service point out that the notifications of pulmonary tuberculosis per 100,000 population after the introduction of the scheme were markedly higher in the counties where a large proportion of the dairy herds were attested: "the difference was found to be highly significant, as was the correlation coefficient (*r = 0·58 with 20 degrees* of freedom) between the percentage increase notifications and the percentage of attestation." They go on to say:

SCOTLAND (COUNTIES WHERE MORE THAN 50% OF THE DAIRY HERDS WERE ATTESTED)

County	Years	Notifications of pulmonary tuberculosis		Years	Notifications of pulmonary tuberculosis		Increase or decrease of notifications per 100,000 of population
		No. (per annum)	Per 100,000 of population		No. (per annum)	Per 100,000 of population	
Lanark ..	1920–24	2369	31	1946–50	3153	39	+ 8
West Lothian	1925–29	155	38	1946–50	694	157	+19
Peebles ..	1920–24	39	51	1946–50	83	109	+58
Ayrshire ..	1935–39	890	62	1945–49	1215	76	+14
Wigtown ..	1920–24	56	36	1946–50	130	82	+46
Dumbarton ..	1920–24	399	53	1946–50	534	65	+14
Renfrew ..	1930–34	524	36	1946–50	1017	63	+27
Burgh of Glasgow..	1930–34	139	2	1946–50	222	3	+ 1
Kirkcudbright	1920–24	156	84	1946–50	153	99	+15
Perth and Kinross..	1930–34	261	41	1946–50	348	51	+10
Zetland ..	1926–30	236	220	1946–50	110	114	−106

SCOTLAND (COUNTIES WHERE LESS THAN 16·5% OF THE DAIRY HERDS WERE ATTESTED)

County	Years	Notifications of pulmonary tuberculosis		Years	Notifications of pulmonary tuberculosis		Increase or decrease of notifications per 100,000 of population
		No. (per annum)	Per 100,000 of population		No. (per annum)	Per 100,000 of population	
Kincardine ..	1920–24	126	60	1946–50	49	21	−39
Ross and Cromarty..	1927–31	561	179	1946–50	398	132	−47
Sutherland ..	1920–24	108	121	1946–50	66	97	−24
Berwick ..	1920–24	184	130	1946–50	106	85	−45
Caithness ..	1920–24	93	66	1946–50	91	80	+14
Roxburgh ..	1920–24	283	126	1946–50	165	72	−54
Banff ..	1920–24	232	81	1946–50	119	47	−34
Aberdeen ..	1920–24	1210	80	1946–50	322	21	−59
Inverness County..	1931–35	353	86	1946–50	353	83	− 3
Inverness Burgh..	1925–29	134	114	1946–50	140	100	−14
Perth ..	1920–24	549	87	1925–29	324	51	−36

> "In the above results each county *has of necessity* been considered as an independent unit. This is only justified if the type of milk consumed in the counties considered is not greatly upset by the flow of milk between counties. However, unless this flow of milk is considerable—and even then its effects may cancel out—it is not likely to upset the above findings."

They add that "if the policy of attestation was accompanied by other measures which could affect the number of notifications of pulmonary tuberculosis—for example, a greater drive to detect tuberculosis in the high-attested than in the low-attested cattle counties—this itself could explain the trends in the Scottish figures." But they agree that, if their reservation and their alternative explanation can be ruled out, the data reproduced in the tables well support my thesis that the policy of attestation has actually led to an increase in pulmonary notifications.

High Wycombe.
L. PITCHER.

DENTAL TREATMENT OF CHILDREN

SIR,—Undoubtedly "wastage" does occur in the New Zealand school dental nurses scheme, since a proportion of dental nurses leave the service a few years after completing their training—*often before the cost* of that training has been justified. If we introduce dental ancillaries in this country and recruit mainly women for training, we may experience a similar economic loss. No-one can possibly say in advance, however, whether the degree of "wastage" would be as great as in New Zealand; and it could, in any case, be reduced by recruiting men as well as women for training.

This kind of economic loss is inevitable whenever women are trained for skilled work, and it applies to the training of women as dental surgeons with even greater force than to their employment as dental ancillaries. Women dentists usually retire upon marriage and the *loss to the community* is greater, since their training has been so much more expensive than would be that of an ancillary. Had Mr. Rosenstiel any experience of the very real problem of "wastage" of women dentists from the school service, for example, he might be less tempted to dismiss my argument as mere "shadow-boxing" (Nov. 29, p. 1083).

Mr. Rosenstiel contends that it is "an established fact that the high wastage factor in the New Zealand school dental nurses scheme nullifies the advantage of short training." *To whose satisfaction*, one wonders, has this "fact" been "established"? *If it had been established* to the satisfaction of public *opinion in* New Zealand, presumably the scheme would have been wound up long ago and some other method of solving the problem of children's dental health would have been tried in its place. In fact, of course, the dental nurses scheme there has been expanding continuously throughout its thirty years' existence, and it is hoped soon to extend its benefits to adolescents who have been cared for by the *dental nurses throughout* their school careers.

Evidently the New Zealanders have found they can only have a children's dental service worthy of the name when the dental profession is supplemented by ancillaries, and if this method entails a degree of "wastage" the price has to be paid for the sake of the nation's health.

There are twice as many qualified dentists in New Zealand, in proportion *to* the size of the population, as there are in this country, which gives some measure of the shortage of dentists from which we suffer. If the dental health of the United Kingdom is not much better

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1. *Lancet*; 1951, ii, 786.

than that of the population of New Zealand (it is difficult to believe that it can be, after so many years of neglect), the dental profession here could be doubled in size and we should still need to supplement it with ancillaries to have a school dental service as comprehensive as that in New Zealand.

There are, of course, many real problems associated with the training and employment of dental ancillaries. If we, in this country, do not always feel that the solution reached in the New Zealand scheme best suits our own conditions, at least the experience gained there shows that the problems themselves are not insoluble.

SENIOR SCHOOL DENTAL OFFICER.

REACTION TO PROCAINE

SIR,—When using procaine in the treatment of muscular rheumatism there is always a lurking fear of procaine sensitivity, an extreme example of which was described by Dr. Penny (Nov. 1). This can be most alarming. Even if there is no immediate reaction, patients usually complain of an access of pain lasting several days before relief ensues. The investigation described below was originally started with a view to finding an effective substitute for procaine.

Treatment of muscular rheumatism by the injection of myalgic spots is entirely empirical since we do not yet know their pathology. On the assumption that a local ischæmic area might be the cause of pain, a minute amount of a vasodilator, 'Trafuril,' was injected and was found to act just as well as procaine. It seemed time to initiate a carefully controlled experiment. The first step was to establish the effect, if any, in a control series injected with physiological saline. To my surprise this seemed to have just as good an effect as either procaine or trafuril.

Dr. Harry Coke kindly provided me with a numbered series of ampoules containing either ½% procaine or physiological saline. From time to time as the ampoules were used and their effect recorded, the key to the series was consulted by an independent observer and the results in each case allocated. The observations were entirely objective, no notice whatever being taken of subjective response.

The technique was as follows:

The presence of a myalgic spot was assumed when on deep digital pressure the patient winced. After cleansing the skin the position was marked with ink and the syringe filled from a numbered ampoule. The needle of the syringe was touched with an indelible dye so that there could be no mistake as to the position of the puncture. At each puncture fresh dye was applied to the needle.

To find the myalgic spot the needle point was used as a probe. When the patient winced a fractional amount (0·1–0·2 ml.) of the fluid was pushed home. Usually further probing from the same spot disclosed one or two more tender points, which were treated likewise. On the record, however, injections through one point in the skin counted as one. The needle was then withdrawn. If the injections had been properly carried out, further pressure on the point of entry did not produce a wince. Other myalgic spots were then sought and treated in exactly the same way.

A week or a fortnight later the patient was seen again and pressure applied to the areas marked with the dye. If there was no wince on pressure at the spot or within 1 in., the result was class I. If a wince could be produced within 1 in. the result was class II. Where a wince occurred as before the injection, the result was class III. The figures were then transferred to their respective columns.

EFFECT IN 100 CASES WHERE MYALGIC SPOTS WERE INJECTED WITH PROCAINE OR SALINE OR WERE NEEDLED

—	Procaine	Saline	Needle alone
No. of cases	44	56	16
No. of myalgic spots	161	162	16
Class I	113	108	0
Class II	21	22	1
Class III	27	32	15

It soon became clear that sodium chloride and procaine were equally effective; so a further series of controls was desirable. 16 myalgic spots were "needled" without introducing any fluid. Here also the wince was abolished, but the effect was transient. All cases were class III, except 1 doubtful class II, when examined after a week. The results in 100 cases are shown in the accompanying table.

This experiment does not throw much light on the problem beyond establishing that the relief afforded by injections of procaine is not, as has been assumed, due to its anæsthetic property. Two advantages of injecting saline are the absence of any risk of sensitivity or of a local reaction with increased pain.

London, W.1. H. WARREN CROWE.

REVIEW OF MEDICAL ESTABLISHMENTS

SIR,—There are times when the most reticent of us are bound to be drawn into the correspondence columns. The letter which was penned by Sir Russell Brain (Nov. 22) is one such occasion. He is obviously correct in his righteous indignation, and few amongst your readers who have read the contents, and between the lines, will fail to be moved, as he undoubtedly is. What I find most interesting in his letter is his reference to the implied promise of security of tenure to consultants, &c.

Sir Russell is, of course, in a difficult position. Yet he cannot be absolved from all blame for the present consequences of the misdeeds of his immediate predecessors. A good deal of criticism went, and still goes, unheeded. Some of us maintain that the Joint Consultants and Specialists Committee represents only the colleges and a small party of interested members of the teaching schools. There must, however, be other members of the staffs of the teaching schools who, in the aloofness of their academic ivory towers, must now realise that they have been isolated. They, too, must bear their share of the burden of guilt.

The Terms and Conditions of Service were first turned down but within the short space of one week, and without reference to the periphery for their views, were accepted by the self-appointed spokesmen. I claim that in this area alone (western area of the South-west Metropolitan Region) was some attempt made at cohesive action to call a halt to this autocratic method. I warned my colleagues at that time that, if they did not make a stand over the terms of service, the whip of bureaucracy would one day hit them hard, and that their cries would go unheeded.

My prognostications appear to have been correct. Sir Russell must surely know that the committee of which he is chairman is not a joint body; there is no equitable representation of the consultants outside the teaching hospitals. He must also be aware that in the provinces resentment and frustration are widespread among consultants. He has a great opportunity now of infusing a new spirit of coöperation by the simple process of creating a more democratic representation on the so-called Joint Committee. I am satisfied that this is a necessary prerequisite for a successful outcome to any complaints, of which lack of "security of tenure" is only one.

Bournemouth. ARNOLD CLARK.

SIR,—The letter from Sir Russell Brain reveals a situation which is ominous for all those holders of posts in registrar grades who had hoped to become consultants. The Ministry's letter to boards of governors must bring to a standstill any plans for the expansion of the consultant service, and although not so directed the regional boards cannot fail to have observed the trend of ideas.

To the average senior registrar approaching the end of his four-year term it had recently become clear that his only real chance of a senior appointment lay in the expansion of the consultant service. When the North-west Metropolitan Regional Hospital Board found it possible to create some 40 new posts (as announced in the middle of this year) it seemed that the way was clear and that other regions might follow suit. The new posts were created to close the gap in the hospital service caused by the reduction in senior-registrar establishment and it seems to us that similar action is needed elsewhere. Now instead comes a standstill order, and to the naïve eye of a registrar it appears that the Ministry are alarmed by the initiative of the North-west Metropolitan Board and are taking steps to avoid the extension of their fair and far-sighted policy to other areas.

To the Registrars Group it has always appeared that the Ministry have either disclaimed responsibility for their problems or misjudged their size. At the present time the Joint Committee are in the middle of discussions with the Ministry, and one of their main points has been the need for expansion of the consultant service. This new instruction reveals either a cynical disregard for the Joint Committee—and those whom they represent—or else a major degree of incoördination between the departments which decide and the departments which discuss.

It is to be hoped that Sir Russell's views will have the widest possible support, and that employing authorities will not be deterred from making the additions to consultant staffs that will be needed when their senior registrars go. Registrars everywhere will support Sir Russell and the Joint Committee in their efforts to secure a fair solution to the registrar problem.

R. M. FORRESTER

Chairman, Registrars Group,
British Medical Association.

SEASONAL VARIATIONS OF ALCOHOLISM

SIR,—Such is the difficulty of assessing alcoholism in statistical terms that the yearly number of convictions for drunkenness has to serve as evidence. *Offences of Drunkenness, 1951*,[1] states that the number of offences proved was 51,932 in England and 1744 in Wales. The report also gives the number of offences by month; this is welcome since figures bearing on seasonal variations of alcoholism are hard to come by, although they abound for suicide.

In a previous communication,[2] discussing the monthly distribution of 9601 first admissions to institutions for the alcoholic in Zürich during 1912–44, it was shown that such admissions were most numerous in June and least numerous in October. Although admissions for alcoholism and convictions for drunkenness are not the same thing, it is tempting to compare their seasonal trends. This is done in the accompanying table. It shows that with the exception of October, November, and, notably, December, the seasonal trend is very similar. Offences of drunkenness were most numerous in July in England and in Wales; and least frequent in February in England, and in December in Wales. The fact that for the festival month of December offences of drunkenness rank second in number (England), while admissions for alcoholism rank sixth (Zürich), is interesting to speculate on.

COMPARISON, BY MONTHLY DISTRIBUTION, OF 9601 ADMISSIONS FOR ALCOHOLISM IN ZÜRICH DURING THE YEARS 1912–44 WITH 51,932 OFFENCES OF DRUNKENNESS IN ENGLAND AND 1744 IN WALES DURING THE YEAR 1951

Month	Admissions, 1912–44 (%)	Offences, 1951	
		England	Wales
January	8·8	7·0	6·6
February ..	8·6	*6·7*	7·4
March	9·5	8·2	7·3
April	8·1	7·6	8·7
May	8·7	8·6	9·7
June	**9·6**	8·9	9·3
July	8·1	**9·8**	**11·7**
August	7·6	9·1	10·9
September ..	7·4	8·4	8·4
October	*7·2*	9·0	8·3
November ..	8·2	7·6	6·1
December ..	8·2	9·2	*5·6*

The figures for the months with most admissions or offences are in bold type; those for the months with least admissions, &c., are in italics.

Despite their inherent smallness, the figures for Wales are given for comparison; with alcoholism, we have to take our figures where we find them. With minor exceptions the seasonal trend in Wales is similar to that in England. A pronounced discrepancy, however, is shown for the month of December. Whether this has reasons of its own, or is merely accidental (considering the relative smallness of the figures for Wales), cannot be answered here.

Isleworth, Middlesex. H. PULLAR-STRECKER.

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1. Offences of Drunkenness, 1951. Cmd. 8685. H.M. Stationery Office, 1952.
2. Pullar-Strecker, H. *Lancet*, 1952, i, 555.

SKIN LESIONS OF ACUTE LUPUS ERYTHEMATOSUS AND ACUTE X-RAY DERMATITIS

SIR,—Some workers, including Ungar and Warren,[1] have held that radiation lesions of the skin depend largely on changes in the underlying dermis. A similar view of the action of carcinogenic hydrocarbons on the epidermis was first advanced by Orr.[2] Devik[3] states that bombardment of the skin by alpha particles produces only slight damage to the epidermis of mice, even when extremely heavy doses are given, and that this is probably because the alpha particles do not reach the capillaries of the dermis.

While studying the development of acute skin lesions in mice exposed to a single focal dose of 3000 or 4000r of 60 kV X rays, it was noticed that the histological changes in the radiated skin closely resembled those accepted as being characteristic of the skin lesions of acute lupus erythematosus. The published descriptions of the histology of acute X-ray dermatitis in man provide a similar correlation of the skin changes in the two conditions. In addition to purely histological resemblances, certain similarities also exist in the behaviour of the lesions. The various features of resemblance that may occur in the course of the two conditions may be summarised as follows:

EPIDERMAL CHANGES

(1) Hyperkeratosis with hyperkeratotic plugging of follicles.

(2) Atrophy of epidermis with vacuolation degeneration of basal cell layer. Formation of intra-epidermal and sub-epidermal vesicles. Degeneration of basal appendages and follicles, with depilation.

(3) Pigmentation of epidermis.

DERMAL CHANGES

(1) Swelling, fragmentation, and fibrinoid degeneration of collagen fibres. Metachromatic staining of ground substance.

(2) Destruction of elastic tissue in areas of severe reaction.

(3) Nuclear pyknosis and degeneration of fibroblasts.

(4) Inflammatory cellular infiltration of slight degree in proportion to degeneration of tissue involved.

(5) Intense hyperæmia and telangiectasia of small vessels; fibrinoid degeneration of arteriolar walls has been described in the skin in lupus erythematosus, and may also occasionally be observed in X-ray lesions.

SIMILARITIES IN BEHAVIOUR OF LESIONS

(1) Exacerbation by sunlight.

(2) Lesions of acute lupus erythematosus are suppressed by cortisone. Acute X-ray dermatitis may be similarly suppressed.[4]

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1. Ungar, J. jun., Warren, S. *Arch. Path.* 1937, 23, 299.
2. Orr, J. W. *J. Path. Bact.* 1938, 46, 495.
3. Devik, F. *Acta radiol., Stockh.* 1951, 35, 119.
4. Marshall, A. H. E. 1952 (in the press).

(3) Malignant change is rare or unknown following acute upus erythematosus, and is very rare following a single acute -ray lesion. In the chronic skin lesions of the two conditions, owever, malignant change may take place.

Some of the changes given above are also seen in nimals in the early skin reaction following painting with arcinogenic hydrocarbons.

It is clear that caution is needed in the interpretation f these similarities. No single change given above is athognomonic of lupus erythematosus or of acute X-ray dermatitis. As Klemperer[5] points out, fibrinoid ecrosis of collagen is not peculiar to the group f "collagen" diseases, or to the lesions of hypersensitive tates, but may be produced by various agents, including imple mechanical trauma. The same lack of specificity might be adduced against the action of cortisone in the wo conditions. The existence, however, of a correlation etween some of the separate lesions and characteristics f the two conditions suggests the possibility of a basic imilarity of the pathological processes involved. In this onnection it is possible that lupus erythematosus is ot the only "collagen" disease affecting the skin that esembles radiation lesions, since the pathological changes n scleroderma may possess a considerable resemblance o those of the rare "post-radiation sclerosis."

Any similarity between the pathological processes in acute lupus erythematosus and X-ray lesions probably consists in the infliction of a similar type of damage on the collagen and ground substance of the dermis, although the agents by which the damage is produced in the two conditions may be quite unrelated. This hypothesis implies that the acute degenerative change in the cells of the epidermis, and possibly in other elements of the dermis, following exposure to X rays is mainly secondary to the primary collagen lesion, a view accepted by some workers in the case of the similar changes in acute lupus erythematosus. Whether such a concept of radiation damage could apply to other tissues than the skin requires further investigation, but clearly does not exclude the occurrence of direct cellular damage in such sensitive tissues as the bone-marrow and germinal epithelium.

In view of the commonly accepted concept of radio-equivalence between chemical carcinogens and ionising radiation, such a theory of radiation damage might also be applicable to experimental skin carcinogenesis.

Fibiger Laboratory, University
Institute of Pathological Anatomy,
Copenhagen, Denmark.

A. H. E. MARSHALL.

INTUSSUSCEPTION DUE TO ECTOPIC PANCREATIC TISSUE

SIR,—Mr. Kitchin's account (Nov. 15) of an intussusception in a 6-year-old girl caused by ectopic pancreatic tissue at the site where a Meckel's diverticulum is usually found is extremely interesting but by no means unique.

Pancreatic tissue may in fact be found in a Meckel's diverticulum,[6] and no less than 14 examples of this had been reported by 1934.[7] As long ago as 1904 Bize[8] operated on a girl, also 6 years old, and found an intussusception caused by a diverticulum containing pancreatic tissue. He suggested that the diverticulum was not of the Meckel's type but due to traction by the tumour.

The clinical history in Mr. Kitchin's case is typical of that in cases of an intussusception which starts by invagination of a Meckel's diverticulum—a history clearly described by Harkins.[9] This can be distinguished from the common variety of intussusception because it occurs in older patients, a history of previous attacks is common, the course is milder until the major illness, vomiting is more intense, and if a mass is palpable at all it is more apt to be on the right side.

Mr. Kitchin is to be congratulated on his excellent result in a frequently lethal condition.

King's College Hospital,
London, S.E.5.

SELWYN TAYLOR.

ANÆSTHESIA FOR TONSILLECTOMY IN CHILDREN

SIR,—There must be few anæsthetists of experience who would not support Dr. Bullough in his plea (Nov. 22) for consideration for the feelings of children who are to undergo tonsillectomy or, for that matter, any other operation. Many, however, will question the wisdom of taking to the operating-theatre a child fortified only by atropine.

Both methods described by Dr. Bullough are undoubtedly less unpleasant than induction with ethyl chloride. I use one or other of them myself to anæsthetise conscious children. This is rarely necessary, because for the past six years I have employed rectal premedication —formerly with paraldehyde but now with thiopentone. Both have been satisfactory; but thiopentone, being given in smaller bulk, is the easier to administer. Subsequently anæsthesia is induced with nitrous oxide, oxygen, and ether, in much the same way as Dr. Bullough describes. The only disadvantage I have encountered is that now and again the child parts with some of the drug. When this happens the child is not unconscious, but is nearly always so sleepy that he is very easily anæsthetised and remembers little or nothing of the proceedings. Even should the whole dose be returned the position is no worse than that when Dr. Bullough's routine is followed.

Dr. Bullough states that the child's only recollection of his visit to the theatre is the prick of a needle. I find it hard to believe that this is so; and surely children do not often accept the prick of the needle so willingly as Dr. Bullough suggests. Would it not be even better if the child were to have no recollection at all of his visit?

Sutton, Surrey.

JOHN H. WILLIS.

SIR,—Dr. Bullough is to be congratulated on his excellent article on intravenous thiopentone for the induction of anæsthesia for tonsillectomy in children.

I have been using intravenous thiopentone for induction of anæsthesia in children where there has been no premedication other than atropine, with so far no untoward results, in a variety of cases. I have never used an amount greater than that required to produce unconsciousness. I have usually given a $2^1/_2$% solution to children aged 4–6.

The terror which induction of anæsthesia can produce in fully conscious children is illustrated by the following case.

> An Army officer, aged 23, subsequently decorated for gallantry in the field, refused to have an anæsthetic for removal of two ingrowing toenails. He was warned that it was a painful procedure, but insisted that it was preferable to losing consciousness. He retained vivid and terrifying recollections of induction of anæsthesia ten years previously. He insisted that severe pain was preferable to what he described as "that ghastly feeling of suffocation."

Wokingham, Berkshire.

MARGARET JOAD.

SIR,—I have been using the technique described by Dr. Bullough since early 1949. During this period some 500 cases, in patients aged 3–12, have been covered, in association with five different surgical colleagues.

True laryngospasm has not been encountered. I have not noticed that this method has much effect on operative bleeding, which seems to vary a good deal between one operator and another. Most of the children have been surprisingly coöperative; and postoperatively

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5. Klemperer, P. *Ann. intern. Med.* 1948, 28, 1.
6. Taylor, S. *Lancet*, 1947, ii, 786.
7. Hunt, V. C., Bonesteel, H. T. S. *Arch. Surg.* 1934, 28, 425.
8. Bize. *Rev. Orthopéd.* 1904, 5, 149.
9. Harkins, H. N. *Ann. Surg.* 1933, 98, 1070.

the tendency to "climb the wall," as with medium-acting preoperative barbiturates, is absent—an important consideration with present-day shortage of nurses.

I can strongly recommend the technique.

Maidstone. A. W. H. Ashbery.

CAUSE AND TREATMENT OF LEG ULCERS

Sir,—Dr. Anning's interesting article (Oct. 25) on the ætiology of "varicose" ulceration has caused the usual divergence of opinion regarding this all too common complaint. There are those who are blaming the superficial venous system and those who lay the onus on blockages and valvular defects of the deep veins of the leg.

As a contribution to this argument I would like to suggest that the majority of ulcers have not one but many antecedent causes. Incompetence of the valves and varicosities of the superficial venous system are usually present in association with deep vein damage. In addition, superadded factors are often present—to quote but a few, fungoid infection, lymphatic obstruction, obesity, or anæmia. When considering treatment all these factors must be remembered and the appropriate therapy applied to each and every one of them.

London, W.1. R. Rowden Foote.

ADRENOCORTICOTROPIC ACTIVITY AND DIABETES IN ACROMEGALY

Sir,—In a leading article[1] you mentioned, that in animals A.C.T.H. potentiates the diabetogenic action of the growth hormone. In man overproduction of the growth hormone alone does not produce diabetes. Coggeshall and Root,[2] in a follow-up of 153 cases of acromegaly, found that the incidence of glycosuria was 36% and of diabetes only 17%. The majority of acromegalic patients do not have diabetes, even in the active phase of the disease.

Last year we studied in 8 acromegalic patients and in 2 patients with gigantism the adrenocorticotropic activity in relation to the carbohydrate metabolism. We found that of the 10 patients, who were examined by the modified Thorn test,[3] 7 showed diminished adrenocorticotropic activity. These 7 patients with a negative eosinopenic response had a normal or low sugar-tolerance curve, while the 2 acromegalic patients with a normal Thorn test were diabetic. In the 3rd acromegalic patient with diabetes the test was not performed, because the illness was severe. This case eventually came to necropsy where we found, in addition to a greatly enlarged hypophysis (4·1 g), enlarged adrenal glands. The adrenals weighed 18·7 + 14·5 = 33·2 g.; and histologically they showed mainly hyperplasia of the zona fasciculata.

In our series overproduction of the growth hormone gave rise to glycosuria only in the cases where production of A.C.T.H. was unimpaired. Overaction of the growth-hormone-producing cells may suppress production of A.C.T.H. either directly or indirectly by pressure of the eosinophilic adenoma on the hypothalamus. The variable course of the diabetes in acromegalic patients may be connected with changes in the influence of the eosinophilic adenoma on the production of A.C.T.H. Daughaday et al.[4] determined the urinary excretion of the free corticosteroids and 17-ketosteroids of an acromegalic patient with diabetes. The excretion of these substances —which reflects also the functional activity of the adrenal cortex—increased with the severity of the diabetes, while during remissions it decreased to a subnormal value.

The findings of Reid[5] and Engel et al.[6] in animals corroborate our hypothesis that in man overproduction of growth hormone produces diabetes only where production of A.C.T.H. is not suppressed. According to our findings, in most cases of acromegaly production of A.C.T.H. is decreased; and this may be one reason why not every patient with acromegaly or gigantism is diabetic.

I. Bach
E. Gyulai
Á. Virányi

Municipal Hospital,
Budapest.

PITUITARY GROWTH HORMONE

Sir,—I read with interest the article by Dr. Black and his colleagues.[7]

From experience of pituitary transplantation in a large number of cases[8] we have invented 'Proserin' (transplantation injection of pituitary gland). The effect of two injections of proserin 6–8 mg. per kg. body-weight persists for about five months. In adults one injection of 40 mg. suffices to cure alopecia areata.

I think that Wilhelmi's growth hormone[9] is too weak to promote growth in man. Daily administration of 60–100 mg. is a very large dosage compared with that of proserin. We have had no case of hypo-insulinism with treatment by proserin in our very small dosage. The growth-promoting mechanism cannot be explained by a pure chemical substance. Only the operation of many factors will set this mechanism in action. This is the reason why a pure hormone has to be given in much larger doses than a complex preparation.

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Faculty of Medicine,
Kyushu University, Japan.

Syuzô Naka.

DOWNWARD TREND IN BREAST-CANCER MORTALITY?

Sir,—The letter from Professor McKinnon last week attacks me by name in nearly every paragraph, and so perhaps some reply is due.

Who would think, reading his letter, that my lecture was concerned with the many reasons other than improved treatment which influence individual hospital survival-rates, the facile belief that any improvement noted must be due to the particular treatment method adopted, and the fact that the prognosis depends more on the nature of the tumour than on any other factor?

In the course of this lecture on the general subject of progress in the treatment of breast cancer,[10] I said that there were a number of reasons why there has been no great fall in the general mortality-rate from this disease. I concluded this section by remarking that, nevertheless, if you take the Registrar-General's figures for breast-cancer deaths and make corrections "both for the growth of the population and its increasingly adverse age composition a slight downward trend in mortality-rate for England and Wales appears." This is a fact; these figures are the Registrar-General's; this trend is there, and it has a greater negative slope than can readily be accounted for by chance. I did not then say what I thought it might be due to. My colleagues and I[11] had, however, previously offered some possible explanations, such as a decrease in incidence, greater accuracy in death certification, earlier treatment, or more efficient treatment, all of which Dr. McKinnon rejects in favour of

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1. *Lancet*, 1952, i, 35.
2. Coggeshall, C., Root, H. F. *Endocrinology*, 1940, 26, 1.
3. Recant, L., Hume, D. M., Forsham, P. H., Thorn, G. W. *J. clin. Endocrin.* 1950, 10, 187.
4. Daughaday, W. H., Perry, W. E., McBryde, C. M. *Ibid*, p. 410.
5. Reid, E. *Nature, Lond.* 1951, 168, 878.
6. Engel, F. L., Viau, A., Coggins, W., Lynn, W. S. jun. *Fed. Proc.* 1951, 10, 39; *Endocrinology*, 1952, 50, 100.
7. Black, K. O., Macdougall, I., Reid, E., Young, F. G. *Lancet*, 1952, i, 19.
8. *Mem. med. Sci.* 1950, 1, 107.
9. Wilhelmi, A. E., Fishman, J. B., Russell, J. A. *J. biol. Chem.* 1948, 176, 735.
10. Smithers, D. W. *Lancet*, Sept. 13, 1952, p. 495.
11. Smithers, D. W., Rigby-Jones, P., Galton, D.A.G., Payne, P.M. *Brit. J. Radiol.* 1952, suppl. 4.

the explanation that it only represents a trend confined to older people which is itself artificial.

Dr. McKinnon's explanation may well be correct, but it is based on an unexplained artificiality, and has been frequently maintained with a heat out of all proportion to its importance since general mortality-rates cannot be sound indicators of the value of treatment for small groups of patients in hospitals. My lecture dealt with this and even gave seven different reasons why results may have improved in special hospitals, only two of which had anything to do with treatment. Ultimately we may look for improvement in results of treatment for patients with breast cancer in national mortality statistics, but first that improvement must be sufficient to show itself through the general nation-wide mortality, stand out from variations in morbidity and in the "book-keeping" troubles of which Dr. McKinnon makes so much, and be accepted by doctors to the extent that they are more ready than at present to write other causes of death on certificates for patients who have once been treated for this disease. In the meantime we should not be unduly worried by the fact that Dr. McKinnon is not prepared to believe that any improvement has taken place until this stage is reached, and should continue to expect attack if we remark on the downward trend in the age-standardised mortality from breast cancer even when we do not give it prominence or attach much importance to it.

Dr. McKinnon's argument is that since the downward trend in death certification from breast cancer is only to be found at present in older people where the rates are more subject to error, this is not good evidence that treatment has lowered mortality. I did not say in my lecture that it was. In fact I have said before that the difficulties with death certification are greatest in the old and that this may explain the fall. It is not more difficult to diagnose breast cancer in the old; in fact generally the older the patient the easier the diagnosis. What is difficult, particularly in the old, is to decide whether to certify death as due to breast cancer or to some other cause when a person dies who has once been treated for breast cancer. The tendency is to give preference to cancer whenever there is doubt, even in some patients who have been treated many years before and lived their normal span of life. The Registrar-General's office added to this difficulty up to 1940 by altering the certified cause of death to cancer in some cases where this was mentioned as a subsidiary cause. Since 1940 they have accepted the doctor's certificate. Three-quarters of Dr. McKinnon's letter, in fact, is concerned with the refutation of an implication I did not make, presumably because he feared that someone else may take the fact I stated to be evidence against a belief he holds.

It does not help us to understand this problem or to improve the lot of our patients when someone takes the attitude of a knight with sword in hand defending the castle of cancer from all those who believe that it may be attacked by education and earlier and better treatment.

The last part of Dr. McKinnon's letter deals specifically with his inability to find evidence that early diagnosis in breast cancer makes any difference to length of life. He might look at table 26 in an article by my colleagues and myself[2]; explain why we call the disease "cancer of the breast" if it does not start there and then spread elsewhere; tell us why it is not more important to be quick about a patient with a tumour which tends to spread early than about one which tends to spread later; account for the fact that the Royal Cancer Hospital 10-year survival-rate for patients with grade-2 breast tumours with a history of less than 3 months is 38·6%* and with a history of more than 9 months only 16·2%†; and, in fact, generally let us know why, because he cannot find figures which he is prepared to regard as "clear-cut and conclusive," he should keep insisting that what clinicians have found from practical experience, concluded from the evidence of their own observations and established from their study of the natural history of the disease, is nonsense.

Royal Cancer Hospital,
London.

D. W. SMITHERS.

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* Life table method based on 165 patients initially at risk.
† Life table method based on 141 patients initially at risk.

R.M.B.F. CHRISTMAS GIFTS FUND

SIR,—The distribution of Christmas gifts will be made in a few days. I ask your readers who have not yet responded to the President's appeal to forward their contributions as soon as possible to the Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15, marked "Christmas Gifts."

I hope there will be a very generous response to this reminder.

F. A. JULER
Hon. Treasurer.

Obituary

FRANK HARWOOD JACOB

M.D. Lond., F.R.C.P.

Dr. Jacob died on Nov. 25 at his home in Malvern, where he had lived since his retirement from the staff of the Nottingham General Hospital in 1937. He was 80 years of age.

He qualified in 1895 from King's College Hospital where he had held in turn the Warneford, Sambrooke, Rabbeth, and Clothworkers scholarships. After holding house-appointments at King's, in 1898 he obtained his M.B. degree and he took up a resident appointment at Nottingham General Hospital in the same year. Three years later he was appointed to the staff of the hospital as assistant physician, becoming physician in 1905. He also joined the staff of the Nottingham Children's Hospital. Dr. Jacob was twice president of the Nottingham Medico-Chirurgical Society, and in 1921 he was elected F.R.C.P. After his retirement from the staff of the Nottingham General Hospital a ward was named after him in appreciation of his services. His *History of the General Hospital, Nottingham* appeared in 1951.

Of his years of busy and useful retirement R. and W. H. McM. write:

"Frank Jacob retired to West Malvern in company with a brother and two sisters, also unmarried. They chose a house high up on the hillside with an unrivalled panoramic view of the Herefordshire landscape and of the Welsh mountains beyond. In a downstairs room he unpacked his books and spread his papers. His knee-hole desk was placed in the bay window, so that whilst at work he could enjoy the hills and the changing skies in the west. The walls and table-tops of his library were peopled with photographs and memorabilia of Nottingham, and ere long a growing pile of manuscripts told of his interest in the medical lore of that city.

"He loved the countryside, especially the remote hamlets and churches which he and his brother explored together. Then there were the birds: he knew them individually by song and antics. Jacob was often to be found in the garden clad in a shaggy Harris-tweed jacket, navy-blue roll-top pullover, aged grey trousers and a battered turned-down felt hat: round his neck hung the much-used field-glasses, at hand his staff and a generous supply of apples, and on his knees the poems of Alfred Noyes. He was tallish with fresh colouring, a twinkling grey eye, ruffled sandy-grey hair and moustache, and a soft musical voice. 'Halloaloalo' was his usual greeting. With his slight limp he would advance to meet you, always friendly if a little shy.

"When war broke out Jacob insisted on working again. He assisted the local doctors and his help was always in demand. On these occasions he seldom completely abandoned his informal country attire although he was punctilious in wearing a jacket with intact elbows. One would see him standing at the door of a surgery talking to a patient leaning on his great staff which he was seldom without. At clinical meetings in Worcester, which he always found time to attend, or when his opinion at the bedside, always given so generously, was sought he was more formally dressed. Many a problem did he modestly succeed in solving with his years of accumulated wisdom.

"After the war he felt free to retire once more, and he resumed in earnest the task of writing the history of the Nottingham General Hospital. His library took on a less orderly and busier aspect. On summer days he withdrew with his papers to a sheltered summer-house in an overgrown pleasance adjoining a wood."

HAROLD EDWARD RIDEWOOD

M.D., M.S. Lond., F.R.C.S.

FIFTY years ago Ridewood qualified at the London Hospital, and during his years as a resident and as surgical registrar he made a good and lasting impression on his colleagues both as a man and as a surgeon.

He was born at Enfield in 1878, the son of the headmaster of Enfield Grammar School. He took the London M.D. in 1904, and the B.S. and M.S. in 1906 and 1909 (both with gold medal); and he also took the F.R.C.S. in 1906. He seemed to be destined for the surgical staff, and it was a great loss to the "London" when in 1910 he left England and found scope for his surgical talent in Canada, starting in Victoria, British Columbia. During the first world war he served in the C.A.M.C. as lieut.-colonel, working at Cliveden, Mudros, and Wimereux, and later with No. 1 Canadian Casualty Clearing Station, and as a surgical consultant. After the war he returned to Victoria where he steadily acquired a large and varied practice, and his comprehensive hospital experience in both medicine and surgery came to full fruition. That was a time and place where a surgeon had also to be a physician and a master of his craft so as to be able to undertake general surgery in the fullest sense. Ridewood by his gifts and by his experience was the very man and he did not spare himself. He had great dexterity and speed as a surgeon, as his former colleagues at the London knew well; and behind it all was an energetic and manly spirit with a rare judgment. It was no wonder that he acquired and maintained a great reputation throughout Western Canada as a great surgeon, and became a highly valued and beneficent member of a wide community.

Ridewood was a small lithe figure, energetic but not restless, eager not only to learn but to apply his knowledge. One felt that he was proud and thrilled by his work and purpose, and it was a service to others—for he was not self-seeking. His enthusiasm was contagious. Among his colleagues and friends he was lively and cheerful; and the same qualities were carried to his patients, inspiring them also with confidence and affection. His life work as a surgeon was a pattern which has seldom been woven so beautifully and to such good purpose.

He married in 1919 and had one son and three daughters. His home life was successful and happy, and his character and achievements were proudly felt in his own home. He returned to England to seek relief from the malignant disease from which he died in London on Nov. 8.

J. P.

ARNOLD LOEWENSTEIN

M.D. Prague

Prof. Arnold Loewenstein, who died in Glasgow in October, was born in Carlsbad. He took his M.D. in 1906 at Prague, where he became assistant in the eye clinic and later professor extra-ordinarius. A few months before the outbreak of the late war he came to this country as an exile and was given shelter in the Tennent Institute of Ophthalmology in the University of Glasgow. There he worked happily for the rest of his life and added to his world-wide reputation for devotion to his chosen specialty. Outside his work he had many interests and he was devoted to the mountains and scenery of Scotland. He wrote with confidence upon a wide range of topics based upon his exceptional experience. Until the end he maintained an active correspondence with many workers in many lands. His death is a great loss to European ophthalmology and international friendship.

W. J. B. R.

Notes and News

A CHRISTMAS-CARD CAROL

Piping voices in the porch,
Christmas greetings on the mat
(Evidences of the restive
Human spirit feeling festive),
Help to foster those digestive
Pleasures we are aiming at.

Life in Labrador is tough,
Weather searching, people poor.
If your friends are fond of seeing
Skating, sledges, huskies, skiing,
Bears and seals and Christmas-treeing,
Send them cards from Labrador.[1]

A graver card: N.A.M.H.
Gives health of mind the pride of place.
For troubled minds, distorted feeling,
Familiar world estranged and wheeling
A child and donkey, sure of healing,
Make a pilgrimage of grace.[2]

Creatures that on earth do dwell—
Fur and feather, fin and wing,
Lions, leopards, conies, asses,
Reindeer, moles (and all Fougasse's!)—
For friends of these unvocal masses
UFAW has the very thing.[3]

Children also have their charm:
And some, alas, are evil-starred.
In tundras snowy, tropics reedy,
Blue of eye, or black and beady,
Sixty million still are needy.
UNICEF provides the card.[4]

PAIN IN THE BACK

IN the course of his Gilbert Scott lecture at the Charterhouse Rheumatism Clinic, London, on Nov. 20, Sir Adolphe Abrahams spoke of difficulties in diagnosis. Pain in the back ("the worst of all diagnostic terrors"), he said, "may be due to a lot of local conditions, such as postural strain, hypertrophic arthritis, a protruded disc, spondylitis, spondylolisthesis, some forms of fibrositis; but it may also be due to various infections—tuberculosis, brucellosis, typhoid—or it may be due to malignant disease of the spine, primary or metastatic. It may also be due to visceral disease. One sees middorsal pain in cancer of the œsophagus; one sees pain in the back as well as the abdomen with cholecystitis, sometimes severe pain over the right inferior angle of the scapula in the absence of epigastric pain. One sees it in that very elusive condition, diaphragmatic hernia; and one sees it of course in perforated gastric ulcer; and one sees severe backache in cancer of the pancreas. One sees it in diverticulitis, and above all (perhaps one of the worst terrors) one sees it in cancer of the prostate, which I am informed accounts for 5% of deaths in men above the age of 50, and when very often there is nothing whatever to suggest disease of the prostate, not even nocturia."

LIFE STORY

EVERY elderly doctor has a story to tell, and between the wars medical autobiography enjoyed a great vogue. In a style conversational and somewhat staccato, Dr. Nicoll[5] tells the story of a Scottish minister's son, educated at George Watson's, who graduated in medicine at Edinburgh. If he errs a little on the side of prolixity, he writes with engaging frankness and sincerity, and his book is full of the joy of living. Especially attractive is the account of his life and work in the Highlands. Of the illness that compelled an early retirement he writes with courage and cheerfulness; of

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1. Sold for the benefit of Grenfell's medical work in Labrador and [illegible] Association of Great Britain [illegible] don, S.W.1.
2. T[illegible] Health, 39, Queen Anne [illegible]
3. The Universities Federation for Animal Welfare, 284, Regents Park Road, London, N.3. Decorated gummed tape and ribbon, labels, and postcards also supplied.
4. S[illegible] of the United Nations International Children's [illegible] ICEF), Russell Square House, Russell [illegible]
5. T[illegible] he Autobiography of a Doctor. By J. T. BELL NICOLL. London: Hodder & Stoughton. 1952. Pp. 256. 12s. 6d.

his religious beliefs and experiences with deep conviction. Doctors and those who like them will enjoy the tale. Particularly should it commend itself to those north of the Tweed.

INFORMATION SOUGHT

ON Nov. 13 the body of Patricia Curran, aged 19, was ound in the grounds of her home at Whiteabbey, Belfast. She had received a number of stab wounds.

The police inform us that they wish to interview a man born about 922, 6 ft. in height, of thin build, with sharp features and a noticeable *old* scar on the left side of his face, running from the eye to the mouth. The scar is said to pucker up the mouth a little and pull the eft eye slightly. Information may be given to Superintendent Capstick, c/o Inspectors General Office, R.U.C., Waring Street, Belfast (tel. Belfast 25421) or to Detective Sergeant Tebbell of New Scotland Yard (tel. Whitehall 1212, ext. 253).

University of Oxford

On Nov. 22 the following degrees were conferred:

D.M.—P. M. Peters, G. L. L. Reynolds, G. D. Walker, R. A. B. Drury.

University of Cambridge

Mr. S. Storey, M.P., has informed the university that the trustees of his settlement for charity will, over the next six years, provide £17,780 for research in the department of medicine on leukæmia and allied diseases. The benefaction is to be known as the Elisabeth Storey fund.

Royal College of Physicians of London

Dr. Maurice Davidson will deliver the FitzPatrick lectures at the college, Pall Mall East, S.W.1, on Tuesday and Thursday, Dec. 9 and 11, at 5 P.M. The subject of the lectures is Medicine in Oxford, a Historical Romance.

Royal College of Obstetricians and Gynæcologists

At a meeting of council held on Nov. 29, with Mr. Arthur Gemmell, the president, in the chair, Prof. Lutherus Johannes te Groen of Pretoria University was elected to the fellowship. Diaa Seif-Eldin was admitted to the membership.

Dr. Henry Roberts and Dr. James Walker were appointed William Blair-Bell lecturers for 1953.

Royal Medico-Psychological Association

At recent examinations for the D.P.M. the following were successful in part II:

D. S. G. M. Bailey, D. R. Moore, D. G. D. T. Smedberg, W. L. Walker.

A Course for Teachers

The Postgraduate Medical School of London is holding a conference-course on teaching on Jan. 9 and 10. A series of demonstrations by young teachers to a small group of undergraduate students, ranging from beginners to those about to sit their examinations, will form the basis of discussions on technique. Dr. John Burton, director of the Central Council for Health Education, and Miss M. L. Johnson, research associate in the anatomy department, University College, London, will open a discussion on group methods of instruction. Other speakers will include Prof. G. Payling Wright (Teaching and Learning), Dr. Keith Simpson (Museums in Teaching), and Prof. Max Rosenheim (Introduction to Research). Further particulars may be had from the dean of the school, Ducane Road, W.12.

Cortisone Produced in Britain

Dr. Ripley Oddie, medical director of Bayer Products Ltd., gave a luncheon in London last week to celebrate his company's synthesis of cortisone acetate (see *Lancet*, Nov. 15, 1952, p. 992). He explained that, using at present an intermediate product imported from the United States, rather more than the final third of the stages of synthesis were carried out in the English laboratories. He hoped that the amount of cortisone produced would by next March be about a third of what was now used in this country, and by next August more than the present total. Sir Henry Cohen said that in therapeutics cortisone had been variously assessed as the elixir vitæ and as a glorified aspirin; but unquestionably it was a valuable research tool. The history of endocrinology in recent years had shown the importance of different kinds of worker coming together, and for such coöperation or symbiosis medicine provided an appropriate milieu.

The guests included Sir Robert Robinson, F.R.S., Sir John Charles, Sir John Taylor, Mr. Geoffrey Keynes, Mr. Tudor Thomas, Sir Horace Evans, Prof. E. C. Dodds, F.R.S., and Mr. Eric Miller, assistant chemist of Bayer Products, who was responsible for the synthesis.

London Hospital Medical Society

On Monday, Dec. 8, at 5 P.M., at the London Hospital E.1, Prof. J. F. Brock, of Cape Town, will speak to this society on Kwashiorkor. Professor Brock has been carrying out an investigation on this disease for the World Health Organisation (see *Lancet*, Nov. 29, 1952, p. 1070).

International Neurological Congress

The fifth International Neurological Congress will be held in Lisbon from Sept. 7 to 12, 1953, under the presidency of Prof. Antonio Flores. The programme will include discussions on Vascular Diseases of the Brain, in which Prof. P. C. P. Cloake and Prof. Norman Dott will speak: on the Parietal Lobe, in which Dr. Macdonald Critchley and Dr. D. E. Denny-Brown will speak; and on Metabolic Diseases of the Brain, in which Sir Russell Brain will speak. Information may be had from Dr. F. M. R. Walshe, F.R.S., 11, Wimpole Street, London, W.1, or from the secretary-general of the congress, Prof. Almeida Lima, 53, Avenida do Brasil, Lisbon, Portugal.

Medical Art Society

The next meeting of this society will be held on Wednesday, Dec. 10, at 8 P.M., at 11, Chandos Street, London, W.1, when Mr. David Birch will discuss members' work.

French Appointment

Dr. Frank Falkner, who is at present research medical officer to the Institute of Child Health, London, has been appointed research fellow and director of growth studies to the Centre Internationale De L'Enfance, Paris.

CORRIGENDUM: The title of the report by the Nuffield Provincial Hospitals Trust mentioned in our leader on Hospital Costs last week was, of course, An Experiment in Hospital *Costing*.

EMERGENCY BED SERVICE.—In the week ended last Monday, applications for general acute cases numbered 1335. The proportion admitted was 88·53%.

Sir Andrew Davidson, chief medical officer of the Department of Health for Scotland, has been elected an honorary fellow of the American Public Health Association.

Births, Marriages, and Deaths

BIRTHS

BRYCE-SMITH.—On Nov. 9, at Cleveland, Ohio, to Peggy (née Adams), wife of Dr. Roger Bryce-Smith—a daughter.

FLEMING.—On Nov. 23, to Yvonne (née Foden), wife of Dr. J. A. C. Fleming—a daughter.

GIBSON.—On Nov. 21, at the Lambeth Hospital, London, to Sarah (née Wells), wife of Dr. Michael Gibson—a son.

HAYTER.—On Nov. 25, at Maidenhead Nursing Home, to Elizabeth (née Hallett), wife of Dr. A. G. Hayter, of Marlow—a daughter.

MUNDIE.—On Nov. 23, to Dorothie Betty (née Clement), wife of Dr. J. H. F. Mundie, Memorial Hospital, Bulawayo, Southern Rhodesia—a son.

WILMOT.—On Nov. 29, at Tyrone County Hospital, Omagh, N.I., to Patricia (née Harmsworth), wife of Mr. T. J. Wilmot, F.R.C.S.—a son.

MARRIAGES

CAREY—TOPPING.—On Nov. 29, Richard John Carey, M.R.C.S., of Bristol, to Margaret Rosamond Topping, M.B., of Dulwich, London.

MUIR—WILSON.—On Nov. 18, William Adams Muir, M.B., of Kokstad, Cape Province, to Nancy Elizabeth Wilson, of Bosham, Sussex.

DEATHS

BUNCOMBE.—On Nov. 25, Guy Hope Buncombe, M.R.C.S., of Gorleston-on-Sea, aged 52.

GARDEN.—On Nov. 26, at Didsbury, Manchester, William Sim Garden, M.D. Aberd.

GOFFE.—On Nov. 28, Ernest George Leopold Goffe, M.D. Lond., of Green Park, Ferring, Sussex; formerly of Kingston upon Thames, aged 85.

HENDERSON SMITH.—On Nov. 26, at Harpenden, John Henderson Smith, M.B. Edin.

INGLES.—On Nov. 12, John Stewart Ingles, M.A., M.B. Edin., of Shrubbery Avenue, Worcester, aged 58.

JACOB.—On Nov. 25, at Brockhill Road, Malvern, Frank Harwood Jacob, M.D. Lond., F.R.C.P.

LATHAM.—On Nov. 16, in Nigeria, John Hulme-Latham, M.R.C.S., lieutenant, R.A.M.C.

MURRAY-SHIRREFF.—On Nov. 25, at Lambridge, Bath, Graham Murray-Shirreff, M.R.C.S.

REEVES.—On Nov. 23, Gordon Harry Reeves, PH.D., D.SC., F.R.I.C., of the biochemistry department, St. Bartholomew's Hospital, London, aged 58.

WICKHAM.—On Nov. 21, in Salisbury, Catherine Mary Wickham, L.R.C.P.E., late of Rajkot, Kathiawar, India, aged 87.

Diary of the Week

DEC. 7 TO 13

Monday, 8th

UNIVERSITY OF LONDON

5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. P. György (Pennsylvania): Blood Group and Related Polysaccharides in Growth and in Resistance to Disease, with special reference to Human Milk.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1

5.30 P.M. Dr. C. H. Andrewes, F.R.S.: Virus Infections Before and After Birth.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5

5.30 P.M. Dr. E. Stengel: Lecture-demonstration.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1

5 P.M. Dr. T. H. Whittington: Physiology of Accommodation Clinically Considered. Treatment of the Hypermetrope.

HUNTERIAN SOCIETY

8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Dr. A. H. Douthwaite, Dr. H. Gardiner-Hill: Obesity.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1

8.30 P.M. Mr. A. C. Palmer: Results of Injury to Pelvic Diaphragm in Women.

LONDON HOSPITAL MEDICAL SOCIETY, Whitechapel, E.1

5 P.M. Prof. J. F. Brock (Cape Town): Kwashiorkor.

Tuesday, 9th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1

5 P.M. Dr. Maurice Davidson: Medicine in Oxford—a Historical Romance. (First of two FitzPatrick lectures.)

BRITISH POSTGRADUATE MEDICAL FEDERATION

5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. C. E. Dent: Chromatography in Study of Amino-acid Metabolism.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1

5.30 P.M. *Section of Experimental Medicine.* Dr. M. Romansky (St. Louis): Erythromycin. Dr. M. A. Floyer, Dr. J. M. Ledingham: Experimental Hypertension.

8 P.M. *Section of Psychiatry.* Dr. N. O'Connor, Dr. J. Tizard: Resettling Defectives.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1

4.30 P.M. Lord Horder: Fifty Years of Medicine. (First of three Harben lectures.)

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2

5.30 P.M. Dr. D. I. Williams: Erythrodermias.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, W.1

5.30 P.M. Mr. K. I. Nissen: Prevention and Treatment of Deformity in Infantile Paralysis.

CHADWICK LECTURE

4.30 P.M. (St. Mary's Hospital Medical School, Norfolk Place, W.2.) Dr. A. I. G. McLaughlin: Prevention of Dust Diseases of Lungs. (Malcolm Morris lecture.)

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1

5 P.M. Prof. A. A. Moncrieff: Children in Hospital.

MANCHESTER MEDICAL SOCIETY

5 P.M. (University of Manchester.) *Section of Surgery.* Dr. R. W. Fairbrother: Antibiotics.

Wednesday, 10th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2

4 P.M. Prof. F. Wood Jones, F.R.S.: John Hunter as a Geologist.

ROYAL SOCIETY OF MEDICINE

4.30 P.M. *Section of Physical Medicine.* Dr. I. H. Curwen, Dr. B. O. Scott: Short-wave Diathermy and Ultrasonics.

4.15 P.M. *Sections of Pathology and Medicine.* Discussion on Chemotherapy of Tuberculosis.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE

4.30 P.M. Lord Horder: Fifty Years of Medicine. (Second of three Harben lectures.)

ROYAL EYE HOSPITAL

5.30 P.M. Mr. L. H. Savin: Surgery of Ocular Injury.

INSTITUTE OF DERMATOLOGY

5.30 P.M. Dr. H. Haber: Bullous Eruptions.

INSTITUTE OF UROLOGY, St. Paul's Hospital, Endell Street, W.C.2

5 P.M. Mr. A. R. C. Higham: Diminished Fertility in the Male.

MIDLAND MEDICAL SOCIETY

8.15 P.M. (Birmingham Medical Institute, 154, Great Charles Street, Birmingham, 3.) Prof. G. W. Pickering: Natural History of Essential Hypertension.

MANCHESTER MEDICAL SOCIETY

4.30 P.M. *Section of Pathology.* Dr. M. T. Parker: Epidemiology of Enteric and Salmonella Infection in Manchester area.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2

5 P.M. Sir Sydney Smith: Medicine, Magic and Religion—the Persistence of an Idea. (Finlayson lecture.)

Thursday, 11th

ROYAL COLLEGE OF PHYSICIANS

5 P.M. Dr. Davidson: Medicine in Oxford—a Historical Romance. (Last of two FitzPatrick lectures.)

ROYAL COLLEGE OF SURGEONS

5 P.M. Prof. George Perkins: Rest and Movement. (Robert Jones lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION

5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. A. Neuberger, F.R.S.: Biochemical Genetics.

ROYAL SOCIETY OF MEDICINE

5 P.M. *Section of Ophthalmology.* Dr. Alice Carleton, Mr. J. H. Doggart, Dr. Peter Borrie: Association of Eye and Skin Diseases.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE

4.30 P.M. Lord Horder: Fifty Years of Medicine. (Last of three Harben lectures.)

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1

7.30 P.M. Dr. G. W. A. Dick: Epidemiological Notes on some Viruses Isolated in Uganda.

VICTOR HORSLEY LECTURE

5 P.M. (B.M.A. House, Tavistock Square, W.C.1.) Sir James Learmonth: Ischæmia in Surgery.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1

5 P.M. Sir Paul Mallinson: Psychiatry lecture-demonstration.

INSTITUTE OF DERMATOLOGY

5.30 P.M. Dr. R. W. Riddell: Subcutaneous Mycoses.

ALFRED ADLER MEDICAL SOCIETY

8 P.M. (11, Chandos Street, W.1.) Dr. A. Spencer Paterson: Crisis of Adolescence.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY

4.15 P.M. Dr. Bernard Lennox: Simplification of Pathology of Epithelial Skin Tumours.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY

7.45 P.M. (South Kensington Hotel, 41, Queen's Gate Terrace, S.W.7.) Mr. Zachary Cope: Medicine and Modern Society.

UNIVERSITY OF OXFORD

8.30 P.M. (Nuffield Orthopædic Centre.) Prof. R. Merle D'Aubigné (Paris): Late Results in Treatment of Hip Conditions Arthroplasty with Inert Prostheses.

UNIVERSITY OF ST. ANDREWS

5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. I. G. W. Hill: Rheumatic Heart-disease.

Friday, 12th

ROYAL EYE HOSPITAL

5.30 P.M. Mr. Howard Reed: Slit-lamp Appearances and the Diagnostic Value.

INSTITUTE OF DERMATOLOGY

5.30 P.M. Dr. R. M. B. MacKenna: Clinical demonstration.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.

5 P.M. Prof. S. Zuckerman, F.R.S.: Effect of Certain Endocrin States, and in Particular Thyroid Deficiency, on th Development of the Nervous System.

HEBERDEN SOCIETY

4.30 P.M. (Eastman Dental Theatre, Royal Free Hospital, Gray' Inn Road, W.C.1.) Opening of two-day annual meetin

WEST KENT MEDICO-CHIRURGICAL SOCIETY

8.30 P.M. (Miller General Hospital, S.E.10.) Dr. Wilfrid Sheldon Children in War-time. (Purvis Oration.)

Appointments

AINSWORTH, JOSEPH, M.B., M.RAD. Lpool, D.M.R.D.: consultan radiologist. in charge of the diagnostic radiology services West Manchester hospitals.

BOULGER, L. R., M.B. Manc.: pathologist, Nigeria, Colonial Medica Service.

FOX, F. W., M.B. Manc.: asst. M.O., North West Kent area.

PHILIPP, E. E., M.A., M.B. Camb., F.R.C.S., M.R.C.O.G.: second honorary gynæcologist, French Hospital, London.

TURNER, W. M. L., M.D. Lond., M.R.C.P., D.L.O., D.C.H.: consultant pædiatrician, Burnley and district hospitals.

North-East Metropolitan Regional Hospital Board:

BURN, R. A., M.B. Durh., F.R.C.S., D.O.M.S.: part-time ophthalmic surgeon (consultant), East Ham Memorial Hospital.

CRAWFORD, A. S., M.D. Edin., D.A.: part-time anæsthetist (consultant), Harold Wood Hospital and Brentwood Mental Hospital.

DAVIDSON, HILDA, M.B. Lond., D.P.M.: part-time psychiatrist (consultant), Ilford child-guidance clinic.

GIBB, W. E., M.A., D.M. Oxfd, F.R.C.P.: part-time physician (consultant), Metropolitan Hospital.

HALPER, HOWARD, M.R.C.S., D.M.R.E.: part-time radiologist (consultant), South East Essex group of hospitals, and Runwell Mental Hospital.

JOAD, MARGARET, M.R.C.S., D.A.: part-time anæsthetist (consultant), St. Mary's Hospital, Plaistow.

KELLY, R. E., M.D. Lond., M.R.C.P.: part-time neurologist (consultant), Prince of Wales's General Hospital.

KOPELMAN, HARRY, M.D. Lond., M.R.C.P.: part-time physician (consultant), St. Margaret's Hospital, Epping.

LLOYD-DAVIES, D. G., F.R.C.S.E., D.L.O.: part-time E.N.T. surgeon (consultant), Queen Mary's Hospital.

LUNN, G. M., M.B. Camb., F.R.C.S.: part-time surgeon (consultant), St. Leonard's Hospital and St. Matthew's Hospital.

MAXWELL, JAMES, M.D. Lond., F.R.C.P.: part-time physician (consultant), Enfield War Memorial Hospital.

PRENTICE, A. I. D., M.C., M.A., M.B. Camb.: pathologist (consultant), Black Notley Hospital.

VINCENZI, J. E. G., M.R.C.S., D.P.M.: part-time psychiatrist (consultant), Chelmsford child-guidance clinic.

South Western Regional Hospital Board:

BOLTON, J. R., M.B.E., M.D. Camb., M.R.C.P.: consultant physician (with a main interest in geriatrics), Bath clinical area.

DUMOULIN, J. G., M.B.E., M.D. Lond., M.R.C.O.G.: consultant obstetrician and gynæcologist, Plymouth clinical area.

MANDELBAUM, LISA, M.B. Brist., M.R.C.P., D.C.H.: senior registrar in diseases of the chest, Bristol clinical area.

NOBLE, NAIZBY, M.R.C.P., F.R.C.S.E., M.R.C.O.G.: senior registrar in obstetrics and gynæcology, Plymouth clinical area.

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UTERINE INFLUENCES UPON INTRARENAL BLOOD DISTRIBUTION *

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THE uterus is unmentioned in the index—and scarcely mentioned in the text—of Homer Smith's *maximum opus* (1951) on the kidney. So a uterorenal talk may at least help to fill a gap, and will doubtless be provocative. I shall also present some experimental findings which have not before been synthesised and which in large measure have not yet been published.

* * *

So long ago as 1929 Dr. J. C. Beker, of Arnhem in Holland, began a series of publications about pregnancy conditions, particularly eclampsia, associated with renal troubles; the conditions included multiple pregnancy, hydramnios, and hydatidiform mole, with primiparity an aggravating factor, and undue stretching of the uterus appeared to be common to many of the cases. In Beker's view (1942, 1948, 1950) eclampsia—including that which occurs within the week after birth but not eclampsia puerperalis tardissima—was caused by a disturbance in the hæmodynamic equilibrium.

From 1941 onwards, van Bouwdijk Bastiaanse (1949), also in Holland, was similarly engaged in trying to find some ætiological basis for what has been termed "the disease of hypothesis," and there are many others who have been discontent to let pregnant women be exposed to dangers that might conceivably be reduced by a proper correlation of, and insight into, the facts. I cannot mention all these others; but I must name one, for he figures largely in my subsequent story. He was Mr. John Sophian, who for some twenty years was collecting clinical data, though without basing any publications upon them.

* * *

In 1945 Dr. Trueta, the late Dr. A. E. Barclay, and I discussed plans for a thoroughgoing radiographic study of the effects of direct, central, and reflex nervous stimulation upon the functioning cardiovascular system (see Trueta 1945), and we began work that autumn in the Nuffield Institute for Medical Research, Oxford, with Miss M. M. L. Prichard as the fourth member of the team; before long a fifth, Dr. P. M. Daniel, pathologist, was added. When the research had progressed a comparatively short way, certain findings about the blood-flow through the kidney focused our attention on that organ to the exclusion of others—though in retrospect I think we should first have completed our preliminary survey of the whole system, and only thereafter have come back to organs, such as the kidney, that had been specially indicated as worthy of further study.

The main point I wish to make, in the present connection, from our *Studies of the Renal Circulation*, is that we showed, for the first time, a parallel between the distribution of renal ischæmia produced by nervous/humoral action in the experimental animal and the distribution of bilateral renal cortical necrosis pathologically occurring in the human being.[1]

* * *

His reading of our book suggested to Mr. Sophian the hypothesis that distension of the human uterus in multiple pregnancy, hydramnios, and hydatidiform mole might reflexly cause diversion of the renal cortical blood-flow and thereby tend to minor troubles, to oliguria/anuria, and at the worst to bilateral renal cortical necrosis.[2] His hypothesis in its initial form did not, so far as I know, account for renal troubles occurring after parturition, nor did it specify the type of receptor end-organs that he thought would be stimulated as a result of the uterine distension.

In 1948 he discussed the hypothesis with me, and the obvious first test was to ascertain by experiment whether distension of the mammalian uterus could affect the intrarenal blood distribution. The positive results obtained (Franklin 1949) encouraged further experimental work and strengthened Mr. Sophian's belief that the primary change within the kidney in human pregnancy troubles was vascular constriction (Sophian 1949).

* * *

About the same time I began to test another hypothesis—namely, that the renal cortical blood-flow would be diverted in an animal subjected to anoxia/asphyxia. The tests showed that this happened in the innervated but not in the denervated kidney[3] and further, quantitative, work was done later by Miss E. A. Ullmann and Dr. L. E. McGee (Franklin, McGee, and Ullmann 1949, 1951). In the present connection certain results may be mentioned.

The tracheal occlusion test[4] depends for its positive vasoconstrictive reaction on the integrity of the renal nerves; it can, therefore, be used to determine the completeness or otherwise of extrarenal denervation of the kidney. The renal cortical vascular constriction is independent of the changes in general systemic arterial blood-pressure, and is mediated through certain spinal-cord levels. While the small cortical vessels constrict completely, the main renal artery is never fully occluded during the test. Finally, the renal cortical blood-flow diversion in such experiments appears to be the maximal response possible and it has been found not only in the rabbit, but in all the other laboratory mammals studied and also (personal communication from Prof. E. C. Amoroso) in the seal.[5]

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* Based on a lecture, given at the invitation of Prof. N. J. Eastman, in the Department of Obstetrics, Johns Hopkins Hospital, on April 28, 1952, and repeated at the Naval Medical Research Institute, Bethesda, Md., four days later. An abbreviated version formed a communication to the Annual Meeting of the National Academy of Sciences, Washington, D.C. (Franklin 1952). The author was at the time visiting professor of physiology in the University of Illinois.

[1] Unfortunately, the term "renal shunt" was introduced, though not by us, for the diversion of the renal cortical blood-flow which we observed and described. In the absence of a universally accepted definition, this admirably brief term has been more often a stumbling-block than a help.

[2] I understand that he presented a fuller account as a thesis to the Royal College of Obstetricians and Gynæcologists in March, 1948.

[3] A 16 mm. silent colour film, produced in October, 1948, with the technical assistance of Mr. Douglas Fisher, demonstrated this to audiences at home and abroad.

[4] Seeing the effect upon the renal cortical blood distribution of the occlusion of a glass tube tied into the trachea.

[5] At this point in the lecture diversion of the rabbit's renal cortical blood-flow was demonstrated by projection of the first shots of a new 16 mm. silent colour film, *Asphyxia and the Kidney*, produced in 1951 by Professor Franklin with the technical coöperation of Mr. Douglas Fisher and other members of the Wellcome Film Unit. This Wellcome Research Record no. 3 is lent gratis for projection on application to the Wellcome Foundation, 183, Euston Road, London, N.W.1. The shots projected were of the diversion and subsequent recovery (*a*) at normal speed, (*b*) speeded up three times, and (*c*) speeded up twelve times.

I pass now to the main part of my lecture—namely, an account of certain experiments done since 1947 in the department of physiology at St. Bartholomew's Hospital. The subjects were rabbits, anæsthetised with intravenous injection of pentobarbitone sodium solution, followed as necessary by open administration of ether. During the experiments, paling of the kidney surface was taken as evidence of reduction of intracortical blood volume and it was usually not possible to watch more than one kidney. At the ends of experiments the appearance of the second kidney surface also was usually noted, while both kidneys were cut open so that the colour of the cortices and medullæ could be observed, and provide extra evidence.

In 1948 several experiments were performed in collaboration with Mr. Sophian. Suitable quantities of Ringer's solution at body-temperature were injected into uterine horns, bladders, and portions of intestine in order to produce acute distension, ligatures being used as required to prevent escape of the injected fluid. The findings were that distension of any of the three hollow viscera caused reduction in the renal cortical blood volume, intestinal distension being commonly the most effective.

In 1950 and 1951 further experiments were done in which blood was used as the distending agent in order to parallel more closely the concealed accidental hæmorrhage of human obstetrics. Later, when blood had been shown to act like saline, the latter was again used from time to time. Independent assessment of the results was always made by at least two observers. Brief résumés will be given of eight of these experiments.

EXPERIMENT 1 was performed in collaboration with Miss P. J. Lindop and Mr. J. F. Pearce. The uterus was non-pregnant but (?) parous. The ends of a thin plastic tube were tied into the left carotid artery and the right uterine horn respectively, and blood passed into the latter at the rate of 1–2 drops per second. The right kidney surface became progressively paler as the uterus got fuller, and at the end of the experiment it showed, on section in situ, a pale cortex and a congested medulla. The left kidney was not watched during the course of the experiment, but its surface was similarly pale at the end. When the plastic tube was withdrawn from the uterus, blood was still passing through at the original rate.

This experiment showed that distension of a uterine horn with the subject's own blood caused progressive reduction in the amount of blood in the cortices of both kidneys.

EXPERIMENT 2.—As hæmorrhage that is adequate in degree can cause diversion of the renal cortical blood-flow (Trueta et al. 1947), it seemed worth while to eliminate this possible criticism of the previous experiment, even though the blood-loss in it had not been great. In a new test, therefore, two animals were used, a buck providing the blood for the distension of the uterus of a doe which had large mammary glands and was, apparently, puerperal.

The left uterine horn was tied off at both ends, and a narrow 'Polythene' tube had one end inserted, pointing distally, into the buck's common jugular vein at the base of the neck, the other tied in the left uterine horn near its ovarian end. As there were competent valves in both internal and external jugular veins of the donor animal, regular intermittent compression of the main vein as it kept filling with blood was used to propel that blood into the uterus of the receiving animal. The surface of the left kidney of this latter was observed to get progressively paler as the uterine horn became ever fuller with blood. On section in situ, the left kidney showed a pale cortex and congested medulla; so did the right kidney, the difference in degree, if any, being very slight. The kidneys of the donor animal likewise had pale cortices at the end of the experiment, but the medullæ were not congested. The blood in the uterus appeared to be 2–3 ml. in amount.

This experiment showed that distension of one uterine horn of animal A with blood from animal B caused progressive reduction in the amount of blood in the cortices of both kidneys of animal A.

EXPERIMENT 3.—As renal cortical blood volume can be reduced both by renal nerve stimulation and by hormones such as adrenaline, another two-animal experiment was made, the receiver being a (?) virgin doe, and blood transmission being as in experiment 2. This time, however, the blood went to the *right* uterine horn, and the recipient's left kidney was denervated by division of the periarterial nerves, the completeness of the denervation being demonstrated by a tracheal occlusion test. As blood was propelled into the uterine horn, the surface of the innervated right kidney became progressively paler, while that of the denervated left kidney paled much less and was somewhat dusky. On section, the cortex of the right kidney was much paler than that of the left one, though the latter also was subnormal in coloration; the medulla of the right kidney was more congested than that of the left.

It appears, then, that distension of one uterine horn of animal A with blood from animal B caused some degree of (?) hormonal reduction in cortical blood volume in both kidneys of animal A, and in addition a reflex reduction in the same in the ipsilateral kidney, which retained its innervation; the reduction in this kidney, through both influences acting together, appeared to be maximal.

EXPERIMENT 4 was essentially the same as the previous one except that this time the donor's blood passed into the *left* uterine horn of the recipient—i.e., the horn on the side which had the denervated kidney. The uterus was a virgin one, and very little blood sufficed to distend the horn. As it became distended, the surfaces of both kidneys became paler, but the innervated one more than the denervated one. The appearance of the two organs on section confirmed the view that the effects were greater in the right kidney.

Here distension of one uterine horn caused some degree of (?) hormonal reduction in cortical blood volume in both kidneys, and in addition a reflex reduction in the same in the contralateral kidney, which retained its innervation.

EXPERIMENT 5.—The rate of transfer of blood was now increased by using the distal part of the donor's abdominal aorta as the supply vessel. After the aorta had been occluded by an artery clip, cannulæ were tied into it and into the left horn of the virgin uterus of the recipient, and were connected by narrow rubber tubing and adapters. Then the artery clip was removed, and the left kidney surface paled rapidly as the uterine horn rapidly became tense; the right kidney surface was found to be similarly pale when it was examined. Thereafter, the rubber tube was clamped and the uterine horn emptied of blood, with consequent reduction in pallor of the left kidney surface, through (?) not complete return to its previous depth of colour; the right kidney surface could not be simultaneously observed throughout.

Next, a stretch of about 3 cm. of the recipient's smooth colon was tied off at each end, a cannula was inserted, and blood was passed into it from the aorta until it became very tense. As this happened, both kidney surfaces paled. Then the left kidney was denervated, and colour returned to some extent to its surface.

Finally, both kidneys were sectioned. The cortex of the right one was very pale, of the left one somewhat less so. The medullæ were congested, the effect again being more marked in the right kidney.

Thus the rapid introduction of blood into a uterine horn or into a segment of the large intestine produced a rapid reduction in cortical blood volume in both kidneys. The paleness was reduced, though not completely so, when the uterine horn was emptied of blood; it was unilaterally reduced, in the case of the bowel distension and while that distension continued, when one kidney was denervated. The effects were thus both reflex and (?) hormonal.

EXPERIMENT 6.—The left kidney of a doe was denervated, the completeness of the denervation being demonstrated by the results of a tracheal occlusion test. Thereafter, injection of saline at body-temperature into the right horn of the virgin uterus, which became enlarged and tense, caused rapid paling (though much less than that produced by tracheal occlusion) of the right kidney surface. When the fluid was withdrawn from the uterus, the right kidney pallor was reduced but not abolished, and at this stage the left kidney surface was as pale as the right one. Section showed pallor of the cortices and some congestion of the medullæ of the two kidneys, the right one slightly predominating.

While distension of one uterine horn lasted, then, it caused reflex reduction in cortical blood volume in the ipsilateral, innervated kidney; it also produced (?) hormonal reduction in cortical blood volume in both kidneys and this persisted after distension had ceased. The reflex and (?) hormonal effects summated in the innervated kidney.

The next experiment was performed to determine the reflex/(?) hormonal reactions of the kidneys, following functional exclusion of the adrenal glands, to distension produced by injection of normal saline at body-temperature into one uterine horn.

EXPERIMENT 7.—A virgin doe had its left kidney denervated, the completeness of the denervation being confirmed by a tracheal occlusion test. Then both adrenal glands were functionally excluded by ligation of their vessels; for a while the kidney surfaces were somewhat paler than at the outset of the experiment, presumably because the manipulations had caused some extra liberation of adrenaline. Distension of the right uterine horn with saline at body-temperature caused some paling of the right (innervated) kidney surface, but not of the left (denervated) one; the original degree of coloration of the right kidney surface returned when the saline was removed from the uterine horn. At adequate intervals of time, the procedures were twice repeated with the same results. On section in situ, with distension continuing, at the end of the experiment, the right kidney cortex was obviously paler than the left one.

EXPERIMENT 8 was a repetition of experiment 7 in another animal, with identical results.

Comparison of the conditions and results of these last two experiments with those of the earlier ones indicates that distension of either uterine horn in a doe rabbit produces reduction in the cortical blood volume of both kidneys (i) by uterorenal reflex action, and (ii) by action upon the adrenal glands, with consequent hormonal action upon the kidneys. The effect of (i) is conterminous with the uterine distension, the effect of (ii) outlasts it.

* * *

Before adducing further evidence from observations on pregnant animals, I shall cite an experiment performed by Professor Amoroso (see Franklin 1949). In the rabbit, the several conceptus are spaced out in the uterus, and in consequence there is room for each, as it grows, to encroach upon the intervening no-man's land. By ligating the uterus on each side of each conceptus early in gestation, Professor Amoroso restricted the encroachment and thus increased the distension in each conceptual region. This put the uterorenal reflex upon so hair-trigger a basis that mere laparotomy and a touch to a conceptual region caused immediate diversion of the renal cortical blood-flow. I did not myself see Professor Amoroso's experiment, but since then, both with him and with Mr. Sophian and alone, I have noticed how manual compression of a conceptus can cause paling of the kidney surfaces; the latency of the response is so small that the effect is obviously reflex, at least at its outset.

The tension in the rabbit's uterus is maximal at about the 22nd day of gestation (Reynolds 1949). I have not got enough observations to correlate his curves of tension quantitatively with renal surface colour, but I can say without fear of contradiction that when pregnancy is reasonably advanced there is some paling of the kidney surface as compared with what is seen in the non-pregnant animal; the fœtal kidneys are not noticeably affected.

A further line of evidence is one which I have not so far succeeded in duplicating more than once, and then only less completely; it was obtained through a doe giving birth spontaneously during an experiment which Dr. A. M. Miles (now Fergusson) and I had planned for another purpose.

Before parturition began, the left kidney had been denervated; so when things began to happen we were able to compare the effects upon the innervated and denervated organs. The surfaces at the onset were as stated above—i.e., a little off colour as compared with non-pregnant. Then the intestinal movements and the uterine movements increased, the kidney surfaces became paler (denervated somewhat more than innervated), there were strong contractions of the doe's abdominal muscles and strong ventroflexions of its hind limbs, and parturition occurred. Kidney surface paling was increased for some minutes after birth, the innervated side now being paler than the denervated; thereafter there was return to more colour than existed before parturition began. Only the first two fœtuses were delivered spontaneously; the other four had to be evacuated. To begin with, after the evacuation, the right kidney surface was paler than the left, but within a few minutes both were darker than at the outset of the experiment—i.e., they were becoming non-pregnant in colour.

A less successful attempt at spontaneous parturition in another subject gave some extra details, and from the two experiments together one can add the following further points: (i) that after an unsuccessful attempt at parturition the intestines, kidney surfaces, and uterus returned to their previous conditions in about ten minutes, (ii) that during parturition the cortex of the fœtal kidney was paler than the medulla, and (iii) that after complete evacuation red streamlines appeared in the uterine veins.

We have then, during spontaneous parturition, renal cortical blood volume reduced first humorally and then reflexly. The humoral agent is, perhaps or even probably, posterior pituitary secretion, for this could produce the triple visceral effect noted, whereas adrenaline would inhibit the intestinal activity; histamine from the placenta is, I think, less likely because increased activity of the intestine preceded contraction of the uterus. I have still to find out whether posterior pituitary extract pales the denervated kidney to a greater extent than the innervated one, and whether paling produced by it and equal to that which we observed takes about ten minutes to subside. If, however, all that is discovered, the argument will have been strengthened and we shall also have a good idea of the amount of secretion produced in relation to a labour effort. The reflex uterorenal effect occurring after parturition must, I think, be evoked by the strong contracting down of the involuting uterus, and it is of particular interest as suggesting a possible mechanism for puerperal renal effects in the occasional human subject (see Franklin 1949).

Here I should say that, although there is individual variation in the experimental rabbit, the renal cortical blood diversion is usually of minor or medium degree compared with the maximal effect produced by asphyxia. Probably, therefore, we should regard the uterorenal effects in pregnancy and the puerperium as parts of the total physiological adjustment picture, not excessive in degree or very urgent in character. Nevertheless, the mechanisms are there, and more severe uterine distension before birth, or excessive uterine spasm after birth, could result in a greater response.

* * *

In the experimental animal nervously evoked renal cortical ischæmia of sufficient duration can result in renal cortical necrosis. I imagine that there are generic variations in the length of time required, as there are in the lengths of time different genera can undergo complete renal ischæmia, produced by clamping of their main renal arteries, without irreversible changes occurring. Clamping of the artery is a less natural process than stimulation of the renal nerves, for while the latter can completely cut out the circulation to the "cortical" glomeruli it does not cause complete occlusion of the main artery.[6] Adrenaline, administered in unphysiologically high dosage, can shut down the main renal artery, but there is at present no evidence that it does so in the concentrations in which it naturally occurs in the arterial blood passing to the kidney.

Two or three years ago, in conjunction with Mr. Sophian, I planned some experiments to see whether faradic stimulation of the rabbit's renal nerves could result in cortical necrosis. From the literature on the effects of clamping of renal arteries in various genera I thought it would suffice if we could keep the renal cortical blood-flow diverted for 3–4 hours, and I decided to do this by stimulating the renal nerves for 30 seconds every 2 minutes, for the effect of appropriate stimulation outlasts the stimulus.[7] In 1950 I wrote as follows about the results:

> "It appears that about four hours of continuous [renal cortical blood-flow] diversion . . . may be more than the rabbit's kidney can stand. In one instance, however, there was diminution in extent of a superficial area, visibly affected by the stimulation, during a subsequent recovery period of a few hours' duration. Effects which have been produced by such stimulation have included, according to reports by Prof. J. H. Dible and Dr. G. J. Cunningham, localised cortical necrosis, and elsewhere very considerable tissue damage."

Prof. H. L. Sheehan (1950) later examined the sections and gave a more detailed report; he also put the results into one of his new categories of the effects of human renal arterial spasm—i.e., our acute experimental results in rabbits paralleled findings in the human obstetrical field. "A point of interest in one experiment was that the unstimulated kidney showed superficial paling during the recovery of the stimulated one."

Beginning their work somewhat later, I imagine, E. C. Hoff and his colleagues (1951) found that diversion of the renal cortical blood-flow could be produced in acute experiments on cats by electrical stimulation of foci on the anterior sigmoid gyri of the cerebral cortex; the effects were greatly exaggerated when the brain was stimulated through the intact cranium with Offner's brief stimulus therapy apparatus; they were essentially abolished by renal denervation. In the acute experiments there were some changes in tubule cells (fatty degeneration, leading on to pyknosis and fragmentation of nuclei) when stimulations were multiple. In chronic experiments there were pathological changes in the kidneys presenting a picture of lower-nephron nephrosis. "It is suggested," wrote the authors, "that these changes are probably the result of repeated arteriolar vasoconstriction leading to tissue anoxia and alterations in capillary permeability."

* * *

In 1951 I listed the mammals in which evidence had so far been presented of diversion of renal cortical blood-flow under various conditions of nervous and humoral stimulation. These mammals were the rabbit, monkey, dog, cat, rat, mouse, guineapig, and seal—i.e., all those that had been studied. Lövgren has since found it in normal cats barked at by dogs, but not in control animals, and the recent angiographic studies of Daniel, Peabody, and Prichard (1951, 1952) confirm previous findings in the cat, dog, and monkey, add findings in the sheep, and give much interesting extra information. The general pattern of renal vascular response first found by our team at the Nuffield Institute in 1945–47 has, therefore, been demonstrated in all the lower animals so far used, though it remains to be proven beyond doubt in man—or such is the view of a number of nephrologists.

Let us see what has been found in human obstetrics; but first let us state that the various renal clearance tests are rendered difficult in oliguria, and are inapplicable in anuria. So they cannot be used to discover what is happening within the kidney in the severer cases of that organ's failure.

I have been told by Mr. Sophian of two interesting obstetrical cases, about which he was given information. In the first a bag was introduced with the object of inducing labour, but in fact the extra distension resulted in fatal renal cortical necrosis. The opposite side of the story was given in another case in which anuria was abolished by withdrawal of fluid. A number of workers (e.g., Solymoss 1949, De and Sengupta 1951, Solymoss and Molnar 1952) believe that renal cortical blood-flow diversion, of the type that we described in lower animals at the Nuffield Institute in 1945–47, is the mechanism through which human intra-uterine events produce their renal effects, and Sheehan, without adopting this view as such, has given a graded classification implicating vascular spasm as the initial intrarenal step, though it may be followed by vascular paralysis. I myself am still strongly impressed by the case described to me by Prof. T. N. A. Jeffcoate (see Franklin 1950).

> "The patient had concealed accidental hæmorrhage, and anuria from the time of its onset. After twenty-eight hours, when she had recovered from the initial shock, looked well, and had a blood pressure within normal limits, she was operated on and one kidney was exposed. Superficially it did not look pale, but congested. The pedicle was completely denervated without any change becoming apparent on the kidney surface and, when incised, the capsule did not bleed at all, nor did the cortex. On the other hand, as soon as the medulla was reached there was bleeding. The patient died on the fourth day after delivery, and at autopsy both kidneys showed the classical picture of complete cortical necrosis."

* * *

My main object here has been to submit some further experimental evidence about the mechanisms through which intra-uterine and intrarenal effects are related in a particular laboratory mammal. The work owed its inception to a desire to see whether there was in that species a uterorenal reflex pathway such as Mr. Sophian postulated in the human subject. The research has gone farther than the demonstration of such a pathway, but many more points have to be elucidated before the full story is known in even that one mammal—e.g., the exact part played by the adrenal glands has to be revealed and the receptor end-organs in the uterus to be determined.

How far the findings in animals can at present serve as a basis for the explanation of happenings in human obstetrics is a question which each must for the moment answer in the light of his own experience and of that of others as recorded in the literature. We are, however, justified by the positive animal findings in supposing that the human uterus *may* react upon the human kidney in somewhat the same way that the rabbit's uterus *can* react upon that animal's kidney; and a search for the truth is facilitated when one has precise *ideas* of the possibilities to be tested.

I should like to express my thanks to Mr. Sophian, whose hypothesis led to the experimental work which I have described, and who has been an enthusiastic collaborator in parts of that work. His views about the applicability of the findings to the field of human obstetrics are more definite than my own, and are, I understand, being published elsewhere.

References at foot of next column

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[6] In a tracheal occlusion test the constrictor nerves to the artery outside the kidney appear to be maximally stimulated, but if a branch of the artery at the hilus has previously been denervated the part of the cortex supplied by this branch continues to receive a blood-supply while the rest of the cortex blanches.

[7] The choice of intermittent stimulation periods was fortunate, for Miss E. A. Ullmann subsequently found that continuous stimulation results in failure to maintain the end-effect.

ANTRODUODENECTOMY AND X-RAY IRRADIATION IN THE TREATMENT OF DUODENAL ULCER

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PHYSICIANS and surgeons should be dissatisfied with the generally accepted surgical treatment of duodenal ulcer—subtotal gastrectomy with gastrojejunostomy. To remove most of the stomach for a small lesion of the duodenum is often successful, but the operation is not without risk to life, postoperative complications are not uncommon, and the patient's subsequent health is sometimes marred by minor or major discomfort (Wells and Welbourn 1951).

Many alternative operations have been devised, such as vagotomy, usually combined with gastro-enterostomy or pyloroplasty (Healy et al. 1951), and even replacement of the stomach by an excised portion of the colon (Moroney 1951), but none appears to be entirely satisfactory.

A study of patients subjected to subtotal gastrectomy for chronic duodenal ulcer (Grayton Brown 1951, Doig and Wood 1952) encouraged us to seek a better method of treatment. A series of 10 cases were treated by X-ray irradiation of the stomach (Ricketts et al. 1949), but the result was disappointing, 4 cases relapsing after six to nine months. In November, 1951, we decided to combine resection of the gastric antrum and the first part of the duodenum containing the ulcer (antroduodenectomy) with X-ray irradiation of the stomach so as to reduce the high concentrations of acid and pepsin in the gastric secretion which remain after this limited resection. Antroduodenectomy was followed by an end-to-end anastomosis allowing the food still to pursue its physiological course. The patient was thus left with a stomach of good capacity enabling liberal meals to be enjoyed. So far, 12 cases of chronic duodenal ulcer in recent relapse have been subjected to this treatment and the results have been encouraging. Though at least five years must elapse before the true worth of this treatment can be assessed, we report here our technique and early observations.

Antroduodenectomy combined with X-ray irradiation is also applicable to innocent antral and preantral ulcers. Antral ulcers are included in the antroduodenectomy; preantral ulcers are included by extending the excision along the lesser curvature. This will be reported elsewhere.

Three plans for the treatment of chronic duodenal ulcer were tried: X-ray irradiation alone; antroduodenectomy followed two months later by X-ray irradiation; and X-ray irradiation followed two months later by antroduodenectomy.

METHODS OF STUDY

Most of the patients in each group were studied by the following methods:

Clinical observation, special attention being paid to appetite, abdominal discomfort, weight, and general sense of well-being.

Serial histamine test-meals using 0·3 mg. of histamine (indicator, Töpfer's reagent) immediately before and two weeks after operation, immediately before and after irradiation, then usually at monthly intervals for six months, three-monthly till the end of a year, and then six-monthly.

Serial "overnight" test-meals (complete emptying every two hours for twelve hours) at intervals of three to six months. Also occasional insulin test-meals (15 units intravenously).

Serial gastric biopsies before and two months after operation, before and after irradiation, then at intervals of one or two months for six months, and then at longer intervals.

The gastric biopsy fragments were obtained from the body of the stomach with the flexible gastric biopsy tube designed in our clinical research unit (Wood et al. 1949a and b). Sections of these fragments were stained with hæmatoxylin and eosin, Best's mucicarmine, and the trichrome stain described by Motteram (1951). In the present series 138 successful gastric biopsies were performed at 151 attemps on 25 of the cases reported here. There were no complications.

The total experience of our unit with this method of gastric biopsy in patients with a wide range of diseases is 926 successful biopsies on 645 patients at 1060 attempts (Wood 1951). The only complication was immediate hæmorrhage, 10 patients having slight or moderate hæmatemesis, frank melæna, or clinical anæmia; none was critically ill, and all responded well to medical treatment.

X-RAY IRRADIATION ALONE

In September, 1949, we began to treat duodenal ulcer with X-ray irradiation alone, following the lead of Walter Palmer and his colleagues of Chicago (Ricketts et al. 1949) and Holman and Lewis (1941) in Tasmania. Experience caused gradual modification and improvement of our initial technique of irradiation until a satisfactory one was evolved. Briefly, this consisted in giving

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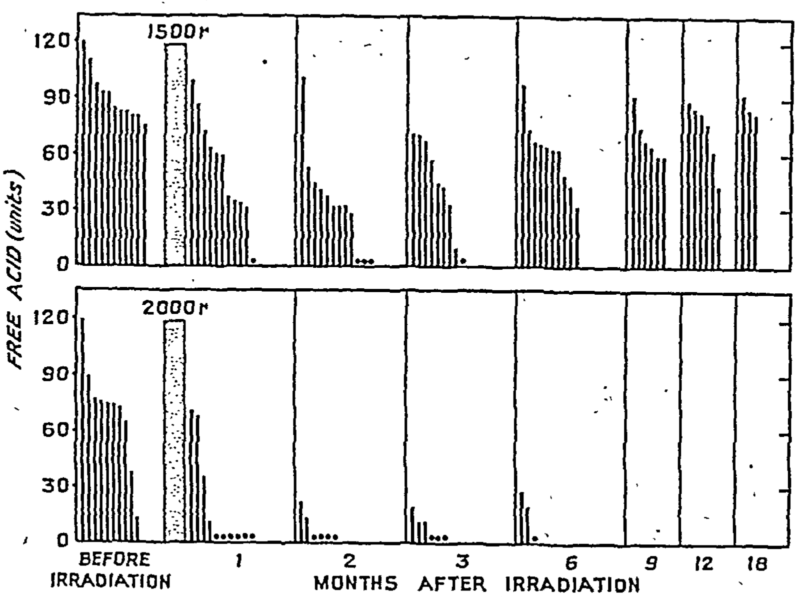

Fig. 1—Effect of X-ray irradiation of stomach on secretion of free acid shown by serial histamine test-meals. Each vertical line represents the greatest increase of free acid in a single test-meal ; dots represent achlorhydria.

It will be noted that 1500r produced reduction in secretion of free acid with a slow return to higher levels after two months. In the few cases receiving a dose of 2000r the response was increased, but sufficient time has not elapsed to observe its duration. This increased response may have been due, in part, to improved technique in centring the irradiation over the stomach. Two patients, who had a second course of irradiation after their gastric mucosa and secretions had returned to pre-irradiation structure and levels, are included twice. Two other patients, who had antroduodenectomy after irradiation, are not included.

2000r during three weeks, great care being taken to ensure accurate centring over the stomach so that a small port could be used. To achieve accurate centring attention was paid to the maintenance of uniform posture and constant gastric distension. With this technique the response was optimal.

Serial histamine test-meals revealed that X-ray irradiation decreased the volume of secretion and the concentration of free acid and pepsin (fig. 1). Serial gastric biopsies showed a corresponding change (fig. 2). Before irradiation the biopsy fragments were usually within normal limits or near normal; after irradiation there was infiltration of the mucosa with polymorphonuclear leucocytes, lymphocytes, and plasma cells, together with slight to moderate atrophy or loss of the normal staining characteristics of the cells secreting acid and pepsin (figs. 3 and 4). The early changes were in the superficial layers, but later an active atrophic gastritis developed. These biopsy findings have been described in detail by Doig et al. (1951).

The greatest change in gastric secretion and in the biopsy fragments took place during the second and third months. This was followed by a return of gastric secretion to the pre-irradiation level and by regeneration of the mucosa. With the dosage first used in this series, 1500r, complete or almost complete recovery was usually evident six to nine months after the irradiation. This recovery time may be prolonged with 2000r, the increased dosage used in our more recently treated cases, but sufficient time has not yet elapsed to ascertain this.

With this technique most patients remained well and able to work during the course of irradiation. A few experienced moderate nausea; one who had had recent hæmorrhage had a slight hæmatemesis. The dosage used produced, at the most, minimal skin erythema.

The case of one of our early patients, a man aged 35, who responded very satisfactorily to X-ray irradiation alone, has been reported in detail by Doig et al. (1951). After irradiation there was a pronounced change in his gastric secretion and biopsy fragments, with restoration to the original levels and structure after fifteen months. When seen in July, 1952, three years after the irradiation, he was still free from symptoms.

The following case is also of interest:

Case 1.—A fitter, aged 18, was admitted to hospital in July, 1950, with a severe hæmatemesis. He had had intermittent ulcer dyspepsia for four years following a hæmatemesis. Barium-meal radiography showed a grossly deformed duodenal cap but no crater. X-ray irradiation 1500r was given five weeks after the bleeding had ceased, and he remained well until last seen two years later. After the irradiation the gastric acidity was reduced for five months and serial gastric biopsies showed moderate cellular infiltration and atrophy, which resolved completely after eight months. Barium-meal radiography showed no change.

Our observations indicated that a dose of 1500r often caused a suboptimal reduction in the gastric secretions (fig. 1). Moreover, often there was very little histological change in the gastric biopsy fragments (fig. 2). The dose was therefore increased to 2000r, and this led to an increase in the average response, in both the gastric secretions and the gastric mucosa, without causing any additional inconveniences to the patient (figs. 1 and 2). Some of this increase in response may be attributed to better centring during the X-ray irradiation.

It soon became evident that one course of X-ray irradiation usually produced immediate and complete

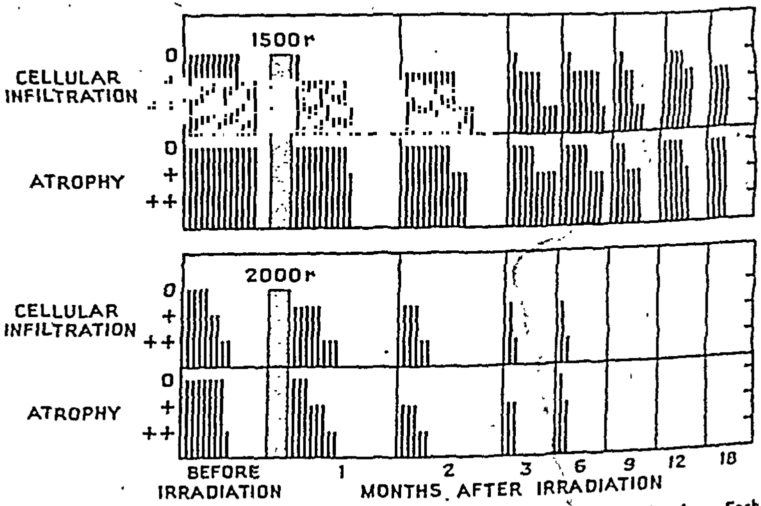

Fig. 2—Effect of irradiation on gastric mucosa shown by serial gastric biopsies. Each vertical line represents a single biopsy result. Reaction of gastric mucosa was judged by cellular infiltration especially in lamina propria, and by atrophy especially of cells secreting acid and pepsin.

It will be noted that with both 1500r and 2000r some general change in biopsy fragments occurred, but change was not severe. Findings suggest that 2000r will cause a greater and more prolonged reponse than will 1500r, but sufficient time has not elapsed to assess this. This improved response to 2000r may have been due in part to improved technique of centring the irradiation over the stomach.

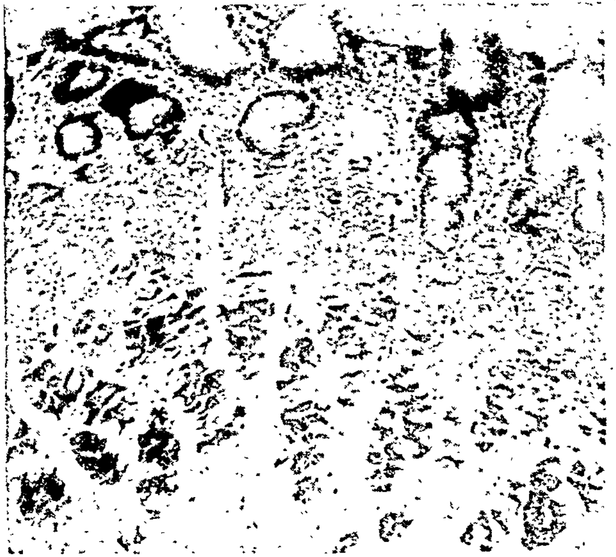

Fig. 3—Fragment of gastric mucosa obtained by biopsy immediately before irradiation in male, aged 51, with chronic duodenal ulcer. Histamine test-meal showed free acid 71 units. Appearances are normal, surface epithelium being regular and cuboidal, gastric pits regular, and acid-secreting and pepsin-secreting cells of tubules staining distinctly dark and being well differentiated. (Motteram's trichrome stain. × 135.)

remission of symptoms. However, these good effects were not always maintained. Of the 10 patients followed up for an average period of seventeen months (range 8–36 months) 4 have remained free from symptoms for eight, nine, twelve, and twenty-two months, and 2 had minor symptoms during twenty-seven and thirty-six months of observation (see table). The remaining 4 had severe relapses after eight, twelve, twelve, and twenty-five months; 1 of these was given a second course of X-ray irradiation (1500r) twelve months after the first, and has been well for a further five months, and the remaining 3 required surgery because of severe and persistent pain (1 case) or pain and vomiting (2 cases, with 1 death after gastro-enterostomy performed for obstruction in a patient with a severe mitral stenosis).

These disappointing results, together with our experience that severe chronic relapsing ulcer of the duodenum rarely showed permanent healing with "medical" treatment, led us to the decision to remove the ulcer by surgical means.

ANTRODUODENECTOMY AND X-RAY IRRADIATION

We were loth, however, to resort once again to the radical operation of subtotal gastrectomy with gastrojejunostomy. It seemed rational to adopt a more physiological and less drastic course by removing only the first part of the duodenum containing the ulcer together with the gastric antrum, and to perform an end-to-end anastomosis (figs. 5 and 6). This left the patient with a larger stomach than is provided by the somewhat similar Billroth-I operation. We call this operation antroduodenectomy to emphasise the limited nature of the gastric resection. We were encouraged to remove the antrum because it is a common site of ulcer formation; moreover Dragstedt et al. (1951) have shown in experiments on animals that, when the stomach is anastomosed to the small bowel, ulceration tends to occur, but this tendency is reduced considerably when the gastric antrum is excised.

As we found that antroduodenectomy per se usually caused no major reduction in the gastric secretion of acid and pepsin, we decided to combine the operation with X-ray irradiation.

Some Surgical Considerations

Consideration of the anatomy of the duodenum led us to realise that duodenal mobilisation is much more practicable than has been generally realised (Ogilvie 1952). It seemed that if most duodenal ulcers are confined to the first part they should be suitable for resection. Further, it was found by examining the duodenum in fresh cadavers that the average distance between the pylorus and the ampulla of Vater was 10 cm. Even if this should be diminished somewhat by scarring, an ample length should be available to allow resection of the ulcer and still leave enough duodenum for an end-to-end anastomosis.

It remained to prove this by operative trial. In the 18 consecutive cases of chronic duodenal ulcer where this has been attempted, including 6 in which the ulcer had completely penetrated into the pancreas, the anastomosis was done and was entirely successful in 16. Complications were encountered, however, in 2 elderly patients.

Case 2.—A man, aged 83, had acute severe duodenal bleeding immediately before and during laparotomy, the common bile-duct having been severed when a hasty resection of a large penetrating ulcer was being performed, but suture of the duct proved successful and the patient was discharged from hospital "fit" three weeks after operation.

Case 3.—A wasted man, aged 73, demanded operation for severe persistent pain caused by a huge ulcer penetrating into the pancreas. An anastomotic ulcer developed, and he died from hæmorrhage ten weeks after operation.

Technique of Antroduodenectomy

Most duodenal ulcers are in the proximal portion of the first part of the duodenum and are easily resected. In those which penetrate, the erosion is on to the anterior surface of the pancreas. This site is usually a safe distance from the common bile-duct and pancreatic duct, but great care must be taken not to damage these structures.

Occasionally, the ulcer lies over the gastroduodenal artery, necessitating dissection further to the right of this vessel. Here there is risk of dissecting near the common bile-duct, which should be identified in the free edge of the lesser omentum and traced down to the duodenum.

Many penetrating ulcers appear irremovable at first, but perseverance will be rewarded by the liberation of a flange of healthy duodenum beyond the ulcer. This somewhat tedious dissection is facilitated by the exposure permitted by modern anæsthesia, and by the fact that

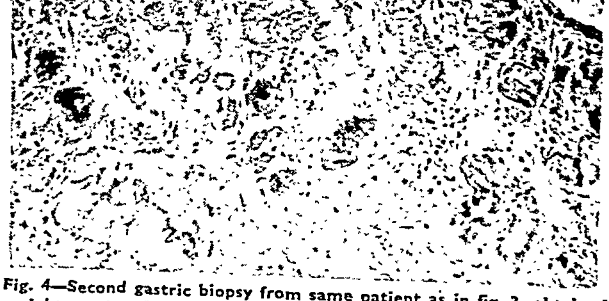

Fig. 4—Second gastric biopsy from same patient as in fig. 3, obtained eight weeks after irradiation 2000r, illustrating typical *irradiation effects*. Cells of epithelium are now irregular, and their cytoplasm stains darkly. Polymorphs are numerous in lamina propria and in dilated pits. Tubules are reduced in number and *most cells secreting acid and pepsin now stain poorly and indefinitely*. Histamine test-meal showed achlorhydria. (Motteram's trichrome stain. × 135.)

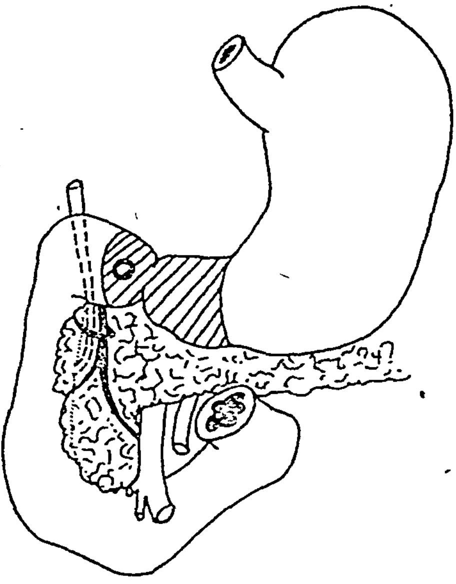

Fig. 5—Relations of ulcer-bearing area of duodenum to pancreas, gastroduodenal blood-vessels, and common bile-duct. Hatched area shows portion excised in antroduodenectomy.

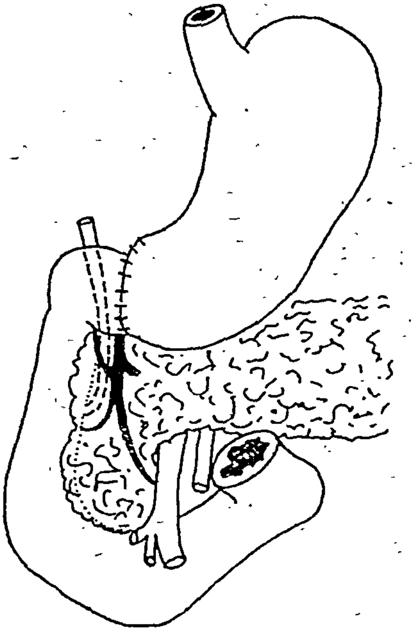

Fig. 6—Appearances following antroduodenectomy and gastroduodenostomy.

only a restricted surgical procedure, gastroduodenostomy, remains to complete the operation.

To aid primary healing it is important to preserve the blood-supply of the cut surfaces of stomach and duodenum to be used in the anastomosis. Healing is also favoured by doing the operation under a cover of penicillin and streptomycin, beginning the day before operation and continuing for at least six days.

Results

Most of our patients suffered little immediate postoperative discomfort. Usually they sat out of bed on the third day after operation, and walked round the ward before the end of a week. Within a month of operation they enjoyed large meals and did not experience any sense of fullness or discomfort.

As previously stated, it was decided to combine X-ray irradiation with antroduodenectomy because this limited resection had little effect on the gastric secretion measured by histamine, insulin, and "all night" test-meals given immediately before and two weeks after operation.

RESULTS OF TREATMENT OF CHRONIC DUODENAL ULCER BY (*a*) X-RAY IRRADIATION ALONE, (*b*) ANTRODUODENECTOMY COMBINED WITH X-RAY IRRADIATION

(a) *Treatment by irradiation alone:*

No. of cases 10 (M 9, F 1); average age 43 (range 17–71).
Reason for irradiation: pain 5; pain and hæmorrhage 5.
Average duration of pain 12 years (range 0–28 years).
[illegible] no symptoms 9; slight hæmorrhage 1.
[illegible] (average 17 months, range 8–36
[illegible] 4; mild relapse 2; moderate or severe relapse 4 (after 8, 12, 12, and 25 months).

(b) *Treatment by antroduodenectomy followed 2 months later by X-ray irradiation:*

No. of cases 10 (M 9, F 1); average age 46 (range 34–73).
Reason for operation: pain and vomiting 6; pain and hæmorrhage 2; pain, hæmorrhage, and vomiting 1; pain only (previous perforation) 1.
Average duration of pain 10 years (range 6–28 years).
Progress during immediate postoperative period good in all cases.
Progress during 2 months between operation and irradiation good in 10.
Progress during irradiation: no symptoms 8; slight or moderate nausea 2.
Progress during follow-up (average 3 months, range 0–7 months): no symptoms 9; slight dyspepsia 1.

Antroduodenectomy was performed in 8 other cases: 2 were preceded by irradiation and have progressed favourably for 3 and 7 months; 3 are about to undergo irradiation 2 months after a successful operation; 2 were considered unsuitable for irradiation owing to old age and low secretion; and 1, aged 73, died from anastomotic ulcer and hæmorrhage ten weeks after operation (no irradiation given).

However, six weeks later, lower concentrations of acid were sometimes recorded.

The ideal plan appeared to be first to reduce the acid by irradiation and then to perform antroduodenectomy two months later, when the secretion of acid was reduced and the inflammation round the ulcer had perhaps subsided. Indeed 2 patients were subjected to this procedure with good results, and we are treating others by this means (see table). Both patients pursued a highly satisfactory course throughout, and are now well four and seven months after operation. After irradiation serial test-meals showed reduced secretion (volume, acid, and pepsin) and serial gastric biopsies moderate irradiation changes. After operation no treatment, either medicinal and dietetic, was ordered or taken. The only restriction was to forbid alcohol, because excessive amounts might reduce the gastric secretion and so impair the significance of the serial test-meals and gastric biopsies (Doig and Wood 1952, Funder and Weidin 1952). The record of one of these patients is as follows:

Case 4.—A male machinist, aged 60, was admitted to hospital in September, 1951, having had severe recurrent ulcer dyspepsia for fifteen years and three major hæmorrhages in the past four years. Barium meal: duodenal ulcer. Histamine test meal: hyperchlorhydria (83 units of free acid). Gastric biopsy: normal. On Sept. 30, 1951, X-ray irradiation 1500r was given without producing any discomfort. There was a decrease in acid secretion to 20 units, and biopsy showed irradiation changes. On Dec. 10 antroduodenectomy was performed for a small chronic ulcer in the first part of the duodenum. Convalescence was good, and the patient remained symptom-free until last seen seven months after operation. Four months after the irradiation the acid was still reduced (48 units) and the biopsy still showed moderate irradiation changes, but during the next five months there was a further increase in acid and resolution of the changes in the mucosa.

However, it seemed unwise to administer deep X-ray irradiation to patients in active relapse, especially when there had been recent hæmorrhage, severe pain, or symptoms of obstruction. So the procedure most often adopted was to perform antroduodenectomy and to follow this two months later by irradiation in a total dose of 2000r given over three weeks.

To reduce the activity of peptic digestion during the period between the antroduodenectomy and the completion of irradiation, a full medical régime was instituted, with powder, belladonna, frequent milk drinks, and diet. At the completion of irradiation this was discontinued.

In this group 16 cases of chronic duodenal ulcer have now been subjected to antroduodenectomy and have progressed as follows (see table): 10 have had both antroduodenectomy and X-ray irradiation from one to eight months ago (average four months) and have enjoyed excellent health free from dyspepsia, taking full unrestricted diet and no antacids or other medical treatment; 3 are about to have their irradiation and are very well; 2 elderly patients with low acid secretion are very well and are being observed by serial test-meals; and 1 died, as previously described.

The following case is representative of this group:

Case 5.—A sorter, aged 61, was admitted to hospital in January, 1952, having had dyspepsia for nine years, together with three severe hæmatemeses. Barium-meal: deformity of duodenal cap. Histamine test-meal: free acid 80 units. Antroduodenectomy revealed a chronic ulcer, 4 × 8 mm., just distal to the pylorus. The postoperative course was uneventful, and after two months the patient was given a course of X-ray irradiation 2000r, during most of which he worked and experienced only slight nausea. A full ulcer régime was observed between the operation and the completion of irradiation. The operation produced no fall in acid secretion (free acid 88 units) or any appreciable change from normal in the gastric mucosa obtained by gastric biopsy. Irradiation caused a fall in acid to achlorhydria, together with cellular infiltration and moderate atrophy in the biopsy fragments.

When last seen six months after operation the patient had remained free from symptoms and had gained 1 st. in weight. He had eaten full unrestricted meals without discomfort and refrained from taking medicinal treatment. Test meal: hypochlorhydria (free acid 20 units). Gastric biopsy: moderate irradiation reaction. Barium meal: normal contours and emptying rate: capacity reduced to about two-thirds of normal.

Barium-meal radiography was done in 5 patients six months after antroduodenectomy, and the results were uniform and most satisfactory. The stomach was of reasonable capacity, appearing to be from half to two-thirds of normal. Emptying was hastened but not excessively rapid. The exact site of the anastomosis was difficult to define, the gastric and duodenal mucosæ fusing imperceptibly. The mucosal pattern was well defined and of normal appearance, there being no suggestion of ulcer.

Gastroscopy was done in 2 patients six months after operation. In both patients the mucosa in the body of the stomach and at the site of the anastomosis appeared normal.

COMMENTS

Antroduodenectomy was rarely difficult, though it demanded a detailed knowledge of the anatomy of the duodenum and meticulous care to provide a successful anastomosis, yet avoiding damage to the surrounding structures, particularly the bile-duct. Assisted by antibiotics and skilled postoperative management, the patients usually recovered rapidly from the immediate effects of the operation and maintained satisfactory progress.

The X-ray irradiation of the stomach to reduce the secretion of acid and pepsin for a period of six to nine months caused little or no discomfort in the dosage recommended, 2000r. After a week of irradiation in hospital the patient received the remainder as an out-patient, the treatment being taken at the end of the day, after work.

Following this scheme of treatment the patients enjoyed a life free from discomfort and pain, free from the irksome demands of "medical treatment" with its strict dietetic régime—powders, belladonna, phenobarbital, endless glasses of milk, and often the fussy dictates of an apprehensive wife and family.

In the present series a comprehensive study was made of gastric secretion and the histology of the gastric mucosa to discover the best dosage of X-ray irradiation. These studies provided valuable data, and it is hoped that a satisfactory régime has now been evolved. Once this has been achieved, gastric biopsy can be discarded entirely, and only an occasional test-meal need be given. Our investigations have placed a considerable burden on our patients, and we are most grateful to them for their cheerful help.

We predict a higher proportion of satisfactory results from this form of treatment than from other methods. For it is reasonable to expect that, with the excision of the vulnerable antrum and first part of the duodenum, and with the depression of acid and pepsin secretion by irradiation for six to twelve months, the body of the stomach and the second part of the duodenum will remain free from ulceration. Experience suggests that those patients who develop ulceration after simple gastro-enterostomy, or subtotal gastrectomy with gastro-jejunostomy, do so during the first year after operation. Our patients are, in part, protected from the action of hyperacidity and high pepsin secretion during this period. Moreover the second part of the duodenum naturally enjoys a high degree of immunity from ulceration, and it may be anticipated that this immunity will continue after antroduodenectomy.

Many years must pass before success can be claimed for the treatment of severe chronic duodenal ulcer by antroduodenectomy and X-ray irradiation; but our hopes have been raised by our early experiences.

SUMMARY

Ten patients with chronic relapsing duodenal ulcer were treated by X-ray irradiation of the stomach, following the work of Palmer and his colleagues (Ricketts et al. 1949). Serial test-meals and gastric biopsies showed a moderate irradiation effect lasting from six to nine months. With return of the secretions and the biopsy findings to their original state 4 of the 10 patients had a severe relapse in their ulcer symptoms, 3 requiring surgery.

Therefore it was decided to combine irradiation to the stomach with local excision of the ulcer-bearing portion of the duodenum and the gastric antrum (antroduodenectomy). In 2 cases irradiation was given before, and in 10 after, the operation. 8 other cases subjected to antroduodenectomy are also reported.

Antroduodenectomy was followed by gastroduodenostomy, thus maintaining the natural continuity of the stomach and the duodenum. Moreover the limited resection left the patient with a stomach of good capacity.

Most of the patients stood the operation very well indeed. The postoperative course was most satisfactory, and the lack of symptoms during the follow-up encouraging. One elderly patient had fatal complications.

Antroduodenectomy per se did not cause a major reduction in the secretion of acid and pepsin.

X-ray irradiation of the stomach using the optimum dosage (2000r) caused little or no inconvenience to the patient. Serial test-meals and gastric biopsies revealed good lowering of the secretion of acid and pepsin, together with pronounced, but not gross, changes in the gastric mucosa.

The early results of the treatment of chronic duodenal ulcer by antroduodenectomy and irradiation are encouraging; but many years must pass before a significant comparison with other methods can be made.

We wish to thank the members of the honorary medical staff of the Royal Melbourne Hospital who have aided us with our study. Our special thanks are due to Mr. Julian Orm Smith and Dr. W. E. King. We are also grateful to Sister M. Hughes for her invaluable help.

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MINOR DEGREES OF PARTIAL THORACIC STOMACH IN CHILDHOOD*

REVIEW OF 112 CASES

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The condition known as a short œsophagus and partial thoracic stomach has been recognised for some years. Recent advances in thoracic surgery and radiological diagnosis have renewed interest in this abnormality, with the evolution of new ideas concerning its ætiology and clinical characteristics.

So-called congenital stenosis of the œsophagus (Beatty 1928, Sheldon and Ogilvie 1929) was shown to be often associated with a short œsophagus and a partial thoracic stomach (Kelly 1930, Findlay and Kelly 1931, Clerf and Manges 1934). Johnstone (1941, 1943) and Allison et al. (1943) later demonstrated that this type of stricture was not a congenital abnormality but was secondary to œsophagitis induced by reflux of gastric contents. This occurs as a result of incompetence of the gastro-œsophageal valve mechanism. Such an incompetence, associated with hiatus hernia but usually without œsophageal stricture, is now known to be relatively common in adults. It is also becoming increasingly recognised that a similar, if not identical, condition occurs in infancy.

Our present preliminary report is based on a study of 112 children with a short œsophagus and a minor degree of partial thoracic stomach (the thoracic part not exceeding 15% of the whole stomach). Infants and children with a greater proportion of the stomach situated above the diaphragm and those with para-œsophageal pouches, herniæ associated with redundancy of the œsophagus, and chalasia of the cardia (Neuhauser and Berenberg 1947) were excluded from consideration. Of the 112 patients 43 have been followed up for four years or more from the onset of symptoms, and the oldest is now aged 36.

INCIDENCE

In the medical literature of the last twenty-two years we have found reference to only just over 100 cases in children; yet in a single year (1951) 18 infants under the age of 12 months with symptoms demonstrated to be due to a partial thoracic stomach have been observed in the Children's Hospital in Birmingham. This is about a fifth of the number with hypertrophic pyloric stenosis treated in the same period. As only infants with relatively severe clinical manifestations are likely to attend hospital, the true incidence cannot be assessed; but it is probably greater than this figure indicates.

There is no reason to suspect any recent alteration in the incidence of this abnormality, and it is therefore reasonable to presume that in the past many cases in infancy have remained unrecognised. Moreover, despite present-day knowledge of the clinical and radiological features, relatively few cases are diagnosed for the first time in children more than 2 years of age. This further suggests that many affected infants become symptom-free in later childhood. Both these suppositions are supported by the records of the Birmingham Children's Hospital for 1940–50 and by subsequent review and radiography of selected children. This review has brought to light 45 children with a partial thoracic stomach previously undiagnosed. Most of these are now *free from symptoms.*

CLINICAL FEATURES

The medical histories of the 112 children showed that vomiting was the principal and invariable symptom, dating from birth or from the neonatal period in 90%. Under the age of 4–6 months it was often projectile and came on during or immediately after feeds. The vomit consisted of most or all of the feed and always contained much mucus; rarely it was bile-stained. Blood was often present in the vomit, usually only as a few flecks. Obvious hæmatemeses were rare. Except on a few occasions the blood was not bright red but altered in appearance and often not recognised by the parents—an important point to remember in history-taking. Constipation was not a prominent feature, and melæna was seldom recorded. The infants appeared hungry and took their feeds well. *A failure to gain weight was usual, and in severe* cases there was moderate dehydration. Visible gastric peristalsis was occasionally observed.

In later infancy all these symptoms and signs might persist, but the vomiting lacked the original projectile quality and visible gastric peristalsis was not observed. At this age the association of vomiting with such factors as coughing, emotion, and recumbency tended to become more obvious. Later this sometimes constituted the most prominent and characteristic symptom.

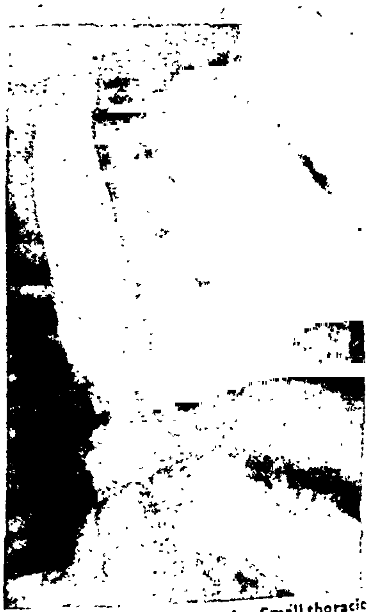

Fig. 1—Infant aged two weeks. Small thoracic loculus of stomach.

According to their clinical course, cases could be divided into three broad groups. In the first group the condition was essentially benign in that the symptoms had ceased or very largely abated by the age of 2 years and later *complications* were not observed. Usually there was clinical improvement on weaning to a mixed diet.

In the second group symptoms persisted longer and there was no significant improvement until the child was 4 years old or more. Even then periodic relapses were occasionally encountered for a *further number of* years. Vomiting when the child was recumbent at night was sometimes a prominent feature; occasionally such night vomiting was the only symptom. In the vast majority of cases vomiting was either not improved, or was aggravated, by the introduction of mixed feeding. Dysphagia was an additional symptom in some children in this group. On occasions food was said *to stick* in the throat or behind the sternum. *Drinking might give* relief; but, failing this, the child would vomit the obstructing fragment and then complete a hearty meal. Other children, even at the age of 2 or 3 years, learned to provoke vomiting to relieve their symptoms by stimulating the back of the throat with the fingers. In a few instances food remained in the gullet for twenty-four hours without causing discomfort except inability to swallow. Such episodes did not necessarily indicate the presence of an organic stricture and might occur after all other symptoms had ceased. Anæmia was apparent in a few children; it was hypochromic and might be explained by chronic blood-loss and dietary insufficiency.

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* Partly based on a paper presented to the annual meeting of the British Pædiatric Association on May 1, 1952, by I. J. C.

In both the foregoing groups the progress of improvement was similar and characteristic. There were remissions of increasing duration interspersed with decreasing relapses. Many of the children in the second group, as in the first, eventually lost all symptoms, although the time of recovery might be delayed until later childhood. A few were left with a tendency to vomit on such provocation as minor ailments and excitement.

The third group consisted of cases with a complicating œsophageal stricture. Here symptoms were predominantly of dysphagia secondary to the œsophageal obstruction. None of these children showed any symptomatic improvement with the introduction of mixed feeding, and most became worse.

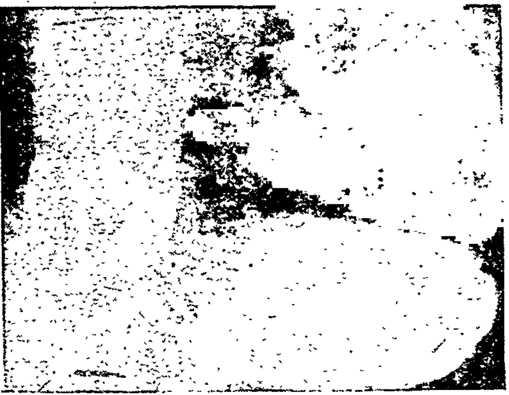
Fig. 2—Child aged 13 months. Showing continuity of gastric mucosal folds through wide diaphragmatic hiatus, and loss of gastro-œsophageal angle.

DIFFERENTIAL DIAGNOSIS

In early infancy the differential diagnosis was chiefly from hypertrophic pyloric stenosis, particularly in view of the projectile vomiting and the visible gastric peristalsis. Important distinguishing features included the history of vomiting from birth, the absence of a palpable pyloric tumour, altered blood in the vomit, and sometimes dramatic response to nursing in a propped-up position. Other conditions to be differentiated at this age included aerography, congenital intestinal obstruction, feeding problems, "pylorospasm," hæmorrhagic disease of the newborn, and cerebral irritation. In later infancy and early childhood renal acidosis, peptic ulceration, cyclical vomiting, and intestinal obstruction might simulate a partial thoracic stomach. During the recovery phase coughing associated with bronchitis or a simple cold might provoke vomiting and so suggest pertussis.

RADIOLOGY

The 112 children here considered received a total of 255 examinations, of which 212 were by one observer (R. A.). Two main features were observed—gastro-œsophageal reflux and a partial thoracic stomach.

If the reflux was severe, barium moved in and out of the stomach synchronously with respiration, but often reflux had to be provoked by manœuvres to raise the intra-abdominal pressure. Occasionally all such tests failed until the child began to cry. Eructation of air could sometimes temporarily mimic the appearances of hiatal incompetence.

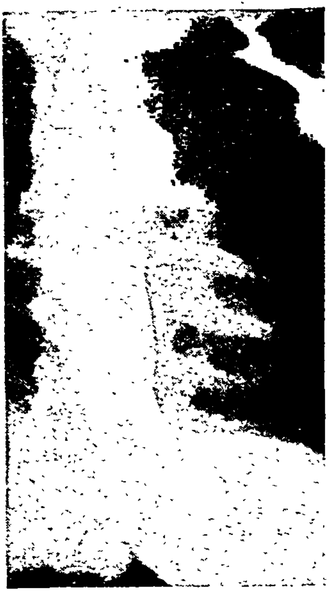
Fig. 3—Infant aged 4 months. Wide hiatus with very free reflux, loss of the gastro-œsophageal angle, and absence of indication of cardia (which at necropsy a few weeks later was found 2 cm. above diaphragm).

The other pathognomonic radiological feature was that the œsophagus had a normal course, without redundancy, but ended above the diaphragm at the highest point of a small, or very small, thoracic loculus of stomach. In the majority of cases there was a constriction representing the cardia; below this the lumen was expanded, often asymmetrically with respect to the axis of the œsophagus (fig. 1). The gastro-œsophageal angle was reduced, and the gastric mucosal folds converged upwards towards the hiatus, which was wider than usual (fig. 2). These folds could be seen to enter the thoracic loculus of the stomach, where they appeared as rather coarse vertical rugæ, although sometimes irregular folds (greater-curvature type) were also present. At the constriction representing the cardia they were gathered together, to diverge again above as finer œsophageal folds. Sometimes the thoracic part of the stomach was evident at a glance; but often it only filled completely for very fleeting periods, especially when reflux was slight or absent, and not infrequently a correctly timed radiograph was unobtainable. This emphasised the great importance of careful fluoroscopy; occasionally several examinations had to be made before the diagnosis was established.

In a few children reflux appeared at first to be due to a wide incompetent hiatus alone. In such the œsophagus was often dilated but appeared as a tube of even calibre, with no locally expanded portion to indicate the thoracic

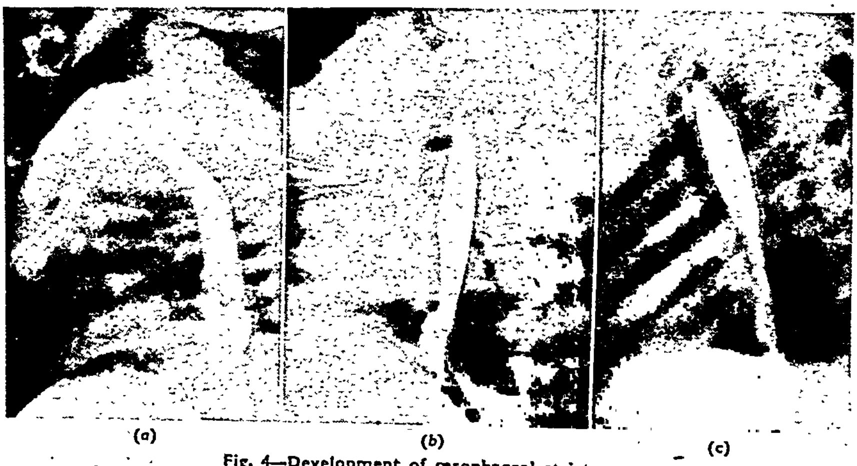
(a) (b) (c)

Fig. 4—Development of œsophageal stricture:
(a) Aged 3 months. Shallow constriction above diaphragm at site of cardia.
(b) Aged 15 months. Ulcer-like niche just above cardia.
(c) Aged 2½ years. Stricture

part of the stomach and with no constriction at the cardia, especially when the gullet was well filled. But close observation usually showed a transient yet recurrent slight constriction just above the diaphragm; minimal amounts of barium showed that the mucosal folds were gathered together at this level, diverging below it to pass vertically into the abdomen. Such appearances might mimic chalasia (hiatal incompetence with a normally situated cardia). This point is illustrated by 1 infant in whom the hiatus appeared wide but there was no indication of the cardia (fig. 3), yet subsequent necropsy confirmed that the stomach was partially thoracic. Berenberg and Neuhauser (1950) regarded a supra-diaphragmatic stomach as rare in infancy, which is contrary to our experience. Perhaps some of their cases of "chalasia" were examples of this type of partial thoracic stomach.

When a complicating stricture was present, the exact point of transition from œsophagus to stomach was often ill defined. Only 1 child developed a stricture while under observation: the shallow indentation at the cardia became deeper, and an ulcer-like niche preceded the stricture (fig. 4). Several other infants showed slight irregularities of œsophageal contour, probably due to œsophagitis, but these resolved without stricture.

Until the time of weaning, no radiological difference was demonstrable between the first and second groups. Though in some infants minimal reflux suggested the probability of an early improvement, gross reflux did not necessarily mean a protracted course. After symptomatic improvement the partial thoracic stomach persisted unchanged, although reduced or absent reflux made it much more difficult to demonstrate. Occasionally barium ceased to regurgitate into the œsophagus although it still passed up into the thoracic part of the stomach; more often an effective closure mechanism seemed to develop at the level of the diaphragm, thus preventing or reducing the amount of barium passing into the thorax.

When a stricture had developed, a stationary state seemed more common than progression. Two children treated by repeated dilatation lost all X-ray evidence of stricture.

TREATMENT

Medical treatment often gave very satisfactory results, particularly when begun early in infancy. The essential basis of such therapy was to maintain the baby in as near an upright position as possible, both by night and by day. This was done with the aid of a specially constructed harness, because elevation of the head of the cot was found to be inadequate.

Feeds to meet the infants' full nutritional requirements were introduced cautiously over several days, because too rapid an increase tended to cause diarrhœa. If vomiting persisted despite an upright position, thickening of the feeds with cornflour or 'Benger's Food' was a valuable additional measure. Home treatment was fully satisfactory if the mother was sensible and coöperative.

We shall not discuss surgical treatment. It is, however, our opinion that in the large majority of cases a minor degree of partial thoracic stomach in infancy is a relatively benign condition. Thus both the *indications for surgery and the assessment of its results* should be studied critically.

PROGNOSIS

It is reasonable to suppose that most children with complicating strictures reach hospital practice, and on an average during the last sixteen years 1 case of œsophageal stricture has been admitted each year to the Children's Hospital, Birmingham. When this figure is compared with the total of 18 infants with a partial thoracic stomach admitted in one year (1951) it suggests that only a very small proportion of all affected children eventually develop a stricture—probably less than 10%. This small proportion is contrary to the impression conveyed by a review of the published reports, according to which [illegible] of about 103 children had an œsophageal stricture.

As already indicated, the effect of weaning to solids seems to be a useful prognostic sign. If weaning produces no symptomatic improvement, a prolonged course with vomiting until the age of 4 years or more is likely. Our observations suggest that about a quarter of all untreated cases fall into this group, which includes the relatively few who develop an œsophageal stricture. The other three-quarters have a benign course, with cessation or great relief of symptoms by the age of 2 years and no subsequent relapse in childhood.

DISCUSSION

Whether the basic defect is a congenital disproportion of the œsophagus or a defect of the diaphragmatic hiatus with a secondary sliding hernia, the cause of symptoms is the same—i.e., the incompetence of the gastro-œsophageal valve mechanism, permitting reflux of gastric contents into the œsophagus. Some workers (Allison 1948, Husfeldt et al. 1951, Belsey 1952) have strongly favoured the view that the hiatal defect is nearly always primary, and this is undoubtedly often true of cases where much of the stomach lies in the chest. Where, however, only a small and often tubular loculus of stomach lies above the diaphragm, a primary hiatal defect seems less certain to be the explanation in all instances. Accordingly we have preferred the non-committal term "partial thoracic stomach" to either "congenital short œsophagus" or "hiatus hernia."

It is apparent that the condition is a relatively common cause of vomiting in infancy, and in the past has often masqueraded under various unsatisfactory diagnoses. Increased use of fluoroscopy will be well rewarded, although not uncommonly it requires considerable experience and sometimes several examinations are needed before the diagnosis is established.

The relatively short and benign course in three-quarters of the children, the gradual symptomatic cure in many of those with more prolonged vomiting, and the low incidence of œsophageal stricture are contrary to the impression conveyed by the literature, in which complicated cases predominate. The eventual outcome in adult life is still unknown, and it is interesting to speculate how many of those patients presenting in later years with symptoms attributable to gastro-œsophageal incompetence have a forgotten history of vomiting in infancy.

SUMMARY

From a study of 112 children with minor degrees of partial thoracic stomach an account is given of the clinical picture, radiology, treatment, and prognosis during infancy and childhood.

This condition is a not uncommon cause of vomiting in infancy and has often escaped diagnosis. At this age constant maintenance of an erect posture, by means of a special harness, is often an effective form of treatment.

The infant's reaction to the introduction to a solid diet is a useful guide to prognosis. If vomiting ceases or abates at this time, gradual complete cessation of all symptoms is usual by the age of 2 years, and there is no recurrence during childhood. If weaning does not cause vomiting to decrease, the course is likely to be longer; but, even so, gradual symptomatic cure is still usual. In both instances the partial thoracic stomach persists but the valve mechanism between gullet and stomach becomes more efficient.

Of children with minor degrees of partial thoracic stomach, only a small proportion develop an œsophageal stricture.

We are grateful to Mr. A. L. d'Abreu, Dr. C. G. Te [illegible] and Dr. Frances Braid for helpful criticism and to the consultants of the Children's Hospital, Birmingham, whose patients we examined. A previous study of infantile vomiting

of uncertain origin undertaken by Dr. B. S. B. Wood (1952) made easier the completeness of our review.

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DIAZOTISATION OF BILIRUBIN AFTER CHOLELITHIASIS WITHOUT VISIBLE JAUNDICE

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In attacks of upper abdominal pain not followed by visible jaundice or by bilirubinuria the rate of diazotisation of the blood-bilirubin may indicate whether cholelithiasis is responsible or not.

Diaphragmatic pleurisy, coronary occlusion, peptic ulcer, pancreatitis, cholelithiasis, &c., may give a clinical syndrome which is extremely difficult to diagnose correctly. When there is visible jaundice, however slight, there are good grounds for suspecting disease of the gall-bladder and bile-ducts; but where there is no jaundice the most thorough examination may fail to make the diagnosis clear. Though an increased urinary excretion of urobilin may be helpful, in our experience this happens too irregularly, and is not specific enough for it to be absolutely reliable. In attacks of cholelithiasis without visible jaundice the blood-bilirubin level may rise slightly, but this is not always conclusive. On the other hand, the rate of diazotisation of the bilirubin may be much raised and is then highly indicative.

Hence this finding makes a complete examination of the gall-bladder necessary or supports a suspected diagnosis of cholelithiasis.

METHODS

The method of Jendrassik and Cleghorn was followed, and a 'Lumetron' 4–2 colorimeter was used. Besides the total amount of bilirubin, the percentage of bilirubin diazotised in ten minutes was determined (for a detailed description see Schalm and Schulte 1950).

Blood was taken by venepuncture some hours after the beginning of the attack or, when the patient was referred to the clinic after a longer lapse of time, as soon as possible. The rate of diazotisation of the bilirubin was observed if possible for a few days afterwards. The values were determined as soon as possible after the sample of blood had been taken. Normal values were up to 1 mg. of total bilirubin per 100 ml., with a diazotisation-rate of 2–10% in ten minutes (1 mg. = 2 units Hymans van den Bergh).

RESULTS

During this investigation 31 cases of upper abdominal pain due to cholelithiasis, without visible jaundice, were collected. The diagnoses in 24 cases were verified by operation; the rest were clinically beyond doubt. In 16 of these cases the blood-bilirubin level was normal, whereas in the 15 other cases there was a slight transient rise in the blood-bilirubin level which did not exceed 2 mg. per 100 ml. All the cases, however, showed an undeniable acceleration of the rate of diazotisation of the bilirubin up to 30–80%, instead of the normal 2–12%, in ten minutes (see table). Bilirubinuria did not develop.

Not every attack of cholelithiasis is followed by this increase in the rate of diazotisation of bilirubin. Even in the same patient one attack may be followed by a distinct increase and the next attack by none. 3 such cases were observed, 2 of them being verified by operation and the 3rd being clinically certain.

On the other hand, in 8 cases of cholelithiasis proved at operation there was no increase in the rate of diazotisation of bilirubin after a typical severe attack of pain. Therefore, though such an increase points to cholelithiasis, its absence does not rule out cholelithiasis.

To find whether gall-bladder disease not causing attacks of pain was accompanied by an increased rate of diazotisation of bilirubin, similar investigations were made in 14 cases in which, in the course of routine examination or laparotomy for other causes, gall-stones were found which had never caused attacks of pain. The findings were well within normal limits. The same was found in 3 cases of lambliasis.

It must be emphasised that the increased rate of diazotisation of bilirubin and the transient rise of the blood-bilirubin level must be closely linked with an attack of upper abdominal pain for them to be of use in the diagnosis of cholelithiasis. The changes are most pronounced within twenty-four hours from the beginning of the attack and decrease rapidly in the next few days. These conditions have to be kept in mind because a single determination of an increased rate of diazotisation

EXAMPLES OF CHOLELITHIASIS AND CHOLECYSTITIS PROVED AT OPERATION AND SHOWING INCREASED RATE OF DIAZOTISATION OF BILIRUBIN AFTER ATTACK OF PAIN

Case no.	Time of taking blood in relation to attack of pain	Blood-bilirubin: Units Hymans van den Bergh: Total	Dir.	Indir.	Rate of diazotisation (% in 10 min.)	Findings
1	12 hr. after ..	1·48	0·64	0·84	54·7	Several stones; inflamed gall-bladder; pancreatitis
	1 day later ..	1·33	—	1·33	2·3	
	Renewed attack ..	2·03	0·40	1·63	29·6	
	7 days later..	1·33	—	1·33	6	
2	Before attack ..	1·24	—	1·24	3·3	4 stones in gall-bladder; slight pericholecystitis
	3 hr. after ..	1·50	0·45	1·05	44	
	17 days later	1·10	—	1·10	4	
3	First day ..	1·75	0·66	1·09	50	Stone in papilla vateri
	2 days later..	1·39	—	1·39	14·4	
	Renewed attack ..	1·89	0·60	1·29	45	
4	First day ..	2·00	0·56	1·44	42·5	2 stones in slightly inflamed gall-bladder
	2 days later..	1·00	—	1·00	6	
5	First day ..	2·33	1·46	0·87	70	Several stones in gall-bladder
	1 day later ..	1·87	—	1·87	10·7	
6	Before ..	0·57	—	0·57	3·5	Several stones in gall-bladder
	18 hr. after ..	2·78	1·06	1·72	50·8	
7	First day ..	3·08	2·22	0·86	77·3	Cholecystography; gall-stone
8	Before ..	1·14	—	1·14	4·4	Stone in common hepatic duct (2 years previously a gall-bladder containing 118 stones had been extirpated)
	12 hr. after ..	2·99	1·58	1·41	62·5	
	12 hr. later ..	3·44	1·97	1·47	65·8	
	1 day later ..	2·21	0·47	1·74	32·6	
9	7 days after	1·06	—	1·06	16	Shrunken gall-bladder filled with stones
	12 hr. after renewed attack ..	3·83	2·64	1·19	75·2	
10	2½ days after	1·71	—	1·71	17·5	Several small stones in gall-bladder
	3 hr. after renewed attack ..	3·91	2·40	1·51	70·1	

with a slightly raised blood-bilirubin level is not pathognomonic; this may be found in the course of a developing or decreasing jaundice due to hepatic damage. In the latter case, however, the swift change combined with an attack of pain is lacking.

To discover whether attacks of abdominal pain other than those due to cholelithiasis could cause the same phenomenon, similar investigations were made in cases of appendicitis. In 4 of these, in which a seriously inflamed appendix was found at operation, the results showed a definite acceleration in diazotisation with a slight or moderate rise of the blood-bilirubin level. Though an attack of cholelithiasis without significant cholecystitis will give a different clinical picture from that of acute appendicitis, it may be far more difficult to differentiate between acute cholecystitis and acute appendicitis. In such cases it is impossible to rely on the rate of diazotisation.

In cases of duodenal or gastric ulcer, perforated duodenal ulcer, pancreatitis, renal colic, extra-uterine pregnancy, and Bornholm's disease the blood-bilirubin level and the rate of diazotisation of bilirubin were completely normal.

The cases of acute coronary thrombosis, however, need some further discussion. In the 3 cases in which the blood was examined a day after the attack of pain normal values were found. In a 4th case normal values were found on the sixth day. In the 5th case normal values were found three days after the attack of pain, but in the subsequent weeks a rise and a fall in the rate of diazotisation were noticed—i.e., soon after the attack of pain the rate of diazotisation was not increased, and the subsequent change in its rate lacked the rapid onset so typical of the increased rate after attacks of cholelithiasis. Though the change came on much later after the attack of pain due to coronary thrombosis and was far less rapid than that after cholelithiasis, the increased rate of diazotisation may be found in principle after coronary occlusion.

The increase in the rate of diazotisation a comparatively long time after myocardial infarction may possibly be a consequence of circulatory insufficiency, since it is well known that the blood-bilirubin level very often rises in congestive heart-failure. In such cases we found that this rise in blood-bilirubin level was always accompanied by a definite acceleration of diazotisation (Schalm and Hoogenboom 1952).

DISCUSSION

The results show that after acute attacks of upper abdominal pain due to cholelithiasis a distinct rise in the rate of diazotisation of bilirubin may be found. This rise is of diagnostic value when the attacks are not followed by visible jaundice or bilirubinuria. It is already observable a few hours after the beginning of the attack of pain, is most pronounced within twenty-four hours of it, and in many cases soon returns to normal. Therefore, in looking for this feature it is necessary to determine the rate of diazotisation soon after the attack of pain. To maintain a margin of safety, only an acceleration in diazotisation to 30% or more in ten minutes was considered to be significant. It is important to compare this value, if possible, with a value determined before an attack, and to check whether any increase found in the rate diminishes considerably in the next few days. It has been shown that value can only be attached to a positive finding. The absence of this rise does not exclude the existence of gall-stones, since in several cases of cholelithiasis proved at operation the temporary increase in the rate of diazotisation was not found after an attack of pain.

Where the diagnosis of cholelithiasis is highly probable and no increase in the rate of diazotisation is found after an attack of pain, it is advisable to look for this rise repeatedly, since not every attack of cholelithiasis in the same patient is followed by such a rise. Calculation of the amounts of quick-reacting (direct) bilirubin and slow-reacting (indirect) bilirubin simultaneously present in the blood by the method described by Schalm and Schulte (1950) appears to explain this phenomenon. After the attack a small quantity of quick-reacting bilirubin enters the blood for a short time, thus causing only a slight rise of the blood-bilirubin level, but a pronounced increase in the rate of diazotisation. This amount of quick-reacting bilirubin joins the, at least initially, normal amount of slow-reacting bilirubin physiologically in the blood.

In 22 out of 24 cases, the stones were located either in the gall-bladder or in the cystic duct. In the 2 exceptions the stone was found in the common hepatic duct. The former localisation of the stones might be expected, because a stone in the common hepatic duct usually causes frank jaundice, and cases with a blood-bilirubin level over 2 mg. per 100 ml. were excluded. Most cases with an obstructed gall-bladder containing stones do not cause frank jaundice; in these circumstances the phenomenon described is of great value.

It must be borne in mind that the rate of diazotisation of bilirubin may increase in appendicitis and in myocardial infarction. In such cases the increase takes place later after the attack of pain than it does in cholelithiasis; but the possibility of confusion remains.

SUMMARY

Determination of the rate of diazotisation of the bilirubin soon after an acute attack of upper abdominal pain, not followed by jaundice or bilirubinuria, may give findings indicative of cholelithiasis, thus making a complete examination of the gall-bladder necessary or supporting a tentative diagnosis.

These findings are a considerable increase in the rate of diazotisation of the bilirubin, already a few hours after the attack of pain, even if the blood-bilirubin level is hardly above normal.

Only a positive finding is of any value. A negative finding does *not* rule out cholelithiasis.

An increase in the rate of diazotisation of bilirubin may be found in some cases of serious appendicitis or of myocardial infarction, but usually later after the attack of pain than in cholelithiasis. In principle, however, these diseases may be sources of confusion.

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CLINICAL ASSESSMENT OF DRUGS WHICH INHIBIT GASTRIC SECRETION

WITH SPECIAL REFERENCE TO HEXAMETHONIUM

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THE final assessment of the value of drugs in the management of peptic ulcer must depend on therapeutic trials; but these are difficult to interpret, whether they are based on relief of symptoms, on relapse-rate, or on rate of healing. It is therefore important to assess the potential therapeutic value of drugs as accurately as possible from their effects on gastric secretion and

TABLE I—EFFECT OF REPEATED INJECTIONS OF C6 ON pH OF GASTRIC CONTENTS DURING THE NIGHT IN PATIENTS WITH DUODENAL ULCERS

Case no.	Test	pH at hourly intervals from 8 P.M. to 9 A.M.													
		8 P.M.	9	10	11	12	1 A.M.	2	3	4	5	6	7	8	9
1	With C6 ..	4·21	2·20	1·50*	1·76	1·82	1·60	1·56	1·70	2·50	2·16	1·76	..	..	..
	Control ..	4·63	1·61	1·28	1·50	1·40	1·30	1·67	1·42	1·75	5·21	2·31	..	..	..
2	With C6 ..	4·26	1·54	1·34*	1·64	..	1·67	..	1·60	1·24	1·35	1·44	..	..	..
	Control ..	1·27	1·27	1·42	1·30	1·20	1·32	1·25	1·25	1·40	1·26	1·46	..	..	..
3	With C6 ..	1·94	..	1·08*	1·24	1·36	1·26	1·25	1·27	1·35	1·76	1·70	..	..	..
	Control ..	1·70	1·20	1·22	1·28	1·21	1·30	1·35	1·35	1·34	1·37	1·48	..	..	..
4	With C6 ..	..	2·54	1·65*	1·38	1·30	1·20	1·20	..	1·67*	1·82	1·37	1·28	..	..
	Control ..	..	1·48	2·11	..	1·24	..	1·28	..	1·41	..	1·36	..	..	..
5	With C6 ..	1·89	1·70	1·45*	1·44	1·36	1·40	1·41*	1·44	1·50	1·54	1·32*	1·43	1·51	1·83
6	With C6 ..	..	1·34	1·24*	1·30	1·50	1·47	1·43*	1·43	1·45	1·54	1·68*	1·56	2·10	2·04
7	With C6 ..	..	1·67	1·40*	1·41	1·76	1·62	1·22*	1·47	1·62	1·72	1·70*	1·68	2·30	1·52
	Control ..	..	1·60	1·56	1·47	1·36	1·58	1·36	1·56	1·32	1·34	1·43	1·32	1·47	1·38
8	With C6 ..	1·70	1·64	1·58*	1·56	1·52	1·60	1·48*	1·49	1·47	1·51	1·56*	1·59	1·55	1·56
9	With C6 ..	..	..	1·39*	1·42	1·50	1·56	1·77*	1·90	2·06	2·07	1·96*	1·91	2·08	2·04
	Control ..	..	..	1·52	1·47	1·54	1·42	1·44	1·54	1·62	1·84	1·62	1·55	1·65	1·52
10	With C6 ..	..	..	1·58*	1·55	..	1·80	1·99*	1·94	2·10	1·89	2·16*	..	2·28	..
11	With C6 ..	..	..	2·28*	1·95	1·91	1·65	1·76*	2·02	2·29	2·96	3·97*	2·25	2·05	1·96
	Control ..	..	..	1·60	1·58	1·55	1·46	1·46	1·56	1·68	1·82	1·86	2·53	2·88	2·08
12	With C6 ..	..	..	1·56*	1·42	1·52	3·25	1·63*	1·81	3·82	3·91	4·22*	1·79	1·72	1·84
	Control ..	..	..	1·88	..	..	1·38	1·38	1·53	1·66	2·02	1·76	1·63	1·42	1·44
13	With C6 ..	..	1·58	1·56*	1·53	1·58	1·94	3·14*	..	5·74	5·18	6·58*	1·78	1·87	1·93
	Control ..	..	1·58	1·31	1·21	1·25	1·20	1·22	1·34	1·52	..	..	2·64	2·81	..
14	With C6 ..	..	..	1·68*	1·44	1·94	3·48	7·21*	7·69	2·92	4·18	6·94*	2·14	1·96	1·90
	,, ,, ..	..	..	2·05*	1·77	1·52	2·03	1·91*	1·94	3·86	4·10	1·98*	1·92	1·82	1·87
	Control ..	..	..	1·90	1·48	..	1·88	1·40	1·75	1·72	1·42	2·32	1·63	1·69	2·22
15	With C6 ..	..	..	1·79*	1·64	2·06	4·22	6·98*	5·52	4·54	6·48	4·56*	1·68	1·62	4·43
	,, ,, ..	..	..	1·88*	2·17	4·07	6·48	1·48*	1·52	1·62	2·65	1·84*	1·87	3·52	2·83
	Control ..	..	..	1·62	1·65	1·38	1·32	1·41	1·74	1·92	2·06	1·54	1·30	1·46	1·43

*Injection of 100 mg. of C6.

motility. For this purpose the drugs must be tested under the actual conditions in which they are to be used in the treatment of patients with gastric or duodenal ulcers. Some of the tests commonly used are misleading because they reveal pharmacological effects which are not relevant to the clinical evaluation of the drugs. Thus it can be shown that, under certain experimental conditions, antisecretory drugs, such as atropine, hexamethonium, and banthine, will inhibit gastric secretion. but it does not follow that they will produce achlorhydria in patients with duodenal ulcers under the conditions of clinical use.

The conflicting reports of the effect of hexamethonium on gastric acidity illustrate the importance of the method employed for assessing the potential therapeutic value of an antisecretory drug. By continuous gastric aspiration, Kay and Smith (1950, 1951) found that hexamethonium iodide (C6) inhibited the spontaneous secretion of hydrochloric acid, a single injection of 100 mg. producing achlorhydria for as long as three hours; it also inhibited gastric motility. On the other hand, Rowlands and Friedlander (1952) noted that C6 did not raise the pH of small samples of gastric juice aspirated at intervals in the course of short experiments on the effect of C6 on pain in patients with peptic ulcers. Paton and Zaimis (1950) have emphasised the fact that the clinical usefulness of drugs which produce neuromuscular block can be established only by testing them under the conditions in which they are to be used. We have therefore applied the sampling technique to determine whether C6, alone or in combination with alkali, will eliminate free acid in patients with duodenal ulcers undergoing routine medical treatment in hospital.

METHOD

The observations were made on patients with radiologically proven duodenal ulcers; no case showed evidence of pyloric stenosis. The effect of single or repeated injections of C6 on the pH of the intragastric contents was studied under the following conditions: (1) in short experiments on fasting patients, (2) during the night, (3) in patients receiving a gastric diet or a continuous milk drip, and (4) in combination with alkali. Details of procedure are given under individual headings.

Small samples (5–15 ml.) of gastric contents were aspirated, usually hourly, through a Ryle's tube, most of the patients being screened to ensure that the metallic tip was in the body of the stomach. The stomach was not emptied at the beginning of the experiments, and continuous suction was never used. No attempt was made to prevent the swallowing of saliva. In those experiments in which observations were made during administration of a milk drip, the drip was given at a rate of 120 ml. per hour, and samples were aspirated after interrupting the drip and clearing the tube with air. In some cases a double-lumen tube was used so that samples could be aspirated simultaneously from two sites within the body of the stomach $3^1/_2$ in. apart.

The pH of the samples was measured with a sealed glass electrode at room-temperature within forty-eight hours of the collection. Preliminary observations showed that the pH did not change by more than +0·1 during storage at 6°C for forty-eight hours.

Hexamethonium bromide (C6) was injected intramuscularly in doses of 100 mg. In some experiments the gastric contents were neutralised by giving 8 g. of a powder consisting of equal parts of magnesium trisilicate, heavy magnesium carbonate, and calcium carbonate.

RESULTS

Effect of C6 on Gastric Acidity in Fasting Patients

The tests were made on 6 patients who had been fasting for ten hours. Samples of gastric juice were aspirated before, and hourly for four hours after, an injection of 100 mg. of C6. The pH did not rise significantly after the injection; the slight changes observed in the pH were within the range of the spontaneous fluctuations in control experiments without C6. As the stomach was not emptied initially in any of these tests, it seemed possible that a more useful indication of the effect of C6 would be obtained by injecting the drug four-hourly for twenty-four to seventy-two hours before starting the test. In every case the pH was below 2·0 at the beginning of the test, and no significant change took place after the injection of the test dose.

Effect of C6 on Gastric Acidity during the Night

In 15 patients the pH was measured hourly from 8 P.M. to 9 A.M., no food being given after 6 P.M.: 11 patients were given injections of C6 at 10 P.M., 2 A.M., and 6 A.M.; 1 received injections at 10 P.M. and 4 A.M.; and 3 were given a single injection at 10 P.M. All the patients had received injections during the day at 10 A.M. and 4 P.M. Control tests were done on most of the patients, omitting the injections of C6.

The results are summarised in table I. C6 had no significant effect on the pH in cases 1–8. In cases 9 and 10 it may have raised the pH of some of the samples by a fraction of a unit, but most of the readings were below pH 2·0. Free acid was absent (pH>3) in one sample in case 11, in four samples in case 12, and in five samples in case 13; but the pH of most of the other samples was below 2·0. The effect of C6 was studied on two separate occasions in cases 14 and 15. In the first test in case 14 free acid was absent in five samples, all of which were very heavily contaminated with bile; in the second test free acid was absent in only two of the samples, and the pH of the remainder was below 2·0. The effect of C6 was also variable in patient 15, free acid being absent in seven samples during one test but in only three samples during the other.

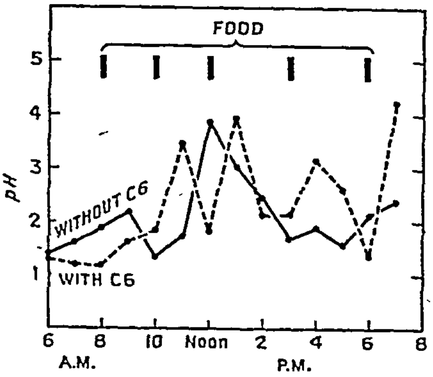

Fig. 1—Effect of C6 on gastric acidity in a patient on a gastric diet. Injections of 100 mg. C6 given at 6 a.m. and 2 p.m.

Thus C6 did not eliminate free acid throughout the night in any of these tests. It produced achlorhydria in 3 patients for from five to seven hours; but, when the test was repeated in 2 of these patients, free acid was absent for only two or three hours. In most of the patients free acid was present in every sample throughout the night, and the pH usually remained below 2·0.

Effect of C6 on Gastric Acidity in Patients on a Gastric Diet

The pH was measured hourly from 7 A.M. to 7 P.M. in 4 patients on a first-stage gastric diet. During the next three days 100 mg. of C6 was given at 6 A.M., 2 P.M., and 10 P.M., and on the third day the pH was again measured hourly. Increases of pH were observed after some of the meals, but there was no evidence that the administration of C6 had any significant effect (see fig. 1).

Effect of C6 in Patients on a Continuous Milk Drip

The pH was measured at short intervals throughout two periods of twenty-four hours in 3 patients receiving continuous milk drips; on the second occasion six-hourly injections of C6 were given in addition. On both occasions the fluctuations of pH were so pronounced that it was impossible to determine from these three tests whether C6 had any significant effect, but the pH often fell below 2·0 despite the administration of the drug. In one of these patients the pH remained above 3 for eight out of twenty-four hours without C6, and for only one out of twenty-four hours while C6 was being administered. In another patient the pH was more than 3·0 for nine out of twenty-four hours without C6, and for thirteen out of twenty-four hours while he was receiving C6. The third patient was kept on the milk drip for four successive periods of twenty-four hours each. During the first three of these he was not given C6 and the pH was above 3·0 for five, fifteen, and eight hours out of twenty-four. During the fourth period of twenty-four hours he was given C6 and the pH remained more than 3·0 for sixteen hours.

Effect of C6 on Gastric Emptying

The following observations show that C6 usually increases the volume of the gastric contents because it delays gastric emptying.

The stomach was emptied as completely as possible at 9 A.M. in 13 patients who had been fasting for fourteen hours, and this was repeated on another occasion after giving C6 at 10 P.M., 2 A.M., and 6 A.M. In 8 of the patients the volume of the resting juice was significantly greater when C6 was given; in the other 5 patients there was no significant difference. The mean volume was 38 ml. without C6 and 127 ml. with C6. The increased volume must have been due to delayed gastric emptying, because Kay and Smith (1950) have shown that C6 reduces the volume of gastric secretion, and there was no evidence of increased regurgitation of duodenal contents, the degree of bile-staining and the pH of the gastric juice being about the same on both occasions.

The delay in emptying was confirmed by the observation that, after the administration of 8 g. of alkaline powder and an injection of C6, a deposit was still present in the gastric samples aspirated three hours later in 4 patients, and five, six, and seven hours later in 3 others.

Effect of C6 and Alkali on Gastric Acidity

As C6 usually failed to produce achlorhydria but delayed gastric emptying, the following observations were made to determine whether it could be used to prolong the effect of alkali. The pH of the gastric contents was raised to more than 4·0 in each of 5 fasting patients by administering 8 g. of alkali, and samples were aspirated hourly or half-hourly until the pH had returned to its initial value. The procedure was repeated on a second occasion, an injection of C6 being given at the same time as the alkali. After the pH had fallen below 4·0, it always returned to its initial value, less than 2·0, during the next hour. C6 prolonged the neutralising effect of the alkali in 4 of the 5 patients by one hour, two hours, three and a half hours, and five hours.

An attempt was made to control the nocturnal acidity in 7 patients by giving injections of C6 at 10 A.M. and 4 P.M., 8 g. of alkali and an injection of C6 at 10 P.M., and further injections of C6 at 2 A.M. and 6 A.M. The results are summarised in table II. In 3 patients (cases 6, 16, and 17) free acid was eliminated for from six to nine hours after the administration of the alkali at 10 P.M., but in the 4 other patients free acid was eliminated for only one hour. The effect of C6 plus alkali also varied in

TABLE II—EFFECT OF 8 G. OF ALKALI AT 10 P.M. AND FOUR-HOURLY INJECTIONS OF C6 ON GASTRIC ACIDITY DURING THE NIGHT

Case no.	Test	pH at hourly intervals from 9 P.M. to 9 A.M.												
		9 P.M.	10	11	12	1 A.M.	2	3	4	5	6	7	8	9
6	Alkali + C6 ..	1·91	1·58*†	3·88	3·34	3·20	1·46*	3·20	4·63	3·35	5·92*	4·15	4·33	2·24
16	Alkali + C6 ..	1·83	1·95*†	7·50	7·58	7·72	6·82*	7·02	6·74	1·59	1·87*	1·54	1·72	1·62
	Alkali only ..	3·17	1·42†	1·68	1·42	1·67	2·13	1·37	1·35	1·46	1·72	2·42	1·98	1·64
17	Alkali + C6 ..	1·48	1·25*†	3·33	3·08	5·53	4·60*	5·42	5·36	5·38	2·86*	1·72	1·85	1·56
	Alkali only ..	1·28	1·17†	5·70	1·41	1·10	1·08	1·18	1·23	2·57	1·62	1·28	1·22	1·37
5	Alkali + C6 ..	1·34	1·44*†	5·76	1·98	1·62	3·12*	1·38	1·40	1·53	1·40*	1·41	1·16	1·25
18	Alkali + C6 ..	1·15	1·48*†	5·97	1·52	1·40	1·65*	1·63	2·31	2·03	1·90*	2·68	2·86	1·53
19	Alkali + C6 ..	..	1·67*†	4·62	2·87	1·57	1·41*	1·56	1·60	2·45	2·22*	..	..	1·82
	Alkali only ..	1·81	1·59†	6·64	1·56	1·26	1·53	1·42	1·14	1·68	1·47	1·58	1·39	1·18
20	Alkali + C6 ..	1·42	1·38*†	3·64	1·85	1·38	1·48*	1·25	1·35	1·30	1·92*	1·50	1·58	1·26

* Injection of 100 mg. of C6. † Administration of 8 g. of alkali.

the same patient at different times. Thus a patient was given alkali and C6 at 10 P.M. on two separate occasions. The pH remained more than 4 for three and a half hours in the first test, but it fell below 2 in less than an hour in the second test.

Effect of C6 on Mixing of Gastric Contents

James and Pickering (1949) have shown that "quite large variations in acidity" sometimes exist at points 3 or 4 in. apart in the body of the stomach, and that systematic differences occur after meals between the acidity in the body of the stomach and the acidity in the pyloric antrum. It seemed possible that C6 might exaggerate such differences by inhibiting motility. If mixing of the gastric contents was inadequate, the pH of small samples might not be representative of the acidity throughout the stomach, particularly after the administration of alkali.

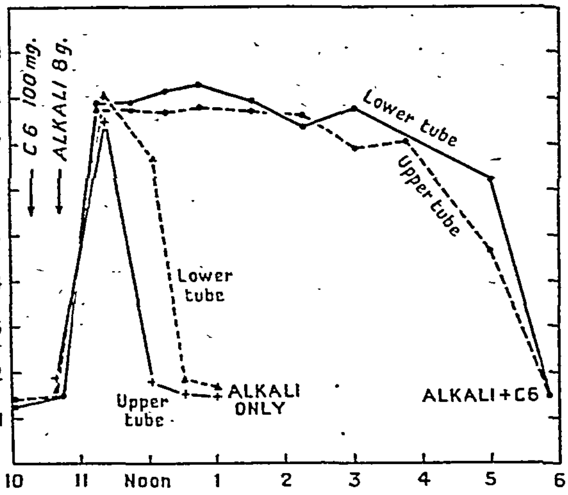

Fig. 2—Effect of alkali alone and of alkali plus C6 on pH of samples of gastric juice aspirated through a double-lumen tube from two sites in the body of the stomach $3^{1}/_{2}$ in. apart.

A double-lumen tube was used in 3 patients to obtain samples of gastric juice from two sites in the body of the stomach $3^{1}/_{2}$ in. apart, after the administration of alkali alone and of alkali plus C6. There was good agreement between the pH of the samples from the two sites in every case (fig. 2), discrepancies occurring only at the end of the tests, when the pH of samples from the upper lumen began to fall a little earlier than those from the lower; but this also happened when alkali was given without C6.

At the end of one of the tests in which both alkali and C6 were given, the stomach was emptied as completely as possible by aspirating its contents in separate fractions of 10–20 ml. after the pH of samples from both tubes had returned to below 2·0. The pH of the first five fractions ranged from 1·70 to 2·13, but the last two fractions had values of 6·7 and 7·2, and both contained heavy deposits. Similar discrepancies in the acidities of different fractions of the gastric residue were observed in other patients, and heavy deposits were present in some of the fractions. The pH of some of the fractions which contained deposits was below 2·0 when measured at the bedside immediately after aspiration; but when measured again, after the specimen had been shaken, the pH was often very much higher. In some cases the pH continued to rise while it was being measured, if the specimen was shaken vigorously. These deposits must have contained some of the alkaline powder which had been given at the beginning of the tests and had not reacted with the hydrochloric acid secreted in the stomach. If alkaline powder is dropped into a beaker containing N/10 hydrochloric acid at 37°C, most of it deposits as a sediment, and little or no reaction takes place until the beaker is shaken vigorously. By inhibiting motility, C6 prevents adequate mixing of the gastric contents, and a variable proportion of a dose of alkaline powder may remain in the stomach for many hours as a sediment without reacting with the acid secretion. To obtain a correct estimate of the acidity within the stomach after the administration of alkali with C6, the samples should not be shaken before the pH is measured. This was not appreciated at first, and some of the pH readings recorded here may be too high because in some of the earlier experiments the specimens were shaken vigorously before the pH was measured.

DISCUSSION

Hexamethonium has been used in the treatment of peptic ulcer since Kay and Smith (1950) reported that it inhibited the spontaneous secretion of hydrochloric acid. They found that a single injection of 100 mg. produced achlorhydria for as long as three hours, and Riddell (1951) confirmed their finding that repeated doses cause "a substantial reduction in the volume and acidity of the night secretion" in patients with duodenal ulcers. *These observations were made by emptying the stomach* at the beginning of the test and then aspirating continuously after giving the drug. On the other hand, the results reported here show that the volume of the gastric contents usually increases after the administration of C6, and the acidity does not change significantly, the pH remaining below 2·0 in most cases. Very few patients showed achlorhydria for even a few hours during the night despite four-hourly injections of C6. Our findings, however, are not incompatible with the pharmacological effects observed by Kay and Smith, but the therapeutic implications are entirely different, if the object of treatment is to eliminate free acid and peptic activity.

The effect of antisecretory drugs, such as atropine, hexamethonium, and banthine, on the volume and acidity of the intragastric contents is determined not only by their action on gastric secretion but also by the fact that they inhibit gastroduodenal motility and thus prolong the emptying-time of the stomach. By aspirating the stomach continuously, Kay and Smith showed that C6 depresses gastric secretion; but this technique masks the effect of the delay in gastric emptying. Thus C6 may cause a statistically significant reduction in the volume and acidity of the gastric secretion, but the volume of the intragastric contents may actually increase, and the pH may not rise significantly. Using the sampling technique we tried to study the effect of hexamethonium under the actual conditions in which it would be used clinically. Continuous aspiration provides important information about the effect of drugs on the spontaneous secretion of gastric juice and on the secretory response to insulin and histamine, but the findings may be misleading if interpreted in terms of the clinical usefulness of the drugs. This also applies to the method employed for measuring acidity and for expressing the results. The titration method, which was used by Kay and Smith,

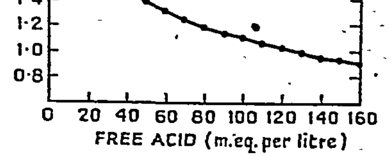

Fig. 3—Relation between pH and titratable free acid.

The results are summarised in table I. C6 had no significant effect on the pH in cases 1–8. In cases 9 and 10 it may have raised the pH of some of the samples by a fraction of a unit, but most of the readings were below pH 2·0. Free acid was absent (pH>3) in one sample in case 11, in four samples in case 12, and in five samples in case 13; but the pH of most of the other samples was below 2·0. The effect of C6 was studied on two separate occasions in cases 14 and 15. In the first test in case 14 free acid was absent in five samples, all of which were very heavily contaminated with bile; in the second test free acid was absent in only two of the samples, and the pH of the remainder was below 2·0. The effect of C6 was also variable in patient 15, free acid being absent in seven samples during one test but in only three samples during the other.

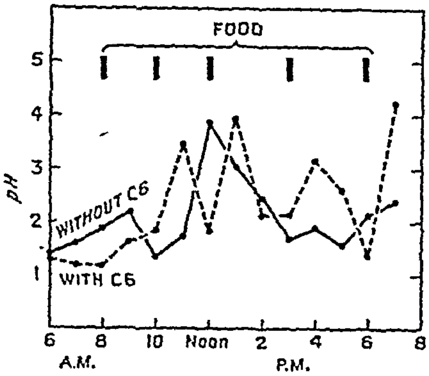

Fig. 1—Effect of C6 on gastric acidity in a patient on a gastric diet. Injections of 100 mg. C6 given at 6 a.m. and 2 p.m.

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The pH was measured hourly from 7 A.M. to 7 P.M. in 4 patients on a first-stage gastric diet. During the next three days 100 mg. of C6 was given at 6 A.M., 2 P.M., and 10 P.M., and on the third day the pH was again measured hourly. Increases of pH were observed after some of the meals, but there was no evidence that the administration of C6 had any significant effect (see fig. 1).

Effect of C6 in Patients on a Continuous Milk Drip

The pH was measured at short intervals throughout two periods of twenty-four hours in 3 patients receiving continuous milk drips; on the second occasion six-hourly injections of C6 were given in addition. On both occasions the fluctuations of pH were so pronounced that it was impossible to determine from these three tests whether C6 had any significant effect, but the pH often fell below 2·0 despite the administration of the drug. In one of these patients the pH remained above 3 for eight out of twenty-four hours without C6, and for only one out of twenty-four hours while C6 was being administered. In another patient the pH was more than 3·0 for nine out of twenty-four hours without C6, and for thirteen out of twenty-four hours while he was receiving C6. The third patient was kept on the milk drip for four successive periods of twenty-four hours each. During the first three of these he was *not given C6 and the pH* was above 3·0 for five, fifteen, and eight hours out of twenty-four. During the fourth period of twenty-four hours he was given C6 and the pH remained more than 3·0 for sixteen hours.

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As C6 usually failed to produce achlorhydria but delayed gastric emptying, the following observations were made to determine whether it could be used to prolong the effect of alkali. The pH of the gastric contents was raised to more than 4·0 in each of 5 fasting patients by administering 8 g. of alkali, and samples were aspirated hourly or half-hourly until the pH had returned to its initial value. The procedure was repeated on a second occasion, an injection of C6 being given at the same time as the alkali. After the pH had fallen below 4·0, it always returned to its initial value, less than 2·0, during the next hour. C6 prolonged the neutralising effect of the alkali in 4 of the 5 patients by one hour, two hours, three and a half hours, and five hours.

An attempt was made to control the nocturnal acidity in 7 patients by giving injections of C6 at 10 A.M. and 4 P.M., 8 g. of alkali and an injection of C6 at 10 P.M., and further injections of C6 at 2 A.M. and 6 A.M. The results are summarised in table II. In 3 patients (cases 6, 16, and 17) free acid was eliminated for from six to nine hours after the administration of the alkali at 10 P.M., but in the 4 other patients free acid was eliminated for only one hour. The effect of C6 plus alkali also varied in

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Case no.	Test	pH at hourly intervals from 9 P.M. to 9 A.M.												
		9 P.M.	10	11	12	1 A.M.	2	3	4	5	6	7	8	9
6	Alkali + C6 ..	1·91	1·58*†	3·88	3·34	3·29	1·46*	3·20	4·63	3·35	5·92*	4·15	4·33	2·24
16	Alkali + C6 ..	1·83	1·95*†	7·50	7·58	7·72	6·82*	7·02	6·74	1·59	1·87*	1·54	1·72	1·62
	Alkali only ..	3·17	1·42†	1·68	1·42	1·67	2·13	1·37	1·35	1·46	1·72	2·42	1·98	1·64
17	Alkali + C6 ..	1·48	1·25*†	3·33	3·08	5·53	4·60*	5·42	5·36	5·38	2·86*	1·72	1·85	1·56
	Alkali only ..	1·28	1·17†	5·70	1·41	1·10	1·08	1·18	1·23	2·57	1·62	1·28	1·22	1·37
5	Alkali + C6 ..	1·34	1·44*†	5·76	1·98	1·62	3·12*	1·38	1·40	1·53	1·40*	1·44	1·40	1·35
18	Alkali + C6 ..	1·45	1·48*†	5·97	1·52	1·40	1·65*	1·63	2·31	2·03	1·90*	2·68	2·86	1·53
19	Alkali + C6 ..	..	1·67*†	4·62	2·87	1·57	1·44*	1·56	1·60	2·45	2·22*	..	..	1·52
	Alkali only ..	1·51	1·59†	6·64	1·56	1·26	1·53	1·42	1·44	1·68	1·17	1·58	1·39	1·18
20	Alkali + C6 ..	1·42	1·38*†	3·64	1·85	1·38	1·48*	1·25	1·35	1·30	1·92*	1·50	1·52	1·26

* Injection of 100 mg. of C6. † Administration of 8 g. of alkali.

or easily irritated ears, a fact they do not always appreciate." There are many deaf persons in whom the greatest efficiency which might be obtained from an aid is reduced considerably because of discharging ears. I report here an investigation of the effect of the insert in active chronic otitis media.

INVESTIGATION

From a large number of patients with chronic otitis media for whom an aid was prescribed or who already used a medresco external aid 22 were selected and examined at the audiology unit of the Royal National Throat, Nose, and Ear Hospital from April to October, 1951, and re-examined on subsequent occasions.

Each patient had the ears, nose, and throat examined thoroughly. The aural discharge was examined bacteriologically; the hearing tests consisted of voice tests in an ordinary hearing environment, amplified speech tests (both unaided and with external and insert hearing-aids), and a pure-tone threshold audiogram by bone and air conduction. Eventually an individually moulded insert was fitted, and an insert type of medresco aid issued. The patients were instructed in maintaining a careful aural toilet and in cleaning the insert (daily with soap and water, afterwards drying it carefully).

Besides the small controlled series we began to prescribe insert aids to patients with discharging ears (from chronic otitis media) who attended at this clinic, as soon as it became apparent that this was not harmful. Further, whenever a patient with an external aid returned with various complaints (discomfort, headache, very conspicuous, hearing not very good), and when the only reason for prescribing an external aid was a discharging ear due to chronic otitis media, the external aid was changed for an insert type. The patients were seen several weeks later at a routine check clinic.

RESULTS

The ages of the patients ranged from 26 to 73 years. In all cases the deafness was of long duration. In 13 it was moderate, conductive; in 6 severe, conductive; and in 3 severe, mixed, predominantly conductive. In all cases the prescription of a hearing-aid was justified because of social disability, and in 9 cases there was also some disability at work. In all cases the hearing-aid helped to restore the ability of auditory communication. 11 patients had had an external aid before, and all of these appreciated the change to the insert type. All the patients had bilateral chronic otitis media, and 8 of them had undergone radical mastoidectomy. In 3 of these cases the insert was fitted in the cavity left by the operation.

In order of frequency the organisms found were *Staphylococcus albus* (9 cases), diphtheroids (8 cases), proteus (7 cases), gram-negative bacilli (5 cases), *Staph. aureus* (3 cases), *Neisseria catarrhalis* (1 case). In 6 cases no pathogenic organisms were detected.

The insert was fitted in 20 moist ears and 2 dry ones (chronic otitis media in a quiescent stage). The 2 dry ears remained dry, 1 after four months' observation and 1 after six months', and no ill effect was observed. Of the 20 moist ears 7 dried up at various periods after inserts were worn, and were still dry after five months' observation. In 1 case traces of discharge were observed and in 1 case the discharge diminished after six months. In 1 case there was more profuse discharge. In the rest of the cases no change was observed after ten months' observation. In none of the cases did the insert cause irritation, discomfort, or inflammation.

In 1 case one ear was moist and the other dry, but the discharging ear could hear better. Therefore the insert was fitted to that ear, with a satisfactory result from the functional point of view and no ill effect from the insert. In 1 case the ear subjected to radical mastoidectomy was moist but could hear better than the other ear, which was dry. The insert was fitted in the radical mastoid ear with good results.

Amplified speech tests were made to ascertain how much hearing was gained with the insert and the external aid. The average unaided hearing loss (at 40% word articulation level) was 53 decibels. The average gain with the insert type was 33 decibels, and with the external type 25 decibels.

DISCUSSION

The insert is made from an acrylic plastic material which is inert to the healthy skin. Allergic contact dermatitis or otitis externa is rare. A badly made insert, however, may have some ill effects. A good insert should be clear and smooth and should fit perfectly. Faulty processing may cause cloudiness or porosity (Denison et al. 1949); the insert then contains bubbles of free monomeric vapour produced by overheating the acrylic material, and this vapour is toxic. There is a theoretical possibility that the gas from the bubbles near the surface may have some ill effect. The rough surface of imperfectly polished inserts may cause irritation. Occasionally a decubitus sore on the auricle can be detected as a result of the pressure of a badly fitting insert. An insert which is not smooth, clear, and well fitting should be rejected.

The observation of the 22 cases, and of a much larger number of patients who attended a routine check, showed no ill effect from wearing an insert in an ear discharging because of chronic otitis media. A combination of discharge and insert does not irritate the skin of the meatus more than the discharge does by itself. The bacteriology of the discharge does not make any difference from this point of view. Patients soon learn that a comparatively dry ear hears better, and the use of the insert aid usually gives them a new impetus to take care of their discharging ears.

It has been argued that profuse discharge may block the insert; but such an ear is unfit for any kind of aid. Profuse discharge itself causes an additional impairment of hearing. The effect of the discharge on the external ear-piece is worse than on the insert. When soiled it is difficult to clean and it may be damaged in the cleaning. Thus a profusely discharging ear should be treated before an aid is prescribed. Almost all cases can be improved with regular aural toilet. If a patient is indolent towards his discharging ear and unwilling to maintain a reasonable aural hygiene, it is very unlikely that he will make a good use of his aid or look after it properly. It is not advisable to give a patient an aid and to neglect the treatment of a chronic otitis media.

When one ear is dry and the other is discharging, the decision about which side should have an insert fitted should be made from the functional point of view. If the hearing is appreciably better in the wet ear, one should not hesitate to prescribe the aid for that ear.

There are obvious indications for the use of an external aid—e.g., various types of chronic otitis externa, anatomical disfigurement of the meatus, stenosis of the meatal orifice, &c. In these cases, too, the bone-conduction aid is an alternative. It is important, however, to remember that the bone-conduction type of aid is less efficient than the air-conduction type as regards both its heavy battery consumption and its very restricted bandwidth of sound frequency. The battery consumption of the more powerful bone-conduction aids is roughly the same as that of the medresco external air-conduction aid, but the external aid scores over the bone-conduction aid on its better frequency characteristic. When a medresco bone-conduction aid becomes available for general use, a tendency may arise to prescribe it for all discharging ears. That would be unfortunate.

The indications for the various types of aid are not difficult to define. The decision must be made from the functional standpoint first of all. Modifying factors may be present, and accordingly a less efficient, but for the individual as a whole a more suitable, aid will have to be is more accurate than pH measurements because, at the high acidities which occur in duodenal ulcer, a small change in pH represents a large change in hydrogen-ion concentration (see fig. 3). Thus C6 may cause a "substantial reduction" in the output of free acid expressed in milli-equivalents per litre, but the change in pH may be very small. However, the pH unit is the more useful for assessing the clinical value of an antisecretory drug, since there is no evidence that a reduction in the output of acid would have any therapeutic significance unless the acid-pepsin factor was eliminated by increasing the pH to 3 or preferably 4. Moreover it can be calculated from Riddell's data that the effect of C6 on gastric secretion is less impressive when expressed in terms of the concentration rather than the total output of free acid. Indeed in one of Riddell's 5 cases C6 reduced the output of free acid during the night by 47·7%, but the concentration actually increased from 69·5 to 82 m.eq. per litre, which corresponds to a decrease in pH from 1·24 to 1·18. The effect on the concentration is the more reliable index in the clinical evaluation of hexamethonium, partly because continuous aspiration obscures the effect of the delay in gastric emptying, and partly because gastric secretion cannot be collected quantitatively in man, because the amount lost through the pylorus is unknown.

Moreover, our results show that hexamethonium, like atropine (Levin et al. 1951) and banthine (Atkinson 1952), produces variable and unpredictable results in different patients, and even in the same patient at different times. C6 is unlikely to raise the pH in a patient with a high rate of secretion, particularly if it causes a pronounced delay in gastric emptying. Thus, one of our patients showed a slight delay in the rate of emptying of a barium meal; C6 had no effect on the nocturnal pH, but the volume of the gastric residue next morning was 800 ml., compared with 100 ml. when no C6 was given. In our series of cases C6 was most effective in an elderly patient whose rate of secretion was so low that it was difficult to aspirate 10 ml. of gastric juice every hour during the night, even when C6 was not given; the presence of a duodenal ulcer was confirmed at operation. Even in this patient the effect of C6 on the nocturnal pH was variable. The clinical value of antisecretory drugs—e.g., banthine—in the treatment of duodenal ulcer is sometimes assessed by studying their effects in normal people. Such an assessment is not valid, because their effects in the presence of normal or low rates of secretion give little or no indication of their value for controlling gastric acidity in patients with duodenal ulcers, most of whom have a very high output of gastric juice.

The variable effect of C6 on the output of acid and on gastric emptying is also illustrated by the tests in which it was given in combination with alkali. Moreover, a drug which inhibits motility may prevent adequate mixing of the gastric contents, and alkaline powder may remain in the stomach for many hours without reacting with the acid secretion. The powder probably sediments in an alkaline pool in the most dependent part of the stomach, and the gastric juice forms a layer above it and flows through the pylorus without mixing. The fact that C6 had no significant effect on gastric acidity during the administration of a gastric diet or a milk drip is in keeping with the observation that it does not affect the secretory response to histamine, meat extracts (Kay and Smith 1951), or test-meals (Douthwaite and Thorne 1951).

It is possible, however, that hexamethonium may facilitate the neutralisation of hydrochloric acid in the duodenum by retarding the flow of gastric juice from the stomach—assuming that it does not depress the alkaline duodenal secretions. This hypothesis could only be tested by aspirating samples of fluid from the duodenal bulb, but there is indirect evidence that the pH of this fluid follows that of the gastric juice very closely. Rowlands and Friedlander (1952) found that C6 did not relieve attacks of pain in patients with duodenal ulcers although it inhibited gastroduodenal motility, but neutralisation with alkali gave prompt relief whether C6 had been administered or not.

Thus, although C6 depresses the spontaneous secretion of hydrochloric acid, it is unlikely to be useful in the treatment of duodenal ulcer, because it has little or no effect on the pH of the gastric contents in most patients. It will eliminate free acid for a few hours during the night in some patients, but its effect is variable and unpredictable, even when the drug is given by injection four-hourly, and its side-effects are unpleasant and may be dangerous.

SUMMARY

The effect of hexamethonium on gastric acidity has been studied in patients with duodenal ulcers by aspirating small samples of gastric juice at hourly intervals.

Its effect was variable and unpredictable. Single injections did not raise the pH significantly in fasting patients, and four-hourly injections eliminated free acid during the night in only a small proportion of patients and for only a few hours. C6 prolonged the neutralising effect of antacids in about half the patients; it had no significant effect on the pH in patients on a gastric diet or milk drip.

The assessment of the potential therapeutic value of antisecretory drugs—e.g., hexamethonium, atropine, and banthine—is discussed. Their effect on gastric acidity must be studied under the actual conditions in which they are to be used in clinical practice. Although hexamethonium reduces the volume and acidity of the gastric secretion, it is unlikely to be useful in the treatment of duodenal ulcer, because it usually increases the volume of the intragastric contents without raising the pH significantly.

We wish to thank Dr. J. B. Harman, Dr. J. C. Hawksley, Dr. Avery Jones, and Dr. E. E. Pochin for allowing us to make observations on patients under their care; and the sisters and nurses at St. Helier, the Central Middlesex, and University *College Hospitals for their kind coöperation.*

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THE INSERT HEARING-AID IN A DISCHARGING EAR

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THE main advantages of the insert type of hearing-aid are its greater acoustic efficiency, its economical battery consumption, and the ease with which a good acoustic seal can be maintained between the insert and the meatus by using an individually made ear-mould. The insert is more comfortable and easier to conceal. Concealment of the aid is important for a great majority of hearing-aid users. Nobody likes to advertise a disability. It has been generally accepted that the insert aid is the one of choice, and the external type is for exceptional cases.

Opinions differ, however, about the insert in discharging ears. Some believe that, in a discharging ear because of a chronic otitis media, it is inadvisable to wear an insert. Gray and Cartwright (1951) said of the 'Medresco' aid: "The insert cannot be worn by patients with discharging or easily irritated ears, a fact they do not always appreciate." There are many deaf persons in whom the greatest efficiency which might be obtained from an aid is reduced considerably because of discharging ears. I report here an investigation of the effect of the insert in active chronic otitis media.

INVESTIGATION

From a large number of patients with chronic otitis media for whom an aid was prescribed or who already used a medresco external aid 22 were selected and examined at the audiology unit of the Royal National Throat, Nose, and Ear Hospital from April to October, 1951, and re-examined on subsequent occasions.

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RESULTS

The ages of the patients ranged from 26 to 73 years. In all cases the deafness was of long duration. In 13 it was moderate, conductive; in 6 severe, conductive; and in 3 severe, mixed, predominantly conductive. In all cases the prescription of a hearing-aid was justified because of social disability, and in 9 cases there was also some disability at work. In all cases the hearing-aid helped to restore the ability of auditory communication. 11 patients had had an external aid before, and all of these appreciated the change to the insert type. All the patients had bilateral chronic otitis media, and 8 of them had undergone radical mastoidectomy. In 3 of these cases the insert was fitted in the cavity left by the operation.

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In 1 case one ear was moist and the other dry, but the discharging ear could hear better. Therefore the insert was fitted to that ear, with a satisfactory result from the functional point of view and no ill effect from the insert. In 1 case the ear subjected to radical mastoidectomy was moist but could hear better than the other ear, which was dry. The insert was fitted in the radical mastoid ear with good results.

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DISCUSSION

The insert is made from an acrylic plastic material which is inert to the healthy skin. Allergic contact dermatitis or otitis externa is rare. A badly made insert, however, may have some ill effects. A good insert should be clear and smooth and should fit perfectly. Faulty processing may cause cloudiness or porosity (Denison et al. 1949); the insert then contains bubbles of free monomeric vapour produced by overheating the acrylic material, and this vapour is toxic. There is a theoretical possibility that the gas from the bubbles near the surface may have some ill effect. The rough surface of imperfectly polished inserts may cause irritation. Occasionally a decubitus sore on the auricle can be detected as a result of the pressure of a badly fitting insert. An insert which is not smooth, clear, and well fitting should be rejected.

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The indications for the various types of aid are not difficult to define. The decision must be made from the functional standpoint first of all. Modifying factors may be present, and accordingly a less efficient, but for the individual as a whole a more suitable, aid will have to be prescribed. However, as I have tried to prove here, the fact that an ear is discharging because of chronic otitis media should not be an obstacle to the prescription of the most efficient (insert type) hearing-aid.

This investigation was started by Dr. J. H. Sherrey, former assistant at the audiology unit, who made the initial examination of the first 22 patients. The amplified speech tests were made by Mr. G. A. Vale, technical assistant. I wish to thank Mr. J. J. Knight, physicist at the Wernher Research Unit, for his valuable coöperation and advice, and Dr. A. S. Smith-Walker, first assistant at the audiology unit, for reading and discussing this paper.

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SARCOIDOSIS TREATED WITH CORTISONE

REPORT OF A CASE

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MUCH has been written on Boeck's sarcoid, which is increasingly recognised as a cause of symptoms due to involvement of any of the body systems. The case reported here is interesting because of the severity of the ocular condition leading to blindness, the involvement of the peripheral and central nervous systems, the establishment of the diagnosis by aspiration liver biopsy, and the use of cortisone in therapy.

CASE-RECORD

A housewife, aged 43, was first seen in the surgical outpatient department at Mile End Hospital on Dec. 27, 1950, with three weeks' bilateral swelling of the parotid glands and a week's loss of taste on both sides of the tongue. There was also a complete right facial paralysis with diminution of hearing in the right ear. The patient was subsequently seen at weekly intervals, the parotid enlargement subsided, and the facial paralysis recovered; but her general condition deteriorated and she was referred to one of us (A. D.), who admitted her on Feb. 6, 1951.

First admission.—Until April 4, 1951, she had low-grade pyrexia between 99° and 100°F. She was sallow, wasted, and slightly icteric. Her superior cervical lymph-glands were enlarged, and small discrete glands were palpable in each parotid region. Her cardiovascular system was normal, and blood-pressure 140/80 mm. Hg. Apart from scattered râles in the left mid-zone anteriorly, there were no abnormal signs in the chest. The left pupil was slightly larger than the right, but otherwise the nervous system showed no abnormality. Radiography of the chest showed calcified enlarged hilar glands and calcified foci in the upper and mid-zone regions of the right lung. A Mantoux test was positive at 1/100, and negative at 1/1000. A direct van den Bergh test was weakly positive in 10 minutes. The serum-bilirubin level was 1·3 mg. per 100 ml., alkaline phosphatase 3 units, colloidal gold 0, thymol turbidity 2, and flocculation 0. Total and differential leucocyte and erythrocyte counts were normal. The patient refused biopsy of an enlarged lymph-gland and lumbar puncture, and before her discharge as an inpatient the lymph-glands were no longer palpable.

Readmission.—Two weeks after leaving hospital she developed sudden painless dimness of vision in her right eye and soon afterwards in her left eye, and was referred by her private doctor to the ophthalmological outpatient department, from which she was admitted for the eye condition. Her pupils were widely dilated and non-reacting, with bilateral vitreous haze and œdema of the choroid and retina. There were no other abnormal findings clinically and no change in the chest radiograph. Cerebrospinal fluid (C.S.F.) was examined on April 23 and thereafter at about monthly intervals (see table) and showed a lymphocytic pleocytosis with increased protein and globulin; the chloride was somewhat low.

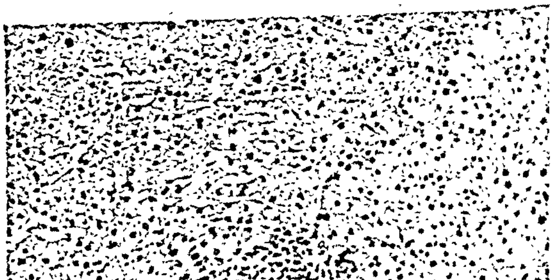
C.S.F. FINDINGS

Date	No. of lymphocytes per c.mm.	Protein (mg. per 100 ml.)	Globulin	Chloride (mg. per 100 ml.)	Sugar (mg. per 100 ml.)	Lange
April 23, 1951	18	110	Excess +	680	62	0001110000
May 11, ,,	53	100	Excess +	..	60	000112100
June 13, ,,	12	78	Slight +	580	57	0011100000
June 28, ,,	11	50	Slight +	690	65	..
July 19, ,,	8	60	..	..	..	..
July 30, ,,	4	70	..	720	..	..
Oct. 9, ,,	4	60	..	730	53	..

Cortisone therapy was given from July 20 to 30.

Progress.—During subsequent weeks there was no change in vision. The patient was somewhat drowsy and insidiously developed bilateral deafness. She had complete amenorrhœa from the onset of the illness, and during this time she lost 3 st. in weight. She did not menstruate again until November, 1951. There was nothing relevant in her past or family history. At this stage sarcoidosis was considered the most probable diagnosis. To exclude toxoplasmosis, considered as unlikely, a complement-fixation test was done by Dr. J. A. Dudgeon, and the result was negative.

Transfer.—The patient was transferred to St. Bartholomew's Hospital on June 30, 1951, and was found to be thin and sallow but not icteric. The cardiovascular system was normal apart from some hypotension, the blood-pressure being 100/60 mm. Hg. The lungs showed only a few scattered rhonchi; there were no enlarged lymph-glands in the neck, axillæ, or groins; the spleen was not palpable; but the liver was slightly enlarged (1 finger-breadth). Apart from the ocular condition the chief finding in the cranial nerves was a bilateral severe nerve deafness. The limbs were thin, but there was no focal wasting. Tone was normal in the arms but was somewhat increased in the legs. Power and coördination were normal, the tendon-reflexes were all brisk, there was bilateral ankle clonus, but the plantar responses were flexor. Sensation was normal. Mr. H. Stallard saw her on July 3, 1951, and found that the visual acuity was diminished to counting fingers on both sides and was not improved by correcting the refractive error. Secondary glaucoma was confirmed in both eyes by tonometry readings; and paracentesis, with daily reopening with iris repositor, was begun. Otological tests showed an old inactive chronic suppurative otitis media on the right side, with a mixed middle-ear and perceptive deafness, and a severe perceptive deafness on the left. Tomograms of the hilar region showed glandular enlargement on both sides with calcification in some of the glands; there was no evidence of an active lung lesion. Dr. R. Terry did an aspiration liver



Photomicrograph of liver-biopsy specimen in sarcoidosis showing occasional follicles of epithelioid cells surrounded by lymphocytes and multinucleated giant cells.

biopsy on July 11. A section (see figure) showed occasional follicles of epithelioid cells surrounded by lymphocytes and multinucleated giant cells; no tubercle bacilli were seen with the Ziehl-Neelsen stain. The appearances confirmed the clinical diagnosis of sarcoidosis.

Treatment and progress.—The eyes were treated with subconjunctival cortisone 0·4 ml. in each eye, homatropine and cocaine, and daily reopening of the paracentesis. The ocular pressure slowly fell to normal over a period of two weeks. Despite the improvement in the appearance of the eyes and the elimination of the ocular hypertension there was little return of vision. Parenteral cortisone 100 mg. was given twice daily from July 20 to 30, and during this period there was striking improvement in her appearance and sense of well-being. She gained 6 lb. in weight, and her blood-pressure returned to normal (from 110/60 to 120/70 mm. Hg). Her erythrocyte-sedimentation rate fell from 22 to 4 mm. in 1 hr. (Westergren). Her hearing also improved; she became able to hear ordinary conversational tones (this clinical improvement was confirmed by audiometry). The C.S.F., however, showed little significant change. In this period, which overlapped with that of local therapy to the eyes, the most dramatic changes took place in the ocular condition; the corneal and vitreous haze cleared completely, and the fundi could now be clearly seen. There was unfortunately still no return of visual acuity.

DISCUSSION

According to Bodley Scott (1938), Jonathan Hutchinson, in 1875, was the first to recognise the condition, although priority is usually given to others. Regarding the frequency of the disease Bodley Scott stated that in histological examinations of lymph-glands excised to establish a diagnosis of Hodgkin's disease, sarcoidosis was found once to every 11 cases of lymphadenoma. He reported 8 cases which occurred within a year. The disease has been reviewed by Longcope and Freiman (1952).

In the present case aspiration liver biopsy established the diagnosis. Although this method has been used for several years in the diagnosis of sarcoidosis, it has not perhaps in this country received the attention it deserves. According to Scadding and Sherlock (1948), van Beek and Haex (1943) were the first to use liver biopsy and obtained positive results in 2 out of 4 cases, although in none of the cases was there clinical evidence of liver involvement. van Buchem (1946) described the results of liver biopsy in 14 cases, of which 11 showed sarcoid lesions in the liver substance. Similar results were reported by Scadding and Sherlock (1948) in this country and by Schiff (1951) in the U.S.A. R. B. Terry, working at St. Bartholomew's Hospital, has had positive liver biopsies in several cases of sarcoidosis in the past year.

Although commonly benign in its course sarcoidosis may produce crippling disability, particularly if the eyes, central nervous system, or lungs are affected. Woods (1949) stated that the eyes are affected in 50% of cases, the commonest lesion being uveitis. Choroiditis and retinitis are comparatively rare, the first recorded cases of retinitis being by Rabut and Hudelo (1925). The eye lesions were comprehensively reviewed by Levitt (1941), Woods (1949), and Hogan (1951). Bodley Scott's (1938) third patient was blind four years after the onset of the eye lesions, by which time myxœdema, which responded to thyroid therapy, had developed. As in the present case, Lewis's (1941) patient had at one stage absent tendon-jerks and Adie's pupil.

Involvement of the central and peripheral nervous systems in sarcoidosis has been reported many times, and recent reviews have been made by Colover (1948) and Pennell (1951). The symptoms and signs are protean, and no part of the nervous system is exempt, although certain syndromes are more commonly encountered than others. Peripheral neuritis, with special affection of the facial nerves, is common. Involvement of the pars intermedia of the pituitary, with diabetes insipidus, is also characteristic. A chronic meningo-encephalitis with lymphocytic pleocytosis in the C.S.F. and hydrocephalus from arachnoiditis around the foramina of exit of the 4th ventricle has also been reported on several occasions. Although the condition is extremely chronic, a tendency to spontaneous improvement is in most cases manifest.

In this patient the signs of involvement of the central nervous system were the initial facial paralysis at the time of parotid swelling and, later, the onset of mental confusion, bilateral nerve deafness, pyramidal signs in the legs, and lymphocytic pleocytosis in the C.S.F. The facial paralysis cleared spontaneously before the diagnosis was established, but the other symptoms persisted for several months. Apart from unequal pupils in the early stage of the illness, there was no ocular involvement until, after five months, the patient returned to hospital because dimness of vision had developed painlessly and suddenly in each eye and examination showed widely dilated pupils, bilateral vitreous haze, and choroidoretinal œdema.

A.C.T.H. and Cortisone Therapy

Apart from the report by Duke-Elder (1951) we have found no other in this country on the therapeutic use of A.C.T.H. and cortisone in sarcoidosis; most of them are American.

Olson et al. (1950) reported two cases of plastic iritis in which there was rapid clearing, within a few hours, of the plastic exudate with A.C.T.H. therapy.

Topical cortisone produced complete remission of iridocyclitis in one case (Steffensen et al. 1951).

Sones et al. (1951) reported two cases treated with systemic cortisone. In one there was clearing of the skin and eye lesions and chest X-ray appearances and diminution in the size of lymph-glands, but no change in the size of the liver and spleen. In the other patient the chest radiograph was normal after nine days' therapy. Sones et al. thought cortisone was most effective in the treatment of acute lesions.

Galdston et al. (1951) reported a case with complete subsidence of polyarthritis after three days' treatment.

West et al. (1951) reported a case where cortisone therapy led to clearing of lung infiltration and lessening of dyspnœa.

Leopold et al. (1951) found no response to subconjunctival cortisone in three cases of anterior uveitis.

The experience of Siltzbach (1952) in the treatment of 13 cases confirms that cortisone exerts a suppressive action on the lesions of sarcoid.

Duke-Elder (1951), in an extensive review of the use of cortisone in ophthalmology, recorded a case of sarcoid in which one eye had been excised three years previously and the remaining eye was beginning a similar granulomatous iridocyclitis. The inflammation subsided and vision was 6/9 within four weeks of the start of cortisone therapy, and there was no relapse after ten months. Duke-Elder contrasted the good results in secondary glaucoma associated with iridocyclitis with the failure to respond in primary glaucoma and secondary glaucoma due to mechanical causes such as hypermature and dislocated lens. He also mentioned the development of ocular hypertension as a complication of the treatment of iridocyclitis by systemic cortisone, and stated that McLean et al. (1951) had found that secondary glaucoma might be precipitated in this way. This complication of therapy is much less likely to develop with topical therapy, but this method of treatment would not, on the other hand, benefit systemic disease.

From these reports and our experience in the treatment of the present case it seems that cortisone is of definite value in the treatment of sarcoidosis. There was no doubt about the great improvement in the general condition of our patient although, owing to shortage of supply, cortisone treatment could not be continued for longer than two weeks. The ocular condition improved dramatically, but unfortunately it was too late to save vision. In view of Duke-Elder's experience it seems it may be of great value in saving vision if used early enough. The relationship between sarcoidosis and tuberculosis has not yet been clarified, but many think that sarcoidosis represents tuberculosis in an anergic person. Because of the dangers of giving cortisone in latent or active tuberculosis its use in sarcoid may not be without danger, and further experience in the use of cortisone will be needed before its therapeutic value can be fully assessed. Possibly a combination of streptomycin and cortisone might be the treatment of choice in carefully selected cases of sarcoidosis.

SUMMARY

A case of sarcoidosis presenting with bilateral parotid swellings and facial paralysis is described.

C.S.F. examination early in the illness showed lymphocytic pleocytosis, which was followed by severe nerve deafness and a confusional state. Secondary glaucoma and blindness developed.

The diagnosis was confirmed by aspiration liver biopsy.

Cortisone was given locally and systemically, with improvement of the general condition and clearing of the ocular exudate. There was, however, no recovery of vision, and chronic glaucoma is present.

We wish to thank Dr. J. W. Aldren Turner and Mr. H. B. Stallard, of St. Bartholomew's Hospital; Dr. R. B. Terry, of St. Bartholomew's Hospital, for the liver biopsy; Mr. G. Ebbage, consultant ophthalmologist, Mile End Hospital; Dr. E. Hardy, consultant pathologist, Mile End Hospital; Dr. J. A. Dudgeon, of the Virus Research Laboratories, Great Ormond Street, for the toxoplasmosis complement-fixation test; and Prof. J. W. S. Blacklock, of St. Bartholomew's Hospital.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Treatment of Non-tuberculous Meningitis

ON NOV. 25 the section of medicine of the Royal Society of Medicine met, under the chairmanship of Sir ALUN ROWLANDS, president of the section, to discuss non-tuberculous meningitis.

Dr. STANLEY BANKS remarked that meningitis was preceded by bacteræmia or septicæmia arising from a primary focus, and associated metastases might require special treatment. The basic pathological lesion was an endarteritis. Capillaries were found stuffed with organisms; and thrombosis infarction, and hæmorrhage might occur.

Dr. Banks emphasised the importance of early diagnosis. Diagnosis was, however, often very difficult in infants, especially in the neonatal period when the only manifestations might be mild fever and refusal to feed. Mild cases could easily be missed in adults.

Treatment consisted in a short course of antibiotics in maximal dosage. Laboratory reports on sensitivity of organisms to antibiotics were essential; and if there was any doubt about sensitivity an adjuvant drug should be given. Because intrathecal administration might give rise to meningeal irritation and to secondary infections, this should be avoided whenever possible. Chloramphenicol and sulphadiazine by mouth gave an adequate concentration in the cerebrospinal fluid (C.S.F.). An effective C.S.F. concentration of penicillin could be achieved by giving enormous doses intramuscularly, such as 1 million units two-hourly; but such a concentration was not reached for eight hours. Systemic administration of streptomycin gave a very poor concentration in the C.S.F., and systemic administration of terramycin gave hardly any. Aureomycin gave a variable concentration, and its appearance in the C.S.F. was delayed for up to forty-eight hours after administration was started. Both aureomycin and terramycin were acid and thus unsuitable for intrathecal injection except in special solutes.

Dr. Banks said that 24–30% of notified cases of meningococcal disease still died; the death-rate had decreased no further since the fall occasioned by the introduction of sulphonamides. Mortality was highest at the extremes of life. Sulphadiazine was still the drug of choice in the treatment of meningococcal meningitis, and as yet the organism was not resistant. Maximal doses must be given; infants should receive not less than 3 g. per day. If the diagnosis was uncertain when the first lumbar puncture was done, up to 20,000 units of penicillin might be given intrathecally. When there was evidence of adrenal damage, cortisone 50–100 mg. daily was given; and if cortisone was not available large doses of adrenal cortical extract should be given instead—e.g., 20–40 ml. intravenously and then 10 ml. hourly for six hours, followed by 10 ml. three-hourly for several days. The eosinophil-count should be kept below 15 per c.mm. Where the patient was comatose from encephalitis the prognosis was grave; but improvement and cure sometimes followed repeated infusion of 50% glucose intravenously.

Pneumococcal meningitis still caused death in one-third of the cases; early diagnosis was imperative. 200,000 units of penicillin should be given four-hourly together with sulphadiazine; and 20,000 units of penicillin should be given intrathecally every day for four or five days. The combination of penicillin with aureomycin was unsatisfactory, the results being worse than with penicillin alone. Better results might be obtained with a combination of chloramphenicol with sulphathiazole, but this had not yet been tried.

In *Hæmophilus influenzæ* meningitis chloramphenicol in a dosage of 250 mg. four-hourly for eight to ten days gave excellent results, which were analogous to those obtained with sulphadiazine in meningococcal meningitis. The C.S.F. usually became sterile in seventy-two hours. There was still no sign of the organism becoming insensitive to chloramphenicol. A combination of streptomycin intramuscularly and intrathecally with sulphadiazine was also effective. It was found that penicillin might be added with advantage even though the organism was resistant in vitro.

Meningitis caused by *Bacterium coli*, proteus, *Streptococcus fæcalis*, or *Pseudomonas pyocyanea* was difficult to treat, and large doses of antibiotics were needed. It was of course essential to know to which drug the organism was sensitive. A combination of streptomycin and sulphadiazine might be used at first, and after twenty-four hours chloramphenicol should be substituted for the streptomycin. In resistant cases all three drugs should be used. In intractable meningitis due to *Ps. pyocyanea* polymyxin B might be given in daily doses of 5 mg. per kg. body-weight systemically and 4 mg. intrathecally.

Recent work had shown that subdural collections of fluid were more common in meningitis than had been suspected. These were usually sterile; rarely collections of encapsulated pus were found. The presence of subdural fluid was suggested by the recurrence, in adequately treated cases, of fever and perhaps by convulsions; in infants the fontanelle might bulge after forty-eight hours of adequate treatment. Dr. Banks said that such collections of fluid often subsided by themselves; surgical interference was only rarely needed.

Dr. J. C. **Broom** spoke about leptospiral meningitis. *Leptospira icterohæmorrhagiæ* and *L. canicola* were the only types met with in this country. The organism might affect the meninges alone, or also the kidneys and liver. The onset was usually sudden with headache, fever, nausea, photophobia, and great prostration; and mental confusion, vertigo, and even paresis of muscles could occur. Sometimes the initial fever subsided, and signs of meningeal involvement and renewed fever developed after an interval of a day or two. Lumbar puncture relieved the severe headache, which was a prominent symptom. The death-rate in leptospiral meningitis was negligible.

Dr. Broom showed that penicillin had no effect on the course of the disease. Experimental work on hamsters indicated that aureomycin and terramycin might be of value, but there was insufficient evidence of their effectiveness in treating this disease in man. There was also the possible disadvantage that aureomycin and terramycin did not enter the C.S.F. in sufficient concentration.

Mr. J. V. **Crawford** discussed surgery in the treatment of meningitis. Prompt and adequate treatment of head injuries was essential if meningeal infection was to be prevented; and he emphasised the importance of closing dural tears. Cases of cerebrospinal rhinorrhœa were often difficult to treat, and before the gap was closed lumbar puncture might have to be repeated several times daily. In patients with a closed fracture of the middle fossa, the dural tear usually healed without surgical interference, but operation was often necessary in open fractures due to gunshot wounds. Herniation of the temporal lobe or the cerebellar tonsil could follow lumbar puncture when a space-occupying lesion was present—a danger that should never be overlooked. Streptococcal infections were particularly dangerous in this respect. When a space-occupying lesion was suspected, percutaneous angiography was often safer than ventriculography; and it was especially valuable in temporal-lobe lesions. However, ventriculography was often necessary to establish the position of a subdural collection of fluid, and it was a useful method of obtaining fluid for culture. In the acute phase of meningitis an exudate might cause obstruction and signs of raised intracranial pressure. Ventricular drainage should then be performed by catheters introduced into the ventricles through frontal burr-holes. This was a simpler approach than the posterior route when neck retraction was present, and it was safer than cisternal puncture. In infants needles were introduced into the subdural spaces or ventricles through the lateral angles of the fontanelle; but in infancy there was a danger of a cerebrospinal fistula after ventricular drainage.

After the acute phase was over, adhesions might produce either an obstructive or a communicating hydrocephalus, and operation was then required. The results from the surgical treatment of obstructive hydrocephalus were quite good, but the relief of communicating hydrocephalus by operation was unsatisfactory.

In the discussion, Mr. D. W. C. **Northfield** drew attention to the importance of a correct technique in performing lumbar puncture. The best agent for sterilising the skin was a 2% solution of iodine in spirit. A small-bore lumbar-puncture needle should be used, and it should be held in several folds of a sterile towel.

LIVERPOOL MEDICAL INSTITUTION

Epidemiology of Salmonella typhi-murium Infection

At a pathology meeting of the Liverpool Medical Institution on Nov. 21, with Dr. R. J. **Minnitt**, vice-president, in the chair, the epidemiology of *Salmonella typhi-murium* infection was discussed.

Brigadier J. S. K. **Boyd**, F.R.S., said that certain bacteria—e.g. *Salmonella typhi* and *S. paratyphi-B*—could be divided into a series of "types" by means of conditioned bacteriophages, each of which had a specific lytic action on a particular type of bacterium. Recent work strongly suggested that the type-specificity of the bacteria was attributable to the resistance they acquired from the "natural" or "symbiotic" bacteriophages which they carried. In a study of the symbiotic phages found in *S. typhi-murium*, it had been confirmed that these were transmitted hereditarily, that the infection of the bacterial strain was virtually permanent, and that most, if not all, strains of *S. typhi-murium* contained such phages. A technique had been devised for isolating and identifying these phages. These fell into two distinct groups, and at present 12 phages had been described: a few more were in the offing. Two different phages were often found in the same strain of bacteria. There were thus a large number of different "marks"—i.e., strains—of *S. typhi-murium* labelled by the symbiotic phage they carried.

Dr. M. T. **Parker** said that in the last two and a half years 446 strains of *S. typhi-murium* isolated from man in the Manchester district had been submitted to Brigadier Boyd for identification of their symbioticphages. The "marking" results agreed almost completely with the suspected epidemiological relationships between the cases.

About one-third of all infections diagnosed in the area were "cross-infections" of infants in hospital. Brigadier Boyd's findings had been extremely useful in demonstrating the persistence of infection in one hospital for eighteen months, and had made it possible to detect spread to three other hospitals and to the family contacts of a number of discharged patients. Inter-ward spread occurred easily, and often was not associated with the transfer of infected patients. Hospital infection could take place at all seasons of the year, but the worst outbreaks had been in the cold weather. Presumably infection of the very young could occur without preliminary multiplication of the organism in food.

Rather less than one-third of all the infections had been in food-poisoning outbreaks, which had followed the familiar pattern. The remainder of the infections had nearly all been single cases in families. These cases were largely confined to the warm weather, presumably because the organism had to multiply before infection occurred. This suggested that the infection was due to "food poisoning," and not to contact infection as in the hospital cases. Analysis of the "marking" results showed that the summer peak of sporadic cases was mainly due to the prevalence of one, or a small number, of "marks" which differed in distribution from year to year and from district to district. These "single-mark prevalences" were spread over several weeks and suggest intermittent contamination of a small part of some widely distributed food, probably in the late stages of preparation.

Dr. R. E. **Rewell** pointed out that *S. typhi-murium* could infect many different species of animals. Some, such as mice, were commonly in association with man, while others—e.g., penguins—were not. In most of them the organism's behaviour resembled that of typhoid fever in man, with alternate alimentary and systemic infection. Mice commonly migrated among buildings for quite long distances and might be a reservoir of infection for sporadic cases in man.

Reviews of Books

Britain's Food Supplies

K. G. FENELON, M.A., PH.D. London: Methuen. 1952. Pp. 212. 15*s.*

THE experienced nutritionist will appreciate the appendix of this book, where 31 tables, beautifully set out and printed, supply the fundamental data concerning the changes year by year, since 1939, in our food-supplies. Livestock population, crop production, home-produced food, annual consumption of main foods, nutrient equivalents of supplies per head per day, food expenditure in the home, food subsidies, comparison of retail prices, supply of milk to school-children, annual expenditure of the Ministry of Food—these and other tables provide a mass of information which previously has never been assembled in so convenient a form. The author, formerly director of statistics and intelligence at the Ministry of Food, naturally handles figures with ease, but he also writes well. The main body of the book, written for the general reader, gives an elegant account of Britain's food problems, past, present, and future. Since so much of our food is imported, there is properly a chapter on the world's food supplies and another on international organisations. The Colombo plan, the Overseas Food Corporation, and the Colonial Development Corporation are also described. Since he is no longer a British civil servant Dr. Fenelon can write critically about such disputed subjects as food subsidies. An informative gastronomic map of England and Wales forms the end papers, enclosing a book which can be recommended to all interested in our food problems.

Human Actinomycosis

V. ZACHARY COPE, M.S., F.R.C.S., consulting surgeon, St. Mary's Hospital and the Bolingbroke Hospital. London: Heinemann Medical Books. 1952. Pp. 80. 12*s.* 6*d.*

FOR the general practitioner this is a timely monograph, because of the new conception of actinomycosis as essentially an autogenous infection by the anaerobic *Actinomyces israeli*, a frequent commensal or semi-parasite in the mouth, and also because of the evidence, from recent studies, that the disease is often overlooked or incorrectly diagnosed and is in fact much more prevalent than was formerly believed. Happily the new revelation of the greater frequency of actinomycotic infections synchronised with the discovery that the disease could be cured by suitable doses of penicillin and some other antibiotics. This lucid account of the disease—its history, ætiology, clinical and pathological features, its various anatomical types, and the methods of diagnosis and treatment—offers the practitioner all he needs to know without burdensome academic details. The use of rhymes to impress vital facts on the memory is an effective, and sometimes amusing, innovation.

Surgical Forum

Proceedings of the Forum Sessions Thirty-seventh Clinical Congress of the American College of Surgeons, San Francisco, California. November 1951. Chairman, Surgical Forum Committee: Owen H. Wangensteen, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders. 1952. Pp. 667. 50*s.*

As would be expected, the papers which make up this volume deal with subjects in the very forefront of surgical thought. In comparison with similar collections of a decade or two ago there is a very striking change. So much of surgery of the human body has been standardised, in the practical sense, that we now find surgeons searching the physical and chemical sciences for assistance in elucidating their problems.

This work deals with electrolytes and body-fluids in normal and shocked persons, the effect of long-continued hormone administration, the action of antibiotics, the elaborate experiments on short-circuiting the heart, arterial grafts, and many other subjects. A careful analytical study of the papers on the blood-fluids is necessary in order to see what bearing they have on current surgical problems, though many of the results, of course, are at present rather inconclusive. The effect of cortisone on the healing of wounds and the formation of adhesions, has been studied, but with no very striking results. Of much interest is the work done on stimulating the growth of bones by an electrolytic couple (constantan-copper) placed near the epiphysis: and this has immediate practical importance. The open treatment of burns forms the subject of another practical paper, and a great deal of experimental work on the heart and blood-vessels is reported.

Ciba Foundation Colloquia on Endocrinology

Vol. 2. *Steroid Metabolism and Estimation.* Editors: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., and MARGARET P. CAMERON, M.A., A.B.L.S. London: J. & A. Churchill. 1952. Pp. 429. 35*s.*

THE Ciba Foundation is doing an outstanding service to medical science in Britain by organising small intimate colloquia, each composed of a restricted number of experts from various countries. The papers read at these meetings, with transcripts of much of the discussions, are just beginning to appear; and the volume under review, the second in the series, contains papers given at two successive conferences in 1950. It is unfortunate that publishing delays are still so great, for the subject of steroid metabolism is moving fast.

This volume contains contributions on the estimation in the body-fluids of progesterone and its metabolites, of œstrogens, 17-ketosteroids, and, of course, corticoids. The shift from the biological assay methods, characteristic of pre-war endocrinology, to methods based on physical and chemical techniques such as infra-red spectrometry, chromatography, fluorimetry, and polarography was, at the time of the meeting, a striking foretaste of things to come. The metabolic breakdown of steroids in the body was also discussed. The adrenal corticoids occupied a place of special prominence in these discussions, and it is interesting to see how far this particular aspect has advanced in the two years since the papers were read.

The meetings gave British workers the opportunity of meeting the late Konrad Dobriner, and hearing at first hand an account of his outstanding work on the application of infra-red spectroscopy to steroid biochemistry.

Fluid Balance

A Clinical Manual. CARL A. MOYER, M.D., professor of surgery, Washington University School of Medicine, St. Louis. Chicago: Year Book Publishers. London: Interscience Publishers. 1952. Pp. 191. 28*s.*

IN this useful pocket manual Professor Moyer covers all the important aspects of fluid balance. After a brief historical survey he summarises basic physiological principles before discussing disturbances of body-fluid equilibrium in terms of volume, osmolar concentration, ionic composition, distribution, and rate of internal exchange of the fluid compartments. He skilfully backs clinical points with laboratory data and illustrative case-reports. His descriptions of therapy and—equally important—complications of therapy are adequate. Neither his subject matter nor his style makes for easy reading. Nevertheless, this manual should find its way into all hospital libraries, and it can be recommended to all surgeons and physicians who are concerned about the morbidity and mortality due to ignorance of, or indifference to, this important subject.

Diseases of the Ear, Nose and Throat (2nd ed. London: H. K. Lewis. 1952. Pp. 438. 37*s.* 6*d.*).—Mr. J. Douglas McLaggan, the original author of this good book, has been joined by Miss Josephine Collier, a colleague at the Royal Free Hospital, in producing a second edition. The several parts are well apportioned, and the approach is essentially practical, emphasis being laid on principles. Applied anatomy and physiology are described clearly and accurately as the basis of clinical practice; and the illustrations include some very good drawings and several radiographs of an unusually high standard. A facile style makes for pleasant reading, and a good index ensures easy reference. Despite the absence of a bibliography, much recent work has clearly been incorporated in the pages of this new edition, which covers the subject amply for the undergraduate, and should also be a popular and convenient source of information for the busy general practitioner.

THE LANCET

LONDON: SATURDAY, DEC. 13, 1952

A Dangerous Trade?

In the churchyard at Aldenham in Hertfordshire the observant visitor will find a monument commemorating a young bacteriologist who died of plague in 1914 while working at the Lister Institute. His was probably the first death in the parish from this cause since 1665. The story of some similar sad accident, not always fatal and sometimes merged in folklore, probably attaches to every bacteriological laboratory. No statistics are available for this country, but a questionary circulated two years ago to about 5000 laboratories in the U.S.A. showed that among their staffs there had been since 1930 at least 1275 infections reasonably attributable to employment[1]; and 39 of these were fatal. Most occurred among those working at the bench; but doorkeepers, typists, and visitors had their share of infections. Certain micro-organisms have had an ill repute for many years. We know of only one man who has worked with *Pasteurella tularensis* and escaped infection; and the American figures confirm the dangers attached to handling brucella. The risk of tuberculous infection seems to be as great from the post-mortem table as from the bench.[2] [3] In the American series *Bacillus anthracis* caused 30 laboratory infections; and this is perhaps not surprising now that we know that the spores retain life despite fixing and staining. No-one would have expected a microscopic preparation to be any more dangerous than a stuffed tiger. With regard to virus diseases, yellow fever has robbed us of many distinguished colleagues; but, considering how tentative are our methods of handling material infected with viruses, these have caused few laboratory infections. The rickettsiæ, however, have done their share of damage and more, and in the U.S.A. the first recognised natural infection with Q fever occurred in a visitor to a laboratory where the disease was being investigated. Among the fungi *Coccidioides immitis* has given rise to many laboratory infections—the more alarming because few outside the areas where coccidiomycosis is endemic have experience of this disease.

Anderson et al.[4] have tried to appraise the risk of spreading infectious matter in the course of everyday laboratory practice. A battery of suction-pumps placed round the field of operations led continuous samples of air to traps from which straying organisms could be recovered; a harmless species of serratia was used as the test organism. The results were alarming. A drop of fluid culture falling 12 in. diffused organisms in the surrounding air. The effect was greatest, as might be expected, when the drop fell on a hard smooth surface, but a few serratiæ could be detected in the air when the drop fell in a pan of phenol. Opening a stoppered bottle which had been shaken, or removing a cotton-wool plug moistened with the culture, had the same effect. The dangers incurred by removing fluid from a vaccine bottle with a syringe and needle seemed about equal whether the contents of the bottle were under positive or negative pressure, but were much diminished if the needle was shrouded with a pledget of cotton wool soaked in alcohol. The risk of flaming a platinum loop charged with too much material is taught to every student, but we are surprised to learn that in the most careful hands large numbers of organisms are dispersed by this device; the springy loop, so pleasant to handle, seems to be the most risky. The dangers proved to be greatest with procedures involving splashing and bubbling; and apparently the surest device for infecting the entire air space is the high-speed mixer often used for disintegrating tissues.

Prevention is not easy. Students will suffer no loss if they limit their attention to organisms of low infectivity. All who work in laboratories should be persuaded to accept such immunising procedures as are available. These are not many, but they apply to some of the more lethal diseases. Directors of laboratories must insist on the duty of reporting not only infections but errors and accidents which may lead to infections. Smadel[5] has set out rules directed at preventing infection by viruses and rickettsiæ; and these can be largely applied to bacteriological technique. The value of face-masks is difficult to judge; there are good masks and bad, and they may be worn sensibly or carelessly. Inoculation hoods should probably be used more widely; and those who work with mixers must remember their habit of distributing a sample of their contents over a wide area. Specialised laboratories have a better chance of devising safe working methods than those dealing with all varieties of infectious material. An intelligent understanding of laboratory dangers by all who work in the building will always be one of the chief safeguards. Many laboratory infections are seen in retrospect to have been avoidable. No risk should be taken knowingly: in the laboratory bravery and foolhardiness are almost synonymous. Anyone who calls on bacteriologists will prefer him who washes his hands three times (soap and water, alcohol, and soap and water) before greeting his visitor to the gallant fellow whose only preparation before shaking hands is to wipe his own on the tail of his overall.

Vitamin B_{12} in Practice

Vitamin B_{12} was discovered during a search for the factor in liver extracts that causes a remission of pernicious anæmia. The further discovery that the vitamin could be extracted from the mother liquor in which *Streptomyces griseus* was grown provided a plentiful and relatively cheap supply, so that preparations of vitamin B_{12} became available for general use. It was soon found that microgramme doses caused a full remission in pernicious anæmia, and sufficient time has now elapsed for us to be able to judge its value in this disease and for reports to have appeared on its action in other anæmias and in other diseases. Conley

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1. Sulkin, S. E., Pike, R. M. *J. Amer. med. Ass.* 1951, 147, 1740.
2. *Brit. med. J.* 1949, i, 907.
3. Long, E. R. *Amer. J. publ. Hlth*, 1951, 41, 782.
4. Anderson, R. E., Stein, L., Moss, M. L., Gross, N. H. *J. Bact.* 1952, 64, 473.
5. Smadel, J. E. *Amer. J. publ. Hlth*, 1951, 41, 788.

and his colleagues[1] at the Johns Hopkins Hospital have published details about 54 patients maintained on vitamin B_{12} alone for one year or more. They found, as others have done, that though an initial response could be obtained with as little as 12·5 μg. intramuscularly, doses of 100 μg. gave a much more satisfactory response. Most patients received maintenance doses of 45 μg. intramuscularly every six weeks; and a few had more—up to 150 μg. every four weeks. CONLEY et al. considered the results satisfactory; they found that there were no relapses and that symptoms, including soreness of the tongue, were quickly relieved and did not recur. The neurological complications of pernicious anæmia seemed to respond to B_{12} in much the same way as they do to liver extracts; that is to say, some patients showed remarkable improvement, while others were hardly affected. To those who did not improve, larger doses were given more often, but without effect. However, no patient was made worse by B_{12}, and there was no sudden onset of neurological symptoms, such as is seen with folic-acid treatment. The figures given in this paper suggest, however, that maintenance treatment with vitamin B_{12} could be better; no less than 16 out of their 54 patients had hæmoglobin levels of under 13·0 g. per 100 ml. after twenty or more months' treatment, and it seems probable that the maintenance dose was too small in these patients. OWREN[2] claimed that liver extracts produced a more complete remission than B_{12}, but CONLEY et al. were unable to confirm his findings. They also attempted to treat and maintain a small group of patients with pernicious anæmia on vitamin B_{12} by mouth: it could be done, but it was expensive, for an initial dose of 5 mg. (5000 μg.), followed by 1–2 mg. every month, was needed. In this country BLACKBURN et al.[3] in Sheffield have described their results with 22 patients who had previously been treated with liver extracts. They were transferred to vitamin-B_{12} treatment, and maintained on it for at least two years. They had larger doses than those given by the Johns Hopkins workers—50 μg. every two weeks for most patients—and the results, as judged by hæmoglobin levels, were on the whole better. But BLACKBURN et al. noticed that in the penultimate six months of B_{12} treatment hæmoglobin levels tended to fall. BREWERTON and ASHER[4] discussed B_{12} treatment from the patient's point of view, and there seems no doubt that their patients preferred it to liver injections. WALKER and HUNTER[5] tried to produce a remission or to maintain patients with single parenteral doses of 1000 μg. repeated at long intervals. Such a dose given to previously untreated patients did in fact produce a remission lasting from four months to as long as a year in one case, but they found that signs of reversion in the bone-marrow could be detected after forty to fifty days, and a patient with involvement of the spinal-cord tracts relapsed in six weeks. They concluded therefore that the technique was not practicable. In the treatment of the other megaloblastic anæmias, vitamin B_{12} does not seem as efficient as folic acid. It was soon reported[6] that vitamin B_{12} was ineffective in the megaloblastic anæmia of pregnancy, and later work in Europe and America has, on the whole, confirmed this view. However, NIEWEG[7] drew attention to 2 patients in Holland who did respond satisfactorily, and in India CHAUDHURI[8] found B_{12} effective in 16 patients who were given only ordinary doses. In the tropical megaloblastic anæmia of non-pregnant patients B_{12} was effective in 4 cases, but folic acid was better in another.[8] At the moment there is no way of distinguishing before treatment the patient who has a vitamin-B_{12} deficiency from one who has a folic-acid deficiency. With an anæmic patient who is well advanced in pregnancy or who has just given birth to a child, time is often too short to allow comparisons to be made, when we know that folic acid is effective.

Vitamin B_{12} is also a growth factor,[9] and WETZEL et al.[10] said that 10 μg. *by mouth* accelerated the rate of growth of children who were undersized because of long sickness or simple malnutrition. Similar results were reported by CHOW.[11] But in this country BENJAMIN and PIRRIE[12] carried out a large controlled survey of the effects of the vitamin in poorly nourished school-children, and they failed to confirm these findings. In fact YUDKIN,[13] who described the stimulating effect of a liver preparation, claimed that the factor responsible was not vitamin B_{12} at all. There certainly seems to be little reason to give vitamin B_{12} as a dietary supplement in convalescence. Good results have also been claimed for B_{12} in the treatment of peripheral neuritis, especially the forms associated with diabetes and alcoholism. MENOT[14] in South Africa found that daily doses of 60–300 μg. intramuscularly rapidly relieved the pains and cramps of this condition; and hyperæsthesia disappeared after about a week's treatment, though absent reflexes did not return. He also discovered that the enlarged and tender livers sometimes found in these patients were relieved by treatment with vitamin B_{12}. SANCETTA et al.[15] gave 12 patients with diabetic neuritis doses of 15–30 μg. daily for seven to fourteen days, followed by a maintenance dose of 15–30 μg. once or twice weekly; 3 of the patients showed complete remission, 3 "almost complete" remission, and 3 were improved. They found that massive doses did not help, and they thought that the degree of vascular damage influenced the response. It is interesting that RABINOWITCH[16] found that an extract of pregnant mammal's liver also relieved diabetic neuropathy, though it contains only traces of vitamin B_{12}. Success has also been achieved in the treatment of ulcerative colitis with B_{12}. RALL[17] had 2 patients who responded to the usual therapeutic doses; both these patients had hyperchromic anæmia, but unfortunately we do not know whether the marrow was megaloblastic or not. Vitamin B_{12} has

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2. Owren, P. A. Proceedings of the 3rd International Congress of the International Society of Hæmatology, 1951, p. 34.
3. Blackburn, E. K., Burke, J., Roseman, C., Wayne, E. J. *Brit. med. J.* 1952, ii, 245.
4. Brewerton, D. A., Asher, R. A. J. *Lancet*, Aug. 9, 1952, p. 265.
5. Walker, W., Hunter, R. B. *Brit. med. J.* Sept. 13, 1952, p. 593.
6. Day, L. A., Hall, B. E., Pease, G. L. *Proc. Mayo Clin.* 1949, 24, 149.
7. Nieweg, H. O. *Lancet*, Sept. 6, 1952, p. 491.
8. Chaudhuri, S. *Brit. med. J.* 1951, ii, 825.
9. See *Lancet*, 1952, i, 197.
10. Wetzel, N. C., Fargo, W. C., Smith, I. H., Helikson, J. *Science*, 1949, 110, 651.
11. Chow, B. F. *J. Nutrit.* 1951, 43, 323.
12. Benjamin, B., Pirrie, G. D. *Med. Offr.* 1952, 87, 137.
13. Yudkin, J. *Brit. med. J.* 1952, i, 1388.
14. Menot, P. *S. Afr. med. J.* 1951, 25, 394.
15. Sancetta, S. M., Ayres, P. R., Scott, R. W. *Ann. intern. Med.* 1951, 35, 1028.
16. Rabinowitch, I. M. *Amer. J. Med.* 1952, 12, 59.
17. Rall, G. A. *Lancet*, 1951, ii, 816.

been singularly free from unpleasant side-effects. Young et al.[18] and Bedford[19] reported allergic types of reaction after injection, but Bedford produced good evidence to show that some factor other than B_{12} in the medium was responsible.

Clearly, the vitamin has an important place in practical therapeutics, and its popularity is no passing fashion. For the treatment of pernicious anæmia in relapse and for maintenance it has already won its place, and all that remains to be settled is the optimum range of dosage. The evidence suggests that we have been too conservative and that larger doses may prove more effective; certainly treatment with liver extracts and desiccated stomach preparations during the past twenty-five years has shown a wide variation in the individual needs of patients with pernicious anæmia. If doctors are unwilling to change the treatment to vitamin B_{12}, their reluctance is understandable, for the older methods, properly used, have given splendid results. Murphy,[20] of Boston, writing from his long experience, pointed out that the death-rate from pernicious anæmia in the registration area of the U.S.A. was 5·8 per 100,000 in 1925 and 1·0 per 100,000 in 1948; and it is likely that many included in the lower rate did not in fact die of pernicious anæmia. Out of 226 of his patients who died, the deaths of only 14 could be directly attributed to pernicious anæmia, and the effect of treatment can be judged from the fact that 46% of this group of 226 died at the age of seventy or over—and 26 of them were over eighty. Similar figures were produced by Wilkinson[21] from his larger series. In 1948, out of 1179 patients still alive, 1 was over a hundred, 7 were over ninety, 99 were over eighty, and no less than 396 had passed the age of seventy. Of these 1179 patients in good health, 87·5% had been treated for more than five years, 760 for over ten years, 283 for over fifteen years, and 41 for over twenty years. These impressive records must be considered when a change in the treatment of pernicious anæmia is contemplated, and we must find the ideal way to give vitamin B_{12} to achieve results as good. The value of vitamin B_{12} in other diseases cannot be regarded as definitely established.

Work for the Cardiac Patient

There are few subjects about which the average layman is foggier than heart-disease. The term worries him greatly, being associated in his mind with dropping down dead. But of course the proportion of patients with cardiac lesions who drop down dead is extremely small; many of them live to a ripe age and die conveniently in their beds. The American Heart Association, which has affiliated associations all over the United States, is greatly interested in returning such patients to work; and, in booklets and leaflets addressed to physicians, patients, and employers, it discusses the working capacity of those with lesions of different degree. In the booklet addressed to physicians[22] it offers the following practical classification:

Functional Capacity

Class I.—Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnœa, or anginal pain.

Class II.—Patients with disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnœa, or anginal pain.

Class III.—Patients with disease resulting in much limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnœa, or anginal pain.

Class IV.—Patients with disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome are present even at rest. If any physical activity is undertaken discomfort is increased.

Therapeutic Classification

Class A.—Patients whose ordinary physical activity need not be restricted.

Class B.—Patients whose ordinary physical activity need not be restricted, but who should be advised against severe or competitive physical efforts.

Class C.—Patients whose ordinary physical activity should be moderately restricted, and whose more strenuous efforts should be discontinued.

Class D.—Patients whose ordinary physical activity should be much restricted.

Class E.—Patients who should be at complete rest, confined to bed or chair.

Studies made in a work-classification unit, which has been running for ten years in the cardiac clinic for adults at the Bellevue Hospital, show that a large proportion of patients with rheumatic, congenital, hypertensive, and arteriosclerotic heart-disease can, and do, work successfully; and follow-up studies of patients with a capacity down to and including IIIC, placed in appropriate jobs and given adequate medical supervision, have not produced any evidence that continued employment affects the heart condition adversely. As for performance, the U.S. Department of Labor compared the output of 1840 cardiac patients with that of 3055 workers without heart-disease doing the same types of jobs in 50 different industries: the difference in performance of the two groups was only 2%, and this was in favour of the cardiac patients. Patients graded IIIC and worse cannot usually work full-time under average industrial conditions, but this does not necessarily mean they cannot work at all.

Doctors are advised to have a short-term and a long-term plan for their patients. During or directly after an acute episode, such as a coronary occlusion, an attack of rheumatic fever, or a bout of congestive failure, the patient needs telling that restriction of his activity is only temporary, and—since the habit of work is only too easily lost—he also needs to be kept occupied with handicrafts, reading, writing, and planning for the future. "Under no circumstances," the booklet asserts, "should the patient be told that he can never again do regular work." On the contrary, the idea that a planned programme of increasing activity will be discussed later should be kept well in his mind. Once the acute condition has settled down the cardiac impairment and the functional capacity of the heart can be assessed. Various factors must be taken into account, of course—the ætiology of the lesion, pathological changes in the heart and vascular system, disturbances of rhythm and the chances of controlling them, abnormal fluctuations in blood-pressure, signs of diminished cardiac reserve, history of previous attacks, and risks of recurrence. The cardiac status can be expressed in terms of the classification already given, and, since this seems to be generally recognised by American doctors, it serves as a convenient shorthand, as well as providing comparable data for research purposes. When it comes to settling the patient in a job the doctor is urged to take special trouble. It is useless for him to say: "You could do light work now," and think no more about it; he must advise the patient, and advise him intelligently, on the work he should do. This means that he must take a detailed occupational history, including the names and addresses of employers, the types of job held, the hours worked, the pay, the patient's educational background and special skills, the aspects of his work he found a strain, the aspects he found easy, the daily travel needed and the method of transport, and the stair-climbing entailed in getting from home to job and back again. It is not unknown for a patient to take a light industrial job which on paper appears to be satisfactory in every way—until someone learns, after his death, that the factory was at the top of a steep hill. The patient can answer most of the necessary questions on a form, but if the doctor is going to find out clearly how much energy the job demands he will have to have a talk with him about it. The same sort of close inquiry is needed when the patient is a housewife, for it has been shown that "managing a household without assistance is the physical equivalent of a full-time industrial job." Nevertheless the average woman with cardiac disease can continue to run her home if she is taught to limit the time she spends on her feet and to change her methods so as to reduce her physical output. One of the association's booklets[2] tells her how to set about it.

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[18] Young, W. C., Ulrich, C. W., Fouts, P. J. *J. Amer. med. Ass.* 1950, 143, 893.
[19] Bedford, P. D. *Brit. med. J.* 1952, i, 690.
[20] Murphy, W. P. *J. Amer. med. Ass.* 1952, 149, 907.
[21] Wilkinson, J. F. *Lancet*, 1949, i, 336.
[22] Returning Cardiacs to Work. American Heart Association, 44, East 23 Street, New York 10, N.Y., U.S.A.

The doctor's final prescription for activity is based on all the information collected. The association recommends that he should then fill in a detailed "work capacity report," which can be used as a guide by social workers and industrial employers. The amount of travelling needed is taken into account; and the doctor, besides giving an opinion on causation, lesion, functional and therapeutic classification, cardiac anxiety, emotional status, and work tolerance, also indicates, by ticks against a list, exactly what physical activities and working conditions are forbidden or limited. The booklet notes that most cardiac patients classed as IB, IIB, and IIC can work 40 hours a week in clerical and sales jobs and in most skilled and semi-skilled occupations; and that many IIIC patients can do sedentary and part-time jobs. Most patients are happier if they can return to their former jobs; but if the job must be changed the doctor ought to be able to suggest alternatives. With a good confident patient, however, reassurance and explanation are often all the help that is needed: he will then go and find an appropriate job for himself. When he is back in work the doctor should see him regularly and assess his capacity afresh.

This is an exacting programme for doctors, but from the point of view of the public as well as the patient it would be well worth achieving. As the association point out in a booklet addressed to employers,[3] the skills of workers with heart-disease can be an asset to industry; but when they are not used the worker himself becomes a liability.

Economy in Hospital Staffing

AN important memorandum from the Ministry of Health (summarised on a later page) asks boards and committees to reduce further their man-power. This reasonable request for economy is in line with national policy; but unfortunately it has been made the occasion for a serious retrograde step—namely, the imposition of central control of hospital establishments, by making it necessary for any increase in staff to be approved by regional boards in the case of staff employed by management committees and by the Ministry in the case of staff employed by regional boards. Neither the need nor the possibility of economy can be disputed. In hospitals there is still scope for the introduction of labour-saving devices and of modern methods of business efficiency. Many hospital committees, however, have already gone as far as they can with direct economies; and further saving in maintenance costs will call for expensive new equipment, the rebuilding of out-of-date laundries and kitchens, or extensive structural alterations, such as may be needed, for example, to introduce a cafeteria system.

The aim of the Ministry's approach may easily be defeated by the antagonism it will create amongst many who have worked hard in the best interests of the service; for central control is feared and detested by those who work at the periphery. If the Ministry had ruled that all staff increases must be balanced by savings under any other headings, hospital authorities would no doubt have coöperated readily; instead it has specified a group of non-medical professional staff and of technical and other staff for a 5% cut. This must cause restlessness, ill-feeling, and distrust not only among individual workers but also among the committee members who are doing their best to provide a good service with limited resources. It may easily lead to friction between management committees and boards, and between boards and the Ministry. Apparently the Ministry has not yet realised that a big peripheral hospital cannot be regarded in the same light as, for example, a post office, which year after year provides the same service and in which the staff can readily be classified. A hospital medical service is constantly remoulded by the rapid changes in knowledge; and many services are related to particular skills which happen to be available at a particular time and place. The peripheral committees should have latitude in making the best use of their resources without having to fritter away time, energy, and temper in referring details to a central authority.

This memorandum naïvely suggests that applications for increases in staff may conveniently be sent up with the annual budget, although some applications may have to be made as the year proceeds. Yet in hospitals opportunities have to be taken as they arise; and a delay of six or nine months is usually unthinkable. On the day when the staff returns are made, a matron may have only ten nurses (below the average number) in her preliminary training school, whereas twenty-five may present themselves next time. Henceforth she must seek permission to take her normal number. Who will investigate her case, and how quickly will it be done? Regional boards are having to cut their own staff and yet take on a heavy new load of responsibility which properly belongs to the management committees, whose members have been hand-picked for their sense of public duty and knowledge of local affairs.

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[2] The Heart of the Home.
[3] These Hands are Able.

A proper spirit of economy throughout the health service must be based on mutual trust. There is no reason why a sense of trust and of service to the community should not be infused down the line from the Minister to the ward-orderly, by personal contact and transference of a sense of individual responsibility from the centre towards the periphery. The Ministry's action, by checking this trend, will cause damage at all levels.

Annotations

PREVENTION AND CURE

PREVENTIVE medicine in this country has already passed through three phases, and the form that the fourth will take is in the balance. The fire and fury of Chadwick and his followers created a new specialty—public health—from among the clinicians, and the driving force of his "sanitary idea," the quality of the men it attracted, and the prosperity of the mid-19th century combined to give us world leadership in the new science of prevention. At the beginning of the 20th century the practitioners of this science were able to extend their sway, first to a wide group of personal preventive services, and after 1929, to a hospital service which rapidly rivalled the old voluntary system. Then in 1948, in the interests of a comprehensive and integrated hospital system, public health was shorn of its hospitals—even of the fever hospitals which it had controlled for nearly a century—and of a number of its other functions, leaving many of its exponents confused and frustrated, as they were for a time in 1854 when Chadwick's Board of Health ceased to exist. Recently there have been signs of a new pattern evolving, and it is instructive to have the views of a distinguished foreigner familiar with this problem in many parts of the world.

In the course of some lectures given during a medical teaching mission to Israel,[1] Dr. Karl Evang, director-general of the public-health service in Norway, distinguished three basic systems of public health: (1) the continental European, originating in Germany and at its inception a great advance, but now too legalistic and bureaucratic; (2) the Anglo-Saxon, more flexible, pragmatic, and crusading; and (3) the Slav or Russian, which has attempted a more complete combination of curative and preventive medicine but which, alas, can seldom be studied except at second hand. The field he allots to public health is comprehensive: it should, he thinks, not only be a specialty in its own right but also be responsible for over-all planning and coördination of the whole system, including curative medicine. In his opinion neglect of curative medicine by the public-health services has been as unfortunate as the similar neglect by the clinicians of such preventive services as maternity and child welfare and tuberculosis. The central government should give centralised direction, but activity should be decentralised: the division of health functions between different government departments is largely historical, and the trend is now towards concentration.

On hospitals, Evang feels that the approach to efficient administration must not be like the approach to a mathematical problem—there are no "right answers." Nor should those who appropriate money for hospital services demand the obvious advantages of "stabilisation of budgets," which inevitably leads to stagnation. On the open versus closed hospital, he favours the closed, with safeguards covering provision of diagnostic facilities for surrounding practitioners and a system of efficient reporting on their patients; selection of staff should be obviously impartial, and there must be flexibility in the allocation of beds. Rigid allocation of beds to specialties is on the way out, as are specialised hospitals—e.g., for tuberculosis and infectious disease. "The modern trend is away from very large hospitals" and a general teaching hospital, including psychiatric, tuberculosis, and infectious-disease departments, should not exceed 700–1200 beds. An administrator with a medical degree, other things being equal, is to be preferred to a layman, and Evang quotes Goldwater as saying that "a stalwart medical superintendent can protect his hospital from the exuberance of the reckless medical enthusiast more effectively than can a non-medical superintendent," as well as guarding clinical medicine from ill-informed lay control. While this does not imply that one of the clinicians at a large hospital should take full responsibility for the administration, he pleads for more clinicians to interest themselves in administration.

> "To my mind this is a vital point: when medical activities proliferate, as they do in modern society, *medical men must take administrative responsibility*. If they do not, if they limit themselves to clinical work, others, ignorant as to all the medical factors involved, will organize the institutions in which medical men will be invited to work. This applies not only to hospital medicine, but also to all other forms of medical activity. This calls for education in health administration, a field which has been neglected in most countries."

While rejecting the complete integration of hospital and health services as being at present impossible and inadvisable in most countries, Evang emphasises the need for "bringing the student and the teaching hospital out of their present 'clinical isolation,'" quoting Newsholme's dictum that "the treatment and prevention of disease cannot administratively be separated without injuring the possibilities of success of both."

THE MASKS OF A VIRUS

THE influenza virus can assume a bewildering variety of antigenic forms; and, so far, the particular strain which causes an epidemic in any year has been recognisably different from all the strains found before. It has been suggested that this continual antigenic novelty, allied to changes in virulence, is of great importance in the annual renascence of the virus; for if it returned to us each year in the same form we would have built up too strong a barrier of immunity to allow it to trouble us again. These are, at the moment, merely speculations, but it is fortunate that the techniques for studying the influenza virus have reached so sophisticated a stage that it is possible to set about testing the truth of this and other hypotheses.

The World Influenza Centre of the World Health Organisation has, since 1947, been making a special study of the origin and spread of influenza epidemics. Although information is obtained from many parts of the world, attention is for the moment focused mainly on Europe. Here the work is grievously handicapped by the Iron Curtain, which forms an effective barrier to the exchange of news about the virus, though the virus itself brushes it aside easily enough. But despite the difficulties and the fact that relatively few people are collecting strains, a brilliant start has been made and information of the greatest interest is beginning to appear. The first report, on influenza in 1948 and 1949, was published two years ago,[1] and now comes the report on the European epidemic of 1950–51.[2] The first report suggested that the influenza epidemic of 1948–49 started in Sardinia and spread northwards through Italy. All the influenza strains isolated in Europe at that time were indistinguishable one from another, and therefore it was supposed that they had all originated from a single focus. When the epidemic of a particular year ends, the virus is lost sight of: it is true that the virus is active at all times of the year somewhere in the world, but it probably also lies dormant around the periphery of the previous epidemic area. How it exists in this dormant state we do not know, but it may be present in an avirulent form in the lungs of people living in these peripheral parts. If then a new variant emerged in one of these people, this could be the starting-point of a new epidemic.

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[1] Public Health Lectures. By K. EVANG, J. E. GORDON, and R. G. TYLER. Boston, Mass. Unitarian Service Committee Inc. 1952. Pp. 122. $1.

[1] Chu, C. M., Andrewes, C. H., Gledhill, A. W. *Bull. World Hlth Org.* 1950, 3, 187.

In the new report, dealing with 1950–51, the explanation suggested is much more complicated, for the strains of A′ virus isolated were of two subtypes, called S (Scandinavian) and L (Liverpool); and moreover there were recognisable, though small, differences among the S strains. It seems therefore that there were two separate influenza-A′ epidemics at the same time throughout Europe, and that the epidemic due to the S-type virus sprang up from several distinct foci. The Scandinavian focus of S strains seemed to originate in November, 1950, from the activation of virus which had disappeared from view after causing local activity in June, 1950. The virus which went to ground in June had already lost its 1949 mask, and was of the S type. Another focus of S strains, apparently of independent origin, showed itself in Eire. From these two centres the S-type virus spread northwards through Ireland and to Great Britain and the Low Countries. The L virus caused a simultaneous epidemic with a high mortality-rate; it appeared first in Liverpool in January, 1951, and in Belfast, whence it spread to other parts of the United Kingdom. At the same time, or soon after, the L virus was found in France, Greece, Israel, Italy, Spain, and Turkey, and there is very little to suggest how it got there. Epidemics caused by this type of virus had been observed in the Southern hemisphere in June and August, 1950. It was first discovered in Australia, and then in India, South Africa, and the islands of the Indian Ocean. But at the time of its irruption into Europe it was also causing epidemics in the U.S.A. and Canada, so that it might have come eastwards across the Atlantic. At the same time as these two A′ epidemics were in progress in Europe, there was also a third one about, for which a B virus was responsible, but this is not considered in the report.

As we have said, the S strains although very similar do show slight differences among themselves. Two separate foci have been described, but it may be better to regard this epidemic as arising in a more complex way at the periphery of the previous area of epidemic spread, with the emergence of a new type of virus capable of causing a new epidemic in communities around the periphery. The L strains were all definitely homogeneous, as had been the 1948–49 virus strains, so this epidemic may reasonably be supposed to have originated from a single individual in whom this new type gained a foothold.

van der Veen and Mulder[3] have described a new type of phase variation in influenza viruses. Virus in the P phase is that recognised hitherto, but the same virus in the Q phase is very poorly reactive with its homologous antiserum in in-vitro laboratory tests. The exact meaning in physical terms of the phase variation is not at present clear; but there is an analogous phenomenon in the rickettsia of Q fever. In the laboratory it is possible to transform a virus from one phase to the other. In the epidemic of 1950–51 the majority of the S types were isolated in the Q phase and the majority of the L types in the P phase. When both types were examined in the P phase they were clearly distinguishable, but in the Q phase it was difficult to tell one from the other. This, however, does not mean that the two are just variants of a single common type; it is difficult to examine Q-phase virus with any precision because all the serological tools are blunted. The experience of these years suggests that Q-phase virus tends to be present in the first stages of an outbreak, and P-phase virus when the epidemic has gained momentum; for a virus which is neutralised only with difficulty by specific antibody will have an advantage in gaining a foothold at the periphery of the previous epidemic area. Once it has got going, it can afford to shrug its shoulders at such additional stratagems.

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[2] Isaacs, A., Gledhill, A. W., Andrewes, C. H. *Ibid.* 1952, 6, 287.

[3] van der Veen, J., Mulder, J. Studies on the Antigenic Composition of Human Influenza Virus A Strains with the aid of the Hæmagglutination Inhibition Technique. Leiden, 1950.

MOSQUITOES AND MODERN INSECTICIDES

THE females of the two chief vectors of malaria in tropical and subtropical Africa, *Anopheles gambiæ* and *A. funestus*, enter native dwellings at night looking for blood. After feeding on the occupants they rest inside the huts until their meal is digested and the ovaries have matured; the gravid mosquitoes then leave the huts in the evenings to deposit their eggs. It has long been thought that if the inside surfaces of the walls could be coated with some substance toxic to the insects, large numbers of them would be destroyed while resting. The advent of D.D.T. and the discovery of its residual properties promised to give us a means of controlling these dangerous mosquitoes; but disappointments were in store. When it was used to spray the walls, D.D.T. seemed to have some unsuspected power of repelling insects, and this counteracted to some extent the effectiveness of its undoubted high toxicity. Investigation was clearly called for.

In 1947 Kennedy[1] showed that mosquitoes are irritated by sublethal doses of D.D.T., which prompt them to fly towards the light in an attempt to escape. Then Muirhead-Thomson's experiments in Tanganyika[2] showed that D.D.T. drove many *A. gambiæ* out of the houses after they had fed. Later, Hadaway and Barlow[3] demonstrated that fine suspensions of D.D.T. were more effective than those containing larger particles. Our knowledge of the situation has now been advanced a step further by Davidson,[4] who, working in Kenya on behalf of the Colonial Insecticides Committee of the Colonial Office, has investigated various preparations containing D.D.T., B.H.C. (gammabenzene hexachloride *B.P.C.*, 'Gammexane') and dieldrin, and studied their effect on *A. gambiæ* and *A. funestus*. He tried at first to repeat Muirhead-Thomson's work, and, though he obtained rather better results with D.D.T., many mosquitoes escaped from the huts alive and were caught in the window traps. Other suspensions of D.D.T. containing smaller crystals were more effective, achieving 40–70% kills over a period of nine months, but some mosquitoes still escaped unharmed. In other huts treated with B.H.C., fewer mosquitoes escaped, and the mortality ranged from 30 to 100% over six months. Muirhead-Thomson found that B.H.C. huts were lethal to all *A. gambiæ* entering them for at least thirteen weeks after treatment. Davidson then tried a mixture of B.H.C. and D.D.T.; this combined the high initial kill of the former and the long-lasting residual effect of the latter, but again many mosquitoes were caught on their way out. The most effective substance used in these experiments was dieldrin; for besides achieving a mortality of 80–100% over nine months, it allowed the lowest proportion of mosquitoes to escape as far as the window traps.

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[1] Kennedy, J. S. *Bull. ent. Res.* 1947, 37, 593.

[2] Muirhead-Thomson, R. C. *Trans. R. Soc. trop. Med. Hyg.* 1950, 43, 401.

[3] Hadaway, A. B., Barlow, F. *Bull. ent. Res.* 1951, 41, 603.

[4] Davidson, G. *Nature, Lond.* 1952, 170, 702.

Because all three insecticides irritated the mosquitoes to some extent, and caused a proportion of them to leave the treated surfaces before they had received a lethal dose, special experiments were devised which showed that D.D.T. excited them most and that the longest contacts were made on dieldrin-treated surfaces. Finally, it was shown that the two species were affected by the insecticides even when they made no contact with the treated surfaces. Mosquitoes were suspended for different periods in cages inside the treated huts, and twenty-four hours after their removal from the huts the number of dead insects was counted. Among those from the D.D.T. huts, the mortality was variable but generally low; B.H.C. continued to give high kills for three months after treatment, presumably by a combination of fumigation and the spread of particles; and dieldrin gave consistently high kills for nine months, mainly, it was thought, by means of airborne particles.

ELECTROLYTE LOSS IN THE SPUTUM

VOMITING, diarrhœa, and sweating are the well-known causes of a loss of fluid and electrolytes which may prove serious and sometimes fatal. Few people would think that the expectoration of large amounts of sputum could prove equally serious. Nevertheless, in an astonishing case recorded by Levinsky and Kern,[1] this did actually happen. Their patient was a Jewish broker, aged 65, who was proved by needle biopsy of the lung to have pulmonary adenomatosis or benign alveolar-cell tumour. This is a very rare condition, and there are only six previous instances where the diagnosis was made in life.

The illness lasted two years, after which the patient died; necropsy was not performed. The outstanding clinical feature was a persistent cough with the expectoration of enormous amounts of watery sputum. For much of the time the amount of the sputum was not less than 400 ml. daily. In one period of four months, during which the patient was under close observation, he produced in all some 20 gallons of sputum, the total weight of which was much more than that of his own body. On many days sputum output exceeded that of urine. At the height of this remarkable phase the sputum increased to almost 2 litres a day, and the patient began to complain of severe malaise, weakness, and muscular cramps. Investigation showed serious deficiencies in the proteins and electrolytes of the body-fluids; the chloride level was particularly low. Administration of fluid, salts, and proteins, both orally and intravenously, produced a remarkable improvement in his general condition, but the copious expectoration continued. The electrolyte content of the sputum approximated to that of the blood, but its protein content was much lower. Levinsky and Kern therefore argue that the bronchorrhœa cannot have represented an inflammatory exudate, but must have been due either to secretion or to filtration from the tumour. The possibility of a fistula between the alimentary canal and the bronchial tree was excluded by careful investigation, including bronchoscopy and œsophagoscopy. In view of the histological similarity between alveolar-cell tumours of man and the pulmonary adenosis of sheep (an epidemic disease known as jagziekte), an attempt was made to infect a guineapig with the sputum, but without success.

The results of treatment in this rare condition are of some interest. Deep X-ray therapy produced a fall in the volume of the sputum to an average of 200 ml. daily, but no further improvement was obtained with a single dose of nitrogen mustard. This case is a pathological curiosity rather than a matter of clinical importance; but the report is none the less memorable for that.

TELEVISION AND THE YOUNG

AT a recent conference Dr. Cyril Garbett, the Archbishop of York, drew attention to four possible dangers of television.[1] It might, he said, occupy too much time and attention, becoming a substitute for intelligent thought and reading; it might encourage people to rely on scrappy information, headlines, and pictures rather than on the printed article; it might accustom children and young people to sensationalism, violence, and brutality; and it could be used to spread subversive political propaganda. It is unlikely that the Archbishop regarded the two last dangers as serious at present in this country; but he was rightly pointing out the uses to which this new means of communication could be put by the unscrupulous.

A report[2] compiled by Mr. Max Gordon, based on the work of a Coventry tutorial class in psychology, suggests that television may have some compensating virtues. Questionaries were sent out to 500 young people of all economic sections between the ages of fifteen and eighteen, most of them living in Coventry, and 275 forms were returned completed. At least 1 in every 4 adolescents in Coventry is believed to watch television, and Mr. Gordon calculates that replies were received from 1 in every 15 of the selected age-group. Questions, however, need to be very skilfully framed if they are to elicit accurate information, and some of the questions put to these young people could have been sent with more advantage to their parents or their teachers. Adolescents, like the rest of us, prefer to think well of themselves; and it is not much use asking them whether television has interfered with their studies, or whether it has made them more loving towards their parents, and expecting an unbiased answer. The replies to such inquiries are better ignored.

Questions on matters of fact, bearing no risk to self-esteem, are likely to be answered reliably; and it seems clear that some of these young people now often stay in to watch television where formerly they would have gone out. Boys watched television on an average of 3·5 evenings a week, and girls on an average of 3·6. One boy in every two had previously been in the habit of going out on 4 or more evenings every week. It is impossible to say off-hand whether this is a good thing or not. In this country most of us believe that family life is important and valuable to the growing child and adolescent; but it is hard to know whether a silent and absorbed group clustered round a television set are experiencing family life in any accepted sense. Again, we need to know where the adolescent used to go during his evenings out: if to a youth club or to evening classes perhaps his life is poorer; if to wander round amusement arcades with "wide boys," himself getting wider and wider, then it is surely richer. One noteworthy finding is that television has stimulated an interest in plays, including the plays of Shakespeare. But informative talks and discussions are not to the taste of these young people; variety, sport, and the news-reel hold the highest places in their esteem. They are not much disturbed by political enthusiasms, it seems, and indeed they like television almost entirely for its entertainment value. Mr. Gordon suggests that television should be made less of a tie, and should invite discriminating attention: the programmes might with advantage, he thinks, be raised to a level halfway between that of the Home Service and the Third Programme of the sound broadcast.

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[1] Levinsky, W. J., Kern, R. A. *Amer. J. med. Sci.* 1952, 223, 512.

[1] *Manchester Guardian*, Nov. 7, 1952.

[2] The Adolescent and Television. To be had from Max Gordon, 5, The Earls Croft, Cheylesmore, Coventry. Pp. 14. 2*s.* 3*d.*

Special Articles

THE MENTAL HOSPITAL SERVICE AND ITS FUTURE NEEDS

A STATISTICAL APPRAISAL

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THE planned development of the mental hospital service depends on successfully forecasting future trends in the incidence and prognosis of mental disorders. Predictions, however, must be based on an evaluation of the current situation. For this purpose the following statistics are available.

STATISTICAL DATA

The Hospitals

The Commissioners in Lunacy, from their appointment in 1846, until the inception of the Board of Control in 1914, published annual reports, illustrated from 1859 by statistical tables. This series is a valuable contribution to our knowledge of mental hospitals, particularly as many of those in use today are basically the same as at the time of their opening in the latter part of the 19th century. The commissioners from time to time used statistics to show the need for changes in policy. One such occasion was in 1904 when they expressed their concern at "the increasing size of County Asylums." They showed that the incidence of and death-rates from "asylum dysentery" increased with increasing hospital size and they cited the following figures for 1902:

No. of beds	*Cases per 1000 persons*	*Deaths per 1000 persons*
Less than 500	3·2	1·1
500–1000	9·8	3·3
Over 1000	14·5	4·3

The commissioners concluded:

> "Justice and economy alike demand that the means which are provided to reinstate in health of mind and body those of the industrial classes who fall by the way should be those which are best calculated to secure that result in the speediest and most effectual manner, and this we believe to be hindered by the undue growth of asylums."

The reports of the commissioners compare well with any published today, even with the valuable annual reports of the departments of mental hygiene of the State of New York, the Commonwealth of Massachusetts, and other American States. The rapid growth of mental hospital service in the 19th century is shown in table I, which also shows the corresponding figures for 1946.

Bed-space

The assessment of accommodation recognised by the Board of Control in mental hospitals is based on a standard which allows about 40 sq. ft. of dayroom space and 50 sq. ft. of dormitory space per patient (Pratt 1948). In hospitals for mental disorders there was in 1950 accommodation for 126,196 patients in recognised bed-space; but, as some of this space was still diverted to war-time uses or was awaiting restoration to its proper use, the effective accommodation was for only 120,1[illegible] patients. The number of patients actually accommodated in mental hospitals was 135,190, and thus the average overcrowding was 12·5%.

TABLE I—PROVISION OF MENTAL HOSPITALS, EXCLUDING BEDS IN WORKHOUSES

Year	County, borough, and State hospitals	Beds	Registered hospitals and licensed houses	Beds
1846	19	5560	Not given	
1851	27	7851	137	7999
1871	54	27,109	122	7078
1881	65	44,101	110	7574
1891	70	56,353	100	8199
1901	80	74,246	82	7928
1914	100	109,494	79	6038
1946	104	127,087*	52	4976

* "Out of this accommodation there remained diverted for purposes arising from the war recognised bed-space for 10,417 patients."

On Dec. 31, 1949 (*Hospitals Year Book*, 1950-51) there were 420,668 staffed beds in hospitals administered by hospital management committees, and of these 146,604 (34·8%) were in mental hospitals. During the first nine months of the National Health Service the total expenditure by H.M.C.s on hospital maintenance was £97,713,914, and of this £18,453,421 (18·9%) was used for mental hospitals. The salaries of consultants and senior hospital medical officers were paid by the regional boards and are not included in the details of expenditure given above. The average maintenance expenditure per staffed bed for different types of hospitals was:

General	£316·9	Convalescent	£153·[illegible]
Isolation	£279·5	Mental	£110·[illegible]
Maternity	£412·4	Mental deficiency ..	£119·[illegible]
Tuberculosis ..	£263·3	Other	£101·[illegible]

Staff.—Hospital statistics for 1949 (Ministry of Health 1952) show that the staff employed in mental hospitals was as follows:

	Whole-time	*Part-time*	*Whole-time equivalent* †
Consultants and S.H.M.O.s ..	252	630	..
Other medical and dental staff	474	116	..
	726	746	..
Staff nurses and S.R.N.s ..	10,905	1316	658
Student nurses	4931	—	—
Other auxiliary nursing staff	2875	4070	2035
	18,711	5386	2693
Total domestic staff	9262	1079	540

† Author's estimates.

The part-time staff figures "are the numbers of part-time appointments," so it is difficult to assess them in terms of whole-time staff. For nursing and domestic staff it has been found in the Birmingham region (private communication) that counting 2 part-time as the equivalent of 1 whole-time appointment was a useful and not too inaccurate approximation. For part-time medical staff in mental hospitals, however, the number of sessions per appointment is likely to be few. In mental hospitals most of the psychiatric staff are employed whole-time, the part-time appointments usually being for consultants in medicine, surgery, dentistry, &c., who pay periodic visits to the hospital. The approximate numbers of staff per hundred beds are then:

Consultants and S.H.M.O.s	0·180
Other medical and dental staff	0·339
Staff nurses and S.R.N.s	8·32
Student nurses	3·55
Auxiliary nursing staff	3·53
Domestic	3·01

From hospital statistics in the Birmingham region I found (Norris 1951) that the average number of nursing staff of all types per hundred available beds for all except mental and mental-deficiency hospitals was 22·8, for mental hospitals 13, and mental deficiency 14; for tuberculosis hospitals (which had lowest staff/bed rates after mental and mental-deficiency hospitals) it was 21: for large general hospitals (highest ratio) it was 60. The allocation of both money and resources to mental hospitals is thus modest.

Bed-occupancy in mental hospitals is high. In table II the percentage occupancy has been calculated on the total bed-complement, because no information to date has shown the average daily number of available beds.

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* Except where otherwise stated figures refer only to mental hospitals and do not include hospitals for mental defectives.

BLE II—MENTAL HOSPITALS (1949) IN ENGLAND AND WALES BY SIZE AND OCCUPANCY

Beds	Mental hospitals		Average no. beds	Average beds occupied daily	% occupancy*
	(No.)	(%)			
ess than 200 ..	7	6·3	113	92	81
200–400 ..	4	3·6	307	229	75
400–600 ..	9	8·1	489	400	82
600–800 ..	13	11·7	710	703	99
800–1000 ..	11	9·9	934	907	97
000–1200 ..	15	13·5	1103	1078	98
200–1400 ..	14	12·6	1310	1220	93
400–1600 ..	8	7·2	1481	1438	97
600–1800 ..	3	2·7	1664	1507	91
800–2000 ..	3	2·7	1953	1876	96
000–2200 ..	8	7·2	2067	1991	96
200–2400 ..	7	6·3	2237	2196	98
400–2600 ..	4	3·6	2505	2313	92
600–2800 ..	—	—	—	—	—
800–3000 ..	3	2·7	2903	2927	101
ver 3000 ..	2	1·9	3087	3055	99
Total ..	111	100·0	1267		

$$^{*}\,\frac{\text{Average no. of beds occupied daily}}{\text{Average no. of beds in hospital.}} \times 100.$$

(In this context "available" means open and ready for use.) The rates given in column six are thus minimum occupancy-rates.

ADMINISTRATIVE USES OF STATISTICS

The main problems facing those who wish to plan the future mental hospital service are:

(1) How many mental beds will be needed, and of what types?

(2) What provisions should be made for outpatient treatment?

(3) How many people, and with what qualifications, will be needed to staff these beds?

In this paper I have dealt with the first problem, for outpatient treatment of mental disorders is, relatively speaking, in its infancy, and until we have more information about the present-day situation we cannot judge what the future needs will be.

If mental hospitals are now short of staff and accommodation, the future position may be expected to deteriorate for the following reasons:

The population of England and Wales is steadily increasing, and will continue to do so for several decades to come under natural circumstances.

The population is ageing, and, since the incidence-rates of certain psychoses increase with age, the population of mental hospitals is likely to increase.

There is a growing awareness both in the medical profession and the lay public that mental disorders are not always incurable, and that it is not a social disgrace to be admitted to a mental hospital for treatment.

Provision of free hospital treatment is likely to encourage earlier admission.

Funds and building resources are insufficient for the proper maintenance of hospital buildings, 96% of which were first put up by 1914. During the late war maintenance was necessarily neglected, and some mental hospitals now urgently need major structural repair.

The demands for young men and women of the requisite educational level for nursing are great, and nursing has to compete for the limited supply with other occupations financially, at any rate, more rewarding.

It might be argued that treatments, such as shock therapy and leucotomy, now undertaken in mental hospitals shorten appreciably the period of hospital stay, and will thus greatly lessen the need for hospital beds. Many statistical papers (e.g., Malzberg 1939, Bond and Rivers 1944, Rees 1949) support this contention, but an important limitation of such work is the comparatively short follow-up. From the annual report of the department of mental hygiene, New York State (1950), we find that 58% of the patients resident in the State mental hospitals suffer from schizophrenia; the average period of hospital life of schizophrenic patients dying in State hospitals in 1950 was 20·3 years. To reduce greatly the need for hospital beds, the criteria of successful treatment are:

Reduction of duration of *total* hospital stay.

A low relapse-rate.

A long period of remission during which the relapsed patient can remain out of hospital.

When comparing control and treated groups the duration of stay for the latter might be significantly shorter, statistically speaking, yet the difference in time may be of little practical significance as regards the need for hospital beds. Alexander (1944, 1945) and Rees (1949) have discussed the difficulties in evaluating the efficacy of therapy. Salzman (1947) found the readmission-rates to be higher and the intervals out of hospital to be shorter among shock-treated patients than among those treated conservatively.

Penrose and Marr (1944) found that at the Ontario Mental Hospital of the patients admitted in one year 30% might be expected still to be on the hospital books four years hence. From the Commissioners in Lunacy reports (1891–1914) we find that of 16,736 patients admitted in 1891, 24·7% were under care four years, and 10·6% under care seventeen years, after admission. The proportion under care four years after admission steadily increased with the succeeding years (table III). Thus improvements in mental hospital care do not necessarily decrease the length of stay in hospital. This is probably partly due to advances in medical treatment which increase the expectation of life inside, as well as outside, mental hospitals.

Statistics are also needed to assess the effect of changes in the Acts relating to mental disorder. In 1930 voluntary admission to mental hospitals was introduced, and the start of the National Health Service in 1948 gave rise to minor modifications of the Mental Health Acts. It would be interesting to have an evaluation of the effects of these changes on mental hospital administration.

TABLE III—DURATION OF STAY

Year	Admissions	% under care at the end of the 4th year
1891	16,736	24·73
1892	16,997	26·40
1893	17,662	25·57
1894	17,440	25·95
1895	18,320	27·02
1896	18,440	26·83
1897	18,618	27·70
1898	19,056	26·99
1899	19,060	26·90
1900	19,462	27·84
1901	20,282	27·28
1902	22,534	28·12
1903	21,760	28·18
1904	21,784	27·80
1905	21,335	27·34
1906	21,565	28·69

ESTIMATION OF REQUIREMENTS

The Ministry of Health (1950) have estimated that this country needs 4 mental beds and 2 mental-deficiency beds for every thousand of the population. On this basis, the number of beds needed in 1949 for the care of patients with mental disorders alone was over 172,000. According to the population projections of the Registrar-General (1951) the number of mental beds required would be about 181,000 in 1960 and 184,000 in 1970. About 28,000 nursing staff (all grades) would be needed in 1960 to maintain the hospital establishments at the 1949 level. Over 300 whole-time psychiatrists, and 600 other medical staff, would be wanted for the mental hospitals of 1960.

This method of estimating requirements by a gross over-all bed/person ratio is unsatisfactory since it does not take into account the differential needs, both quantitative and qualitative, of diverse age-groups. The proportion of people over 65 years of age is expected to be 12·2% in 1960 and 14·2% in 1970 as against 10·8% in 1949. We may therefore expect a proportionate increase in the disorders of old age (e.g., senile dementia) and a decrease in those of the younger age-groups (e.g., schizophrenia). In 1930–34 in the State of New Jersey (Frankel 1951) 38·3% of the total first admissions were due to schizophrenia and manic-depressive psychoses, while 25·8% were due to cerebral arteriosclerotic and senile psychoses. Since then the proportion of the former has decreased and of the latter increased until in 1945–49 the proportions were 28·4% and 38·3% respectively.

The proportion of females to males over 65 will probably increase from 1·40 in 1949 to 1·53 in 1960 and 1·49 in 1970; since male and female wards are rarely interchangeable this, too, will affect the type of beds needed. The qualifications of the staff will likewise depend on these trends, because the staff requirements for acute psychotics are different from those for senile patients.

To estimate mental hospital needs we must take into account age, sex, and diagnosis. Age affects the estimates for the reasons given above, and because the younger a person is admitted with a chronic mental disorder, the longer his average expectation of hospital life is likely to be; diagnosis affects them because the number and quality of staff, and the type of accommodation needed, differ according to the type of mental disorder. Objections may be raised to the inclusion of psychiatric diagnosis on the grounds that opinions on this subject are so divergent that statistics based on them are meaningless. Many medical statisticians, among them Farr (1839), Greenwood (1949), Cohn and Lingg (1950), have pointed out that useful conclusions can be made from data which are themselves imperfect. The annual publication since 1839 by the General Register Office of detailed mortality tables has been of inestimable value in improving the health services in England and Wales, although these have been, and still are, based mainly on diagnoses made by general practitioners who are usually without the diagnostic facilities now considered essential by specialists.

Detailed information about first admissions, in contradistinction to all admissions, to mental hospitals is also necessary to assess the efficacy of modern mental hospital practice. From 1921 until 1941 the annual number of direct admissions to county and county-borough mental hospitals rose slowly from about 22,000 to 26,000, but from 1941 to 1949 the number rose rapidly until in 1949 there were 51,463 admissions to these hospitals (Ministry of Health 1952). Without an analysis of first admissions by age, sex, and diagnosis it is difficult to suggest reasons for this large increase. It may be due among other things to high relapse-rates after early discharge from hospital, to changes in policy concerning the admission and discharge of patients, or indeed to increased incidence-rates.

First admissions as a percentage of total admissions vary considerably with diverse psychoses as is shown by the admissions to mental hospitals of New York State (1950):

	First admissions shown as % of total admissions with same mental disorder
Admitted with:	
Senile psychoses	96·3
Psychoses with cerebral arteriosclerosis ..	91·6
Primary behaviour disorders	89·8
Traumatic psychoses	78·7
Schizophrenia	62·9
Psychopathic personality	64·3
Manic-depressive psychosis	34·4
All diagnoses	71·6

Thus no idea can be obtained of the relative incidence of various psychoses treated for the first time in hospital unless first admissions are given separately from readmissions.

First-admission rates will not be wholly reliable, but they will probably be the best obtainable, since patients and relatives, though they forget or suppress information about an earlier admission, are unlikely to claim one without substance. It is necessary to decide whether or not to include previous admissions for psychiatric care to hospitals other than those classified as mental hospitals. Even when accurate, first-admission rates will not measure the incidence of psychoses, but they will give an estimate of those which require hospital care. Nowadays it is common for a person suffering from depression, for example, to be admitted several times in the course of a few years. Some method of sorting out repeated admissions would be useful. With all its limitations the first-admission rate does give valuable information on this point and should be used until a central case register such as that described below is working efficiently.

THERAPEUTIC TRIALS

The success of all statistical studies aiming to assess the efficacy of treatment of mental disorders depends largely on the adequacy of long-term follow-up studies. At present, this is not only an arduous but often an unrewarding task, for the practical difficulties are formidable. But therapeutic trials are as necessary for the welfare of the mental patient as for any other type of patient; it is advantageous both to the patient and to the hospital to find out what treatment is most likely to be successful.

Since Jan. 1, 1949, a scheme has been in operation to provide statistical data about patients resident in, and admitted to, mental hospitals in England and Wales (Ministry of Health 1949). For every patient resident in the hospital at the beginning of the scheme and for each admission thereafter an index card has been completed which records essential facts about the patient. If these cards, at present collected by the General Register Office and used by them to prepare punch cards for statistical analysis, were afterwards used to provide a central case register covering the current patient population resident in mental hospitals, the burden of follow-up studies would be immensely lightened. On the discharge, or death, of a patient his card would be removed from the current register to the appropriate discharge or death file. The cards of patients later readmitted would be put back into the current register and the information brought up to date. In due course it would then be possible for clinical research-workers to assess the long-term effects of the treatments now in use in mental hospitals.

SUMMARY.

Descriptive statistics of the present mental hospital service in England and Wales are given. Their use in the prediction of future hospital needs are discussed.

It gives me pleasure to acknowledge the assistance given to me by the Board of Control, and in particular by Mr. R. Tomsett. I am grateful to the London County Council for library facilities, and to the departments of mental hygiene of several States in America, including Arkansas, California, Massachusetts, Illinois, Nebraska, New Jersey, New York, Ohio, Pennsylvania, and Virginia, for information about their statistical services.

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References continued at foot of next column

ECONOMY IN HOSPITAL MAN-POWER

LAST year the Select Committee on Estimates[1] expressed the view that substantial economies could be made by a national review of the whole question of hospital staffing, and that regional hospital boards should be given "more extensive power of controlling the size of the staff of the Hospital Management Committees than they possess at present." The Ministry of Health[2] has now called on hospital authorities to make an immediate return of their staff numbers; to reduce staff wherever possible; and to make no increases in staff without approval of the regional board (in the case of staff employed by management committees) or of the Ministry (staff employed by regional boards).

The Ministry circular says that such economies, if operated with proper care and judgment, will contribute substantially towards economy in both money and man-power without detriment to the services provided. In recent months a number of boards and committees have reviewed their establishments, and in some instances reduction in the number of staff has proved possible. "All Boards and Committees are now asked to undertake such reviews with the aim, wherever possible, of making similar reductions, the Regional Board participating in the reviews undertaken by the Management Committees in its area."

Staff numbers should, in future, not be increased unless careful scrutiny has shown real need; and any increase in numbers must receive prior approval.

Each regional board and board of governors is to inform the Ministry, within two weeks, of the total number of staff, according to categories ([*a*] medical and dental staff down to the grade of registrar; [*b*] other medical and dental staff; [*c*] nursing and midwifery staff; and [*d*] other staff). Administrative and clerical staff are not included, in view of the action already taken to secure reductions in their numbers. The numbers shown on the return are not to be exceeded without the Ministry's approval. In the same way each management committee is to inform the regional board within two weeks of the numbers employed by it in categories (*b*)–(*d*); and again these numbers constitute a maximum, not to be exceeded without the Ministry's approval.

> "Applications for increases in these maximum numbers should not subsequently be made without the most careful consideration by the Board or Committee concerned. Before applying, they should be fully satisfied that the increase is justified by exceptional circumstances such as serious undermanning (as, for example, exists in the nursing staffs of some mental and tuberculosis institutions) or substantial increases in work, and that the need cannot be met by reorganisation or in any other way that would avoid the employment of additional staff."

With their returns completed, boards and committees should carry out a detailed review of each category to see what, if any, reduction is possible—e.g., by reorganisation of duties, use of labour-saving devices, or discontinuance of less essential work. The regional board should participate in the reviews carried out by management committees in their area in any way that may be convenient in their local circumstances. Any resulting reduction in staff should be effected as soon as possible.

> "In present circumstances the Minister feels that Boards and Committees should aim at ensuring that the reductions in staff broadly counter-balance in numbers any staff increases which may be approved. The reductions need not of course be in the same categories. Nor will it always be possible for them to be made in the same Management Committee Group, but Regional Boards are asked to do their best to see that this broad aim is achieved in their area as a whole."

Regional boards and boards of governors are asked to aim at reducing staff in category (*d*) ("all other staff") by 5% before October, 1953. A reduction of this order may not be possible in some groups, and a correspondingly greater reduction may therefore have to be sought in others.

> "It is not the intention that there should be a blind or arbitrary cut and if a Board or Committee considers that the effect of any of the reductions would be to curtail essential services, a full report of the circumstances should be made, in the case of Management Committees to the Regional Board, and in the case of Regional Boards and Boards of Governors to the Ministry. In no case should reductions be achieved by transferring domestic work to nursing staff."

Regional boards are asked to tell the Ministry the total numbers of staff in each of the categories (*b*)–(*d*) employed by management committees in their area, and also the total of the committees' administrative and clerical staff; and subsequently at the end of each quarter to make a return of such staff, by categories, showing totals, increases, and decreases. Boards are also to submit similar returns in respect of their own staff.

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[1] Eleventh Report from the Select Committee on Estimates. H.M. Stationery Office, 1951. See *Lancet*, 1951, ii, 590.

[2] R.H.B. (52) 133.

DR. VERA NORRIS: REFERENCES—*continued*

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PREPARATION FOR NURSING AS A PROFESSION

AT the British Social Biology Council's conference on preparation for nursing as a profession, on Nov. 7, the scope of the profession, and the many openings which nursing offers, were discussed in considerable detail.

The nurses on the platform, after stating their profession's alleged inarticulateness, showed much skill in exposition.

NEW TEACHING METHODS

Miss M. B. POWELL, matron of St. George's Hospital, and Miss D. L. HOLLAND, sister-tutor at Guy's, made the medical listener feel that the best of the nursing schools are offering the student nurse many things which are creeping only gradually into the training of doctors. Some student nurses are encouraged to visit the factory, and report back to their group of students on the conditions in which a patient's accident occurred, or to go and see the home from which his social disability or infection arose. These nurses are also given the advantages of the newest educational methods.

Other speakers recognised, however, that these methods are not yet widespread, and some doubted whether they could be generally applied in training-schools throughout the country. Grammar-school headmistresses, these speakers felt, had only heard of four training-schools, all in London. Provincial training-schools often could not afford to select their nurses at all, and were faced with the problem of weeding out the unfit from a mixed bag of applicants—most of whom have left school at 16.

ASSISTANT NURSES

Miss O. M. WAIN, matron of Willesborough Hospital, gave a moving account of her conversion from training the State registered to training the enrolled assistant nurses. She pointed out that this category of nurse was preventing the dilution of the profession by unskilled labour; and in addition this grade offered the girl of inadequate education an opportunity to develop and use her skills without the intensely traumatic experience of facing the enormous academic curriculum required for the State register.

THE HEALTH VISITOR'S BACKGROUND

Miss J. M. CALDER, chief nursing officer of London County Council, raised a highly controversial issue when she said that the nurse's intimate knowledge of disease was the best background for the social work of the health visitor. Unfortunately there seemed to be no professional social workers present to argue this point from the other side. Her suggestion that the National Health Service should be called a National Sickness Service, because it was directed by pathologists (whereas it should more properly have physiologists at the helm), seemed rather to contradict this theme.

THE PRE-TRAINING GAP

The prenursing school at Southampton, under Miss A. CROWE, seems to offer the girl of secondary modern education a liberal way of bridging the gap between leaving school and beginning her training. In general, however, the feeling seemed to be that the gap could be better bridged in other ways: prenursing courses, it was felt, could produce a girl who was sick of the subject before she ever reached hospital. The prenursing candidate was too young to be employed in wards with ill people and tended to lose interest in a goal set too far away. All the matrons and sister-tutors present were enthusiastic about training for the nursery nurse's certificate as a prenursing course; it offers a year of general education in an ordinary unsegregated technical school, and valuable experience of the behaviour of normal young children. As an alternative to this, matrons preferred to take girls who had worked in ordinary occupations before entering nursing; they did not feel that this was necessarily wasteful. The best type of girl for nursing, in their opinion, was one who retained her enthusiasm during the intermediate period without added incentive.

QUALITIES IN THE NURSE

Two of the non-nurses, Miss A. CATNACH and Mrs. N. MACKENZIE, lecturer to the Royal College of Nursing, seemed anxious to stress that the profession was not closed to candidates of low intelligence quotient, though the nurses who spoke called for women of high ability who were potential leaders. Certainly the capabilities needed for nursing listed by the non-nursing speakers were not those which would specially occur to a doctor who had worked in many hospitals with many nurses. Good personal hygiene, well-brushed hair, reliability rather than brilliance, potential manual dexterity, desire to serve, and a sense of what is worth while are qualities on which a rich woman might well choose a companion; but every doctor knows of many nurses with all these qualities who are quite impossible to work with.

A FRESH VIEWPOINT

Dr. ELIZABETH TYLDEN, the last speaker, sounded the first critical note of the conference. She tackled the problem of the selection of the nurse from the point of view, not of what the interviewing matron may look for, but of what the applicant for training in nursing gets when she has been accepted. She felt that some speakers had suggested that girls of high ability were not necessarily wanted in nursing, which seemed a pity. The present training did, however, have certain disadvantages of which highly educated girls might be critical, though newer developments seem to be correcting this. From the point of view of the public, nurses in training were taught to be extremely efficient in the domestic duties of providing warmth and food, disposing of excreta, and keeping patients clean. They are not, however, taught in any formal part of the curriculum to understand the impact of disease on the patient or on the family.

The psychology syllabus seemed to be too academic and was taught by people interested in those aspects of the subject which least concerned the generally trained nurse—by psychiatrists, who were too concerned with mental illness, psychologists, who were interested in academic problems, or sister-tutors, who groaned under yet another academic burden. Moreover, it was taught in the first year, when the nurse was too concerned with her own problems of learning and doing unfamiliar things to deal with it. Dr. Tylden suggested that the help of the professional sociologists, who ran departments in many universities, and of psychiatric social workers, who had an intimate knowledge of family problems, would be more valuable. Both matrons and sister-tutors, she thought, should receive special training in the problems of adolescents and of students; and ward sisters who undertook teaching responsibilities should not merely fill in the General Nursing Council's form, but should receive due training, recognition, and perhaps even pay, as tutors. These teaching sisters should constitute a teaching staff under the guidance and jurisdiction of the sister-tutor; each member of this teaching staff could become the "tutor" of a group of nurses, follow them throughout their training, as guide, philosopher, and friend, and be consulted at the nodal points in each nurse's life, just like a university tutor.

Dr. Tylden also suggested that the nurse's uniform was donned at such an early point in the nurse's career that it could prove disadvantageous. The medical student was accustomed to working without status or prestige, and even in his final year did not carry the label which the nurse carried in the eyes of the public as soon as the uniform was put on. The danger was that the advice which a first-year nurse offered might not be discriminated by patients from that given by her senior. Both the pride and the self-assurance of the new student could thus be tested to the utmost—sometimes beyond breaking-point. The military discipline which protected the nurse of Miss Nightingale's day from charges of immorality and frivolity now seemed out of date. The Army nowadays expects initiative from its privates, rather than blind unreasoning obedience. Teachers of nursing had no need to increase their prestige by wearing special uniform or by exacting particular marks of respect such as the putting on of cuffs. The offices of sister, sister-tutor, and matron carried enormous prestige to students, and needed no such disciplinary aids.

Teaching, too, was better conducted in these days by the teacher behaving merely as an expert witness in a group, not as a mentor. Formal lectures, Dr. Tylden hinted, always improved in quality as soon as they ceased to be compulsory, and teaching was better understood by the student whose views were treated with respect. Manual dexterity could only be acquired through encouragement, and was achieved only with great difficulty in the face of criticism or sarcasm. Some of the special problems of nursing students arose from the limitations of their pre-nursing education, and from their lack of wide general experience of life; and unfortunately most teaching schools supplied only the narrower aspects of sickness within the hospital. The impact of gynæcology, and of nursing in the male wards, on the nurse could be most shattering. Sex teaching in schools was not yet universal, and hence some special instruction in sex seemed desirable for the nurse early in her training if she was not to be shocked through her ignorance. Dr. Tylden thought that some parts of the nurse's training could with advantage be pursued at ordinary technical schools, so that she would be less cut off from the rest of the student community.

In the discussion many speakers held that the uniforms and systems of hospital courtesy did not in fact exert a serious effect on the nurse in training, and that they should not be in any way modified. The seniors in the nursing profession, it was suggested, should remember to make themselves approachable in spite of the system within which they worked. Senior girls in schools should be encouraged to listen to the school broadcasts on sex, and special provision for this kind of teaching within the curriculum would then become unnecessary. The anatomy of the male was in any case included in the curriculum of the G.N.C.; and psychology—in the form of the understanding of how to handle patients—could be acquired by the nurse in training by watching how the sister behaved.

ACTION OF OVARIAN HORMONES ON UTERINE MUSCLE

In a Ciba Foundation lecture delivered in London on Dec. 4, Dr. G. W. Corner, director of the department of embryology in the Carnegie Institution of Washington, described the results of his recent work with Dr. A. Csapo. He said that the differences in biochemical composition between uterine and skeletal muscle were quantitative rather than qualitative. Csapo had demonstrated the existence in the plain muscle of the uterus of the same system that his teacher, Szent-Györgyi, had shown to operate in skeletal muscle. Contractibility in all types of muscle was due to the actin protein molecule; and the myosin with which it was associated was the enzyme that transferred energy, in the form of energy-rich phosphate, from adenosine triphosphate (A.T.P.) to the actomyosin protein complex. Actomyosin fibres had been prepared from uterine, as well as from skeletal, muscle, and these fibres would contract in vitro in a suitable fluid medium when A.T.P. was added. The concentration of both actomyosin and A.T.P. in uterine muscle was one-seventh that found in skeletal muscle, so that the ratio of the one to the other was the same in both varieties of muscle. Uterine muscle required one-quarter of a micromolecule of energy-rich phosphate per gramme of uterine muscle per contraction; and the energy requirements of skeletal muscle, as calculated from the work of Prof. A. V. Hill, were identical.

The quantity of both the contractile protein and the energy-rich phosphate compounds, which supplied the power for the contractions of the uterus, were influenced by œstrogens. In castrated animals the concentrations of actomyosin, A.T.P., and creatine phosphate fell to a low level; but they could be restored experimentally by the injection of œstrogen. The regeneration of A.T.P. that followed the injection was more rapid than that of actomyosin, for the A.T.P. might be an intermediary in supplying the energy for the synthesis of actomyosin. Progesterone had no influence on the concentrations of these components of the contractile mechanism; but it did have an effect by modifying the dynamics of the exchange of potassium between the intracellular and extracellular spaces.

When strips of rabbit uterine muscle which had been acted on by œstrogen alone were suspended in Kreb's solution, the tension developed in them gradually fell as the frequency of stimulation was decreased. A similar phenomenon in cardiac muscle was described some 75 years ago by Bowditch as the "staircase effect." The same results were obtained by Dr. Corner and his colleagues in their experiments on uterine muscle subjected to a constant rate of stimulation by increasing the concentration of potassium in the medium. When the uterine strips were taken from animals which had been previously injected with progesterone, the opposite effect was observed. The staircase went up instead of down as the frequency of stimulation was reduced. Rapid stimulation apparently led to a loss of potassium from the muscle; and progesterone, by decreasing the rate of potassium return, reversed the staircase effect—the assumption being that the potassium concentration in the cell was greater than the optimum level. On the other hand, higher temperatures permitted a more rapid diffusion and so gave a more prominent staircase effect, while the œstrogen-dominated uterus stored on ice lost the staircase effect altogether. Repeated washing of the uterine muscle strip suppressed the staircase effect and reduced the tensions developed. A decrease in the potassium-sodium ratio increased the duration of the contraction in the œstrogen-dominated rabbit uterus. In this connection, Szent-Györgyi had correlated the digitalis effect in the cardiac muscle of the frog with the drug's inhibitory action on the back-diffusion of potassium.

Potassium is needed for the conversion of glucose to glycogen and for the transformation of these forms of carbohydrate to triose phosphate before their complete oxidation to carbon dioxide and water. The energy liberated by these metabolic processes is stored as energy-rich phosphate bonds in A.T.P. and creatine phosphate, so that in this way potassium influences the activity of the myometrium. Progesterone probably exerts its effect by regulating the movement of potassium, thus controlling the availability of this ion to the metabolic system of uterine muscle. This action of progesterone might explain the reversal in response to adrenaline of the uterine muscle of the cat when it becomes pregnant. Œstrogen governs the concentration of actomyosin in uterine muscle, and regulates the quantities of A.T.P. and creatine phosphate, which are the immediate sources of energy for the contractile protein. Progesterone, by its effect on potassium movement, controls the speed of carbohydrate metabolism, thus influencing the rate at which A.T.P. and creatine phosphate are regenerated.

Parliament

QUESTION TIME

Pneumoconiosis

Mr. David Williams asked the Minister of Fuel and Power how many miners in South Wales had been certified to be suffering from pneumoconiosis since Jan. 1, 1952; how many had remained in employment at the collieries; and how many had been employed elsewhere.—Mr. Geoffrey Lloyd replied: In the first half of 1952 there were 456 new cases under the National Insurance (Industrial Injuries) Act and 53 new cases under the Workmen's Compensation Acts. I regret that the available statistics do not enable the subsequent employment history of these men to be traced.

Medical Examination of Z Reservists

Mr. J. Johnson asked the Secretary of State for War whether he was aware of the dissatisfaction found in the past about the composition of the medical boards which examined Z reservists on call-up; and whether, if former prisoners-of-war in the Far East were called up, the Minister would see that the Army medical boards included doctors who were specialists in tropical diseases, as he believed was the case in Australia and New Zealand.—Mr. Antony Head replied: I have been in touch with the Minister of Labour about this and I understand that considerable trouble is taken to see that the fact that men have been prisoners-of-war is marked on their cards, and special inquiries are made about the effect of that imprisonment on their health.

New Military Hospitals

In answer to a question, Mr. Head said that there was a programme for the construction of seven new military hospitals in the United Kingdom, but there was little possibility of building more than one during the next year or so. Everything possible was being done to carry out alterations and improvements to existing hospitals.

In England Now

A Running Commentary by Peripatetic Correspondents

St. Danckwerts' Morn—a joyous day it was!
For all the frost outside, it was not cold;
Into ten thousand bank accounts there pass
Those slips of paper, symbolising gold.
That day no doctor, whether young or old,
Forbore in speech or thought to offer praise
To him whose verdict, just as it was bold,
Brought springtime to all hearts and merry lays;
Enough! Be thankful for this day of days.

* * *

During the late hostilities an old friend of ours incurred the gratitude of an army dentist by inoculating him with a sharp needle. When our friend later developed an apical abscess in an upper incisor, the dentist dismantled the tooth with loving care and substituted an affair of wire and plastic, cunningly wrought by his own hand, and moored invisibly to the adjacent teeth. The substitute was stained with Naafi tobacco juice to match its neighbours, and the general effect was most pleasing. Later, when the moorings relaxed their grip somewhat, the tooth would vibrate agreeably in our friend's head during the purple passages in his lecture on hygiene. This tooth, which we may call the Mk. I prosthesis, had a chequered history, but was ultimately lost at the bottom of the Minch during a rough trip to Stornoway in a tank landing craft.

The Mk. II prosthesis was not obtained until after the war. This time the matter was attended to with due form and ceremony, steaming moulds and plaster casts, and our friend found himself with a large pink serrated job occluding the whole of his hard palate. At one corner of this massive contrivance, as if by accident, was attached a single tooth. Our friend viewed it with considerable distrust, the more so since it transpired that every taste bud he possessed was located in the occluded area. He was spared much anxiety, however, by the resourceful action of his wife, who trod on the prosthesis on the bathroom floor the night he brought it home and snapped off a good three-quarters of the pink part. This allowed some at least of the taste of dried egg to penetrate his dulled senses at breakfast. He was also fortunate enough to shut the prosthesis in a drawer shortly afterwards, breaking off another large portion, and thereby allowing both the prosthesis and his tongue to occupy his mouth at one and the same time. Nevertheless he remains incurably disposed to remove his tooth when anything worth tasting is to be tasted, and when sneezing he has to adopt a complicated manœuvre with his tongue lest the prosthesis should be expelled among the startled bystanders.

Our friend has now taken to academic life, and the other day he was seated in his lab. chewing on a well-earned Blue Danish sandwich when the door suddenly opened and a minor procession arrived, headed by the Vice-Chancellor, who was on a tour of inspection of scientific plumbing arrangements. Our friend rose rapidly to his feet and looked hastily for his tooth; to his dismay he found it was not in its accustomed place on the typewriter. His muttered responses to Authority lacked conviction, but they served, and it was not until he pulled out his handkerchief to mop his brow that the situation was irretrievably lost. With the handkerchief came the Mk. II prosthesis, which arched through the air and fell with a thin clattering noise full at the feet of the entire Drainage Commission.

* * *

The problem of the leisured practitioner has been solved by the Medical Sporting Association, which announces a well-rounded programme for the season 1952–53. The organisers have had in mind especially the needs of consultants, S.H.M.O.s, and registrars, but all doctors are welcome. The Lincoln's Inn Hurdlers offer plenty of sport. The Pall Mall Orientals teach fencing and judo and award fakirships for yoga and the Indian rope trick. The Harley Harriers have a paper-chase every Saturday, assembling at the Harleian. Fox-hunting has a perennial appeal: the Wigmore meets at the Old Wim Pole on Tuesdays and Thursdays at eleven, and at their New Year meet will draw the Adelphi coverts. The Tavistock Square Dancers (telegrams: Honour your partners) have a well-appointed pavilion; quieter but more expensive are the Cavendish Olde Tymers. Details of any of these facilities may be had from the secretary of the M.S.A. at St. Pancras Hospital.

* * *

I don't know whether peripatesis includes travel in a small dinghy with an outboard motor, but anyway we walked the last bit. The occasion was an up-river trip for delegates to a nutrition conference somewhere in Africa. H.E. the Governor selected three of us from the party on the government launch to accompany him, and he proved to be as good a mechanic (marine) and navigator as he is an administrator. The object of this subsidiary trip after we had left the main party exploring James Island, now the size of a tennis court and said once to have housed a garrison of 300, was to see a native village. After a hot trip up a creek bordered by mangrove swamps with interesting bird life—for the benefit of medical bird fanciers my bag was a piebald kingfisher and a large purple heron—we reached the little landing-stage where a large heap of oyster shells was the surprising equivalent of empty tins on a refuse dump at home. Perhaps it was this addition to the staple diet which was responsible for a healthy crowd of young African farmers (groundnuts) who turned out to greet us in the village 100 yards inland. The local chief, with his bodyguard of one (with a dangerous looking shotgun) did all the formalities through an interpreter. The Governor introduced us as three very distinguished doctors, but the chief could hardly have cared less. He was much more interested in discussing His Excellency's recent leave and safe return and the prospects of a good harvest. The village was remarkably clean and tidy, and the inhabitants—despite the chief's obvious no-use attitude for the medical profession—looked well fed and cheerful. The return journey on a dropping tide revealed oysters attached to the lower parts of the mangrove trees where they grow in a happy parasitic sort of life. The heat seemed less intense as we met a slight head wind. Judging by weather reports which have reached the conference by circuitous means we are much better off here than In England Now.

* * *

In a world of change, the changed attitude of patients is perhaps only to be expected. But should we not still be able to claim the unquestioning trust of our own families?

Wife: "I've had a terrible pain in my back all night. I couldn't get a wink of sleep. Do you think it's lumbago?"

Self (*reaching for the marmalade, reading the film critic in the morning paper, and keeping an eye on the clock*): "Oh yes dear, I'm sure it is."

Wife: "What do you think I should do? Do you think I ought to stay in bed?"

Self (*with visions of the chaos that would ensue*): "Oh no, definitely not. You'll get fixed and your back will be much worse. You must keep moving about."

A week later, after the pain has gone, my wife is entertaining some friends to tea.

Wife: "I had a terrible attack of lumbago last week. As usual my husband didn't do a thing about it. That's the worst of being married to a doctor."

Friend: "They talked about lumbago on the wireless the other day. There was a doctor in Woman's Hour."

Wife: "What did he say?"

Friend: "He said you should go to bed straight away and stay there till the pain is better."

Wife: "My husband said I had to keep up and moving."

Friend: "Ah! but the radio doctor was a specialist."

How is this situation to be met? We are betrayed from within the Citadel. What are the B.B.C., the G.M.C., and the B.M.A. doing about this threat to medical family life? How can you play the oracle to your family or your patients if a rival specialist oracle on the radio contradicts you?

Letters to the Editor

AGRANULOCYTOSIS DURING ISONIAZID THERAPY

SIR,—In your issue of Nov. 15 Dr. McConnell and Dr. Cheetham report the development of pellagra in a man after three weeks' treatment with isoniazid in doses of 8 mg. per kg. body-weight per day. I describe here the case of a child who developed agranulocytosis after 3 months' treatment with isoniazid by the same scheme of dosage.

The patient, aged $4^1/_2$ years, was admitted to the Derby City Hospital in a state of semi-coma, and tuberculous meningitis was diagnosed. Treatment was begun with systemic and intrathecal streptomycin, with *p*-aminosalicylic acid, and with isoniazid in daily doses of 4 mg. per kg. body-weight. On the 18th day it was decided to continue treatment with isoniazid alone; the daily dose was increased to 8 mg. per kg. body-weight.

In the 10th week of treatment, and again in the 12th week, the child developed localised staphylococcal infections of the skin without associated constitutional disturbance. Penicillin was administered systemically on the first occasion; but with the recurrence of the infection 2 weeks later no drug was used and the infection subsided spontaneously. Blood-counts were done weekly, and were normal apart from a moderate neutrophil response during the intercurrent infections. In the 14th week there was a further recurrence of the staphylococcal skin lesion. On this occasion it was extensive and the individual lesions were less well localised. An obvious deterioration of the patient's general condition occurred, with listlessness and a rise of temperature to 100°F. Examination of the cerebrospinal fluid excluded relapse of the tuberculous meningitis. A white blood-cell count showed a total of 4900 per c.mm., of which only 1% (49 per c.mm.) were neutrophils. The values for red cells, hæmoglobin, and platelets were all normal. There was no evidence of throat or mouth lesions.

Isoniazid was promptly withdrawn, and aureomycin and penicillin were administered to control the infection. The patient's condition improved clinically within 24 hours. 2 days after withdrawal of the drug the bone-marrow showed active granulopoiesis with 17% myeloblasts, 17% myelocytes, 15% metamyelocytes, and 28% neutrophil polymorphs of the myeloid series. The peripheral blood now showed 363 neutrophils and 2299 immature granulocytes per c.mm. 3 days later, the neutrophils had increased to 6698 per c.mm.; and thereafter progress was satisfactory.

There can be little doubt that isoniazid was responsible for the agranulocytosis, for the blood changes were quickly reversed after the drug was withdrawn. This toxic manifestation is probably related to long-continued administration of large doses of isoniazid. The Medical Research Council report[1] says that only a few toxic effects were observed when the drug was given for 3 months in daily doses of 3 mg. per kg. body-weight up to a maximum of 200 mg. daily. It is doubtful whether this relative freedom from toxicity prevails when the drug is given in large doses over long periods.

I am grateful to Dr. D. V. Hubble for permission to publish this case.

Derbyshire Hospital for Sick Children, Derby.
ANN FERGUSON.

MORE INDUSTRIALISATION OR MORE AGRICULTURE?

SIR,—Five years ago you published articles by me on the economic crisis then facing this country.[2] I queried the wisdom of the extreme emphasis placed on exports, and urged that the proper response to the changed situation was a shift of capital and labour into agriculture. I argued that the cost of foodstuffs would continue to rise both here and abroad, and that only by allowing farmers a much larger share of the national income would it be possible to regain stability.

At that time those who chiefly influenced official policy contested that the high price of food in the world markets was exceptional, that sooner or later it would fall, and that to encourage agriculture at home to achieve a higher level of production by offering higher prices for the produce would prove a shortsighted policy which would leave us stranded when it became possible to buy again in the world market. The counter-argument, that if the earnings from our export trade no more than broadly sufficed to pay for raw materials we should not in any case have the wherewithal to buy food abroad, was then ignored, as in many quarters it still is today. I went further, and urged that, once free trade among individuals was abandoned in favour of national controls over imports and exports, the questions at issue became social questions, and that the further industrialisation of England in the drive for exports was socially a mistaken policy, as well as economically faulty. It was in fact likely to inhibit the natural reaction to the alteration of our economic environment—namely, a doubling or trebling of the man-power and services devoted to agriculture at home.

The course of events since that time has gone far to justify the views thus expressed. The ever-increasing difficulties attendant on an export policy in a world which is more and more hostile to imports are now becoming a commonplace. But the progress towards a revaluation of the part that food must play in our economy is slow and uncertain, and there is even today no adequate appreciation of the need to draw resources into agriculture at home by allowing the scale of rewards to the farmer to go on swinging up and up so long as they bring increased production. If there is one point in our economic machinery more critical for our welfare (and perhaps survival) than any other, it is to be found in the mechanism for reviewing the prices of agricultural produce. It is natural enough for those who represent the consumer to claim that the farmer must not be paid more than a "fair" price, and that his receipts must be related to the cost of production. But this is the wrong basis on which to approach the matter, and the bringing of the complication of a fair profit into what is essentially a matter of supply and demand is a source of endless confusion. The question which must be asked is—assuming we need greatly to step up agricultural production by such and such an amount, how much must the community be prepared to pay the farmers to make this a profitable proposition? If the answer be that to enrol the necessary labour and create the necessary facilities will use, let us say, about twice the proportion of our national income that is thus employed today, the sooner we recognise the fact the better. Only about one-eighteenth of our population is at present engaged on the land—maybe we do indeed need greatly to increase the proportion. As I argued five years ago, such a prospect is by no means altogether dismal: for every step towards that goal means so much the less pressure for machine-made exports, and brings in sight the possibility of manufactures and services for the home market at price levels dictated by abundance rather than by scarcity.

Those who carry some responsibility for forming public opinion on these matters should do their best to prepare the country for still greater emphasis on home-produced food, though it cost twice as much as it does today: and they should at the same time adjust their outlook to a world in which forced exports play a less and less prominent part, and all the thousand things we can make in this country become available to us at prices which will help to comfort us for having to buy food we have grown for ourselves.

YOUR 1947 CORRESPONDENT.

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1. Medical Research Council. *Brit. med. J.* Oct. 4, 1952, p. 735.
2. *Lancet*, 1947, i, 340; 1947, ii, 67.

ESTIMATION OF BLOOD-DEXTROSE

SIR,—In your issue of Nov. 22 I read with great interest the preliminary communication by Dr. Vere on the estimation of blood-dextrose with the ophthalmoscope.

Surely Dr. Vere has adapted his instrument as a saccharimeter? This instrument, which is widely used commercially to measure the concentration of sugar in solutions, depends on the fact that when plane polarised monochromatic light is passed through a solution containing sugar (or other optically active substances), the plane of polarisation of the light is rotated by an amount depending on the wavelength of the light, the thickness of the solution, and the concentration of the optically active substance in the solution.

That Dr. Vere is measuring this rotation is indicated by the fact that a variable analyser rotation is required to produce extinction of the reflex. If the plane of polarisation of the light were not being rotated during its passage through the eye, extinction of the reflex would always occur with the analyser in the same position, whatever the intensity of the light emerging from the pupil.

Royal Eye Hospital,
London, S.E.1.
MICHAEL SHERIDAN.

A "HARLEQUIN" COLOUR CHANGE IN THE NEWBORN

SIR,—Two cases of the condition appositely termed by Dr. Neligan and Dr. Strang (Nov. 22) the "harlequin syndrome" have been observed in a premature-baby unit here during the past month. The signs were exactly as described by them; the pupils were not observed.

The first baby, delivered normally, weighed 4 lb. at birth and was admitted 3 hours later. She was then extremely cyanosed and distressed and was resuscitated with difficulty. The first attack was observed on the 4th day of life, and four further attacks were noted during the next 4 days while the baby was lying naked in an incubator.

The second baby weighed 5 lb. 3 oz. at birth, and had signs of atelectasis for 2 days, during which time she was kept in an oxygen box. Feeding was begun on the 3rd day, but she vomited each feed; during a feed on the 5th day an attack was noticed. The vomiting subsided on the 6th day, and did not recur; no further long-continued examination of the baby when naked was therefore made, and no further attacks were observed.

This syndrome has been sought in mature babies, but in these it has not been detected.

Mill Road Maternity Hospital,
Liverpool.
OLIVE SHARPE
Pædiatric Registrar.

DWARFISM AND AORTIC MALDEVELOPMENT

SIR,—Your annotation of Nov. 29, in which you draw attention to the association of congenital cardiac defects with ovarian agenesis, is timely.

Goldman et al.[1] reported that, in their series of 14 cases of coarctation of the aorta, 4 out of 5 females showed shortness of stature and abnormal digits; and the 3 of these who were adults had clinical evidence of ovarian hypofunction; the other was a girl, aged 8 years.

On the other hand, patients seen at endocrine clinics with growth stunting, neck webbing, and primary amenorrhœa (Turner's syndrome) should be examined carefully for congenital cardiac defects. Of 4 such patients at present attending the endocrine clinic at Stobhill General Hospital, Glasgow, 2 have congenital aortic stenosis.

I think that you are wrong to imply that the association of ovarian agenesis with coarctation of the aorta constitutes Turner's syndrome. The syndrome frequently occurs without demonstrable cardiac defect, and in none of the 7 cases originally described by Turner[2] was coarctation noted. Further, the opinion that ovarian insufficiency accounts for retardation of growth in this syndrome is wrongly imputed to Albright et al.[3] These workers discuss "5 possible causes for the diminished rate of growth in this syndrome . . . and believe it results from decreased adrenal cortical function."

Department of Materia Medica
and Therapeutics,
University of Glasgow.
A. SLESSOR.

ORAL ANTIBIOTICS AND SPONTANEOUS HÆMORRHAGE

SIR,—At a time when oral administration of antibiotic drugs is becoming more frequent, I wish to draw attention to a possible danger in their use. During experiments on rats I have found that chloramphenicol, given by mouth for some days, greatly enhances the animals' susceptibility to a single dose of oral anticoagulant ('Tromexan'). The average prothrombin-time 24 hours after our standard experimental dose of anticoagulant was 22·7 seconds (rat normal is 13·5 seconds); but in animals to which chloramphenicol had been administered for 4 days before the anticoagulant, the prothrombin-time rose to an average of 33·0 seconds.

A likely explanation of this finding is that, by modifying the flora of the gut, the antibiotic indirectly reduces the amount of vitamin K produced. The balance between the absorption of vitamin K and of the anticoagulant is thus disturbed, and the effect of the latter is consequently enhanced. This would be consistent with the results observed in other conditions where vitamin K is deficient.

It seems desirable to bear this experimental finding in mind when oral antibiotics and dicoumarol-like anticoagulants are to be administered concurrently.

Obstetric Unit,
University College Hospital
Medical School, London.
H. PAYLING WRIGHT.

THE OTHER 60,000

SIR,—It seems to be generally accepted that general practitioners form the largest section of registered medical men and women in the country and *that the* majority of medical graduates enter general practice. *It* is rather startling, therefore, to learn from Mr. H. A. Marquand's speech in the House of Commons[4] *that* in 1951 there were fewer than 20,000 doctors engaged in general practice in this country—18,195 principals and 1724 assistants—whereas there were in the *same* year well over 80,000 persons on the Medical Register.[5]

Where, I wonder, are the missing *60,000*? Surely specialist services do not employ more medical manpower than general practice?

Manchester.
N. BERLYNE.

EFFECTS OF HEXAMETHONIUM

SIR,—In answer to queries by Dr. Whiteside and by Dr. Coigley (Nov. 22), the evidence that hexamethonium is a pulmonary vasodilator might account for some of the benefits produced in bronchitis. The drug, however, may have other actions, such as relaxation of bronchial muscle; and it would be premature to ascribe clinical improvement to a possible vascular effect.

In answer to Dr. Cookson's query, the centre of gravity of the body as a whole lies somewhere about the pelvis. As the lungs are above this level with the body in the upright position, some drainage from the thorax in this position might be expected. The point we made, however, was that the cardio-pulmonary *blood volume* seems to decrease in the upright position only when normal innervation is present, and this decrease in blood content does not occur under hexamethonium. It is better to look at the results of the cardio-pulmonary blood volume as a group rather than stress individual answers, as these are as yet open to some experimental error. Our data on vital capacity are not adequate to answer his other query. A complete study of total lung volume would be required before drawing any further conclusions.

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[1] Goldman, M. L., Schroeder, H. A., Futcher, P. H. *J. clin. Endocrin.* 1949, 7, 622.

[2] Turner, H. H. *Endocrinology*, 1938, 23, 566.

[3] Albright, F., Smith, P. H., Fraser, R. *Amer. J. med. Sci.* 1942, 204, 625.

[4] See *Manchester Guardian*, Oct. 31, 1952, p. 2.

[5] See *Lancet*, Aug. 30, 1952, p. 438.

H. R. GILMORE
H. KOPELMAN
J. McMICHAEL.

Postgraduate Medical School
of London, W.12.

ANÆSTHESIA FOR TONSILLECTOMY IN CHILDREN

SIR,—I was most interested in Dr. Bullough's paper (Nov. 22) and wholeheartedly agree that children exposed to psychic trauma have long memories of it.

I am, however, against the use of intravenous thiopentone for children in whom the tonsils are to be dissected with the aid of the Boyle-Davis gag. Laryngospasm is a serious complication which most commonly arises from mechanical stimulus to the larynx itself—for instance, from the insertion of the Boyle-Davis gag, the packing of the tonsillar bed, or the trickling down of blood into the laryngeal area. If the spasm does occur, it is most difficult to prevent the child from becoming cyanotic. I do not use intravenous thiopentone for tonsil dissections unless I am prepared to intubate, which in my opinion is the only safeguard against laryngospasm.

I believe that a certain number of children readily accept the "needle," but in my experience the majority dread it. I knew an anæsthetist who, before inserting the needle, sprayed ethyl chloride on to the cubital fossa.

Whenever possible I visit the children on the day before the operation. While listening to their chest I encourage them to "puff away like a little engine." Boys invariably enjoy that idea, and little girls do not like to fall short. Premedication consists of sodium quinalbarbitone ('Sodium Seconal'), in dosage according to body-weight, which is given per rectum $1\frac{1}{2}$ hours before operation, and atropine gr. $\frac{1}{100}$ half an hour preoperatively.

If the child arrives in the anæsthetic room asleep, ethyl chloride is dropped on the mask, which is held about 3 in. from the face. The mask is gently lowered while the child loses consciousness, and anæsthesia then proceeds in the normal way.

If the child arrives in the anæsthetic room awake, I remind him of the game we played the day before; he or she usually puffs away quite happily, and occasionally even comments on the scent in flattering terms, until unconsciousness supervenes.

I am convinced that the majority of children leave for home with two outstanding memories: (1) the ice-cream they received for tea on the day of admission; and (2) the funny man who came to the ward to play the "engine game" with them.

West Herts Hospital,
Hemel Hempstead.

ERIC GOLDSMITH.

SIR,—I was very interested in Dr. Bullough's article. During twenty years' combined general practice and anæsthetics I had ample opportunity of seeing the great value of adequate pre-anæsthetic sedation of children. The average child who is induced with ethyl chloride when conscious is seriously affected by the experience for six months to a year. When visiting the child at his home, anything that the doctor does or says which reminds the child of hospital produces signs of fear varying from a mild protest to hysterical screaming; and the permanent result is dread of an anæsthetic.

At this hospital we have for many years given bromethol ('Avertin') to children who are having their tonsils and adenoids dissected—a total of over 6000 cases. The results have been highly satisfactory. A generation of children has grown up with no dread, in fact with no memory, of having an anæsthetic. Often a child, when asked by his parents if he has had his operation, replies cheerfully and unconcernedly, "No, Mummy, but I have got a sore throat."

We have absolutely no difficulty with depression of the respiratory centre. Though the child breathes shallowly after bromethol, full oxygenation is maintained and the lightest stimulant—e.g., induction with nitrous oxide—produces deep breathing. The cough reflex is very active, and both it and the respiratory centre are, in our experience, much less depressed than they are by morphine, quinalbarbitone ('Seconal'), or thiopentone. There is no increased tendency to laryngeal spasm.

Anæsthesia is induced either by an ethyl-chloride/ether sequence, or by nitrous oxide, oxygen, and trichlorethylene; either way is smooth and rapid, and maintenance by a Boyle's type of machine with a Boyle-Davis gag requires much less ether than with other types of premedication. Swallowing and coughing return quickly after the anæsthetic, and the child is returned to the ward in the same lateral position as he arrived.

Children, with their high metabolic-rate, are very tolerant of bromethol, and we have had no anxiety of children being "too depressed." Occasionally children are restless during recovery and they are given 'Nepenthe' in the usual dosage. We feel that it is unjustifiable to have the child wide awake, uncomfortable, and possibly crying. If the child can have several hours of light sleep after his operation, with cough and swallowing reflexes active, while all oozing from the tonsillar beds is ceasing, we are delighted. The fear that unless children are quickly awake postoperatively they are liable to inhale blood-clot is, we believe, unfounded; this is more likely to occur as the result of careless dissection and faulty hæmostasis. The inhalation of droplets of whatever is in the mouth does, of course, occur, but much more so if the child is wide awake and crying.

The only disadvantage of this technique which need be seriously considered is the suggestion that basal narcosis makes more work for the nursing staff. This is mainly a matter of organisation. The grouping of the operation cases under the supervision of one nurse until recovery is complete is the best way to solve this problem. The little extra work required—and it is only a little—is well repaid by the peace in the ward, the reduction of vomiting, and the unconcerned children that awaken a little surprised to find they have sore throats.

The ideal place for a child to fall asleep is in bed, and the least disturbing way of achieving this is by a drug administered per rectum.

Warneford General Hospital,
Leamington Spa.

JAMES A. KNOTT.

EXAMINATION OF RIB BONE-MARROW FOR TUBERCLE BACILLI

SIR,—Dr. March and Mr. Barton (Nov. 29) suggest that "ribs removed at thoracoplasty or at resection could be used in orthopædic units for grafting in tuberculous disease of bone without risk of implanting tubercle bacilli into the tissue of the recipient."

I must deny this most emphatically, for in my own experience two patients who received thoracoplasty ribs for spinal fusion for scoliosis developed tuberculosis at the site of implantation. These ribs were from donors who had had pulmonary tuberculosis, but the ribs were resected with care and chosen for the bone bank as being free from adhesions or neighbouring disease. They were placed in streptomycin-penicillin solution as soon as they were taken from the donor and stored at −20°C until used. The washings of the bone were sterile.

The patients developed sinuses at the site of the bone graft, and *Mycobacterium tuberculosis* was recovered from them.

In my experience it is wrong to exclude the presence of *Myco. tuberculosis* in bone by the examination of smears and Löwenstein cultures. If Dr. Marsh and Mr. Barton had implanted the marrow in a muscle pouch in guineapigs their results might have been different; but, be that as it may, two patients who have received apparently healthy ribs have become infected thereby.

London. C. H. LACK.

THERAPEUTIC APPLICATION OF PLASMA CHOLINESTERASE

SIR,—Workers at St. Bartholomew's Hospital[1] report that by intravenous injection of human plasma cholinesterase they have abolished, in a patient, the effect of succinylcholine. The anticholinergic effect became evident when the patient's plasma cholinesterase level had risen by about 50%, at which time the whole-blood cholinesterase had not risen significantly. Dr. Evans and his colleagues, in pointing out that the cholinesterases of plasma and of erythrocytes have different saponifying potentialities, refer to plasma cholinesterase (which is less specific for acetylcholine) as a "pseudocholinesterase."

Perhaps it is mostly emotional bias that makes me dislike this last term. Ten years ago, being convinced that cholinesterase was the major analeptic factor in plasma transfusion for shock, I agitated for the salvage of the discarded cholinesterase-containing beta-globulins from the war-time plasma-fractionation programme, and was overruled on the ground that it was "only a pseudocholinesterase." But is this name reasonable? We know that hæmoglobin, besides performing its physiological function of combining reversibly with oxygen, has an incidental propensity for combining with carbon monoxide, nitric oxide, isonitriles, and divalent silicon compounds; but we do not therefore call it a "pseudohæmoglobin." And the differences in reactivity spectrums between a "specific" cholinesterase, like that of brain or erythrocyte, and a "non-specific" cholinesterase, like that of intestinal mucosa or plasma, is chiefly one of degree. This degree, in turn, is contingent on the enzyme's function. Intracellular cholinesterases (and they are rather ubiquitous) are components of a cholinacetylase-acetylcholine equilibrium, regulating the cell's permeability, particularly for cations. They naturally encounter little except acetylcholine, and they may therefore enjoy a leisurely "specificity." They do so, however, at the expense of a later phylogenetic development, the "extracellular" or transport cholinesterases, whose function is to protect the body against the many exogenous and endogenous cholinergics with which it is periodically called upon to cope. We therefore find them where they will operate: in the saliva of an animal which may mistakenly eat a deadly calabar bean; as a permeability barrier in the wall of the vertebrate intestine, which commonly contains an otherwise overwhelming cholinergic dose of proteolysis products; in the plasma of a human with emotionally engendered acetylcholine flooding from the basal ganglia—or the recipient of a dose of succinylcholine. A cholinesterase with so broad a function must be capable of neutralising a variety of cholinergics besides acetylcholine, and fortunately plasma cholinesterase does this.

From these considerations it was evident that plasma cholinesterase—the *fraction* which I wanted to see stockpiled as an analeptic—might be a therapeutically applicable and versatile anticholinergic. On that basis, Dr. Walter Ward, Dr. Fred Johnson, and Dr. Edwin McLean, of Cutter Laboratories in Berkeley, California, agreed to pursue the plasma enzyme rather than the pharmaceutically more expedient one contained in erythrocytes. While Proewig, in Germany, has reported on the therapeutic activity of the latter,[2] my own experience with plasma cholinesterase, now extended to over 150 infusions in 80 patients, allows me to assure Dr. Evans and his colleagues that it is as innocuous and useful as their observations suggest. I have usually given it in conjunction with packed-erythrocyte transfusion,[3] but it has also been used in other ways and in diverse conditions. In my experience no untoward effect has come of doubling or trebling the plasma cholinesterase level; but in three patients in whom it was quadrupled there was extreme flushing and mental confusion lasting throughout the rise (usually 24-72 hours). In myelosuppressive blood dyscrasias this rise in transport cholinesterase is apt to be followed by a sharp sustained rise in erythrocyte cholinesterase, along with normopoiesis, confirming previous observations with massive plasma and with infusions of cruder cholinesterase preparations.[4 5] Infusion of plasma cholinesterase has not been particularly beneficial in hæmorrhagic shock but it has proved of such value in surgical shock, and in shock accompanying coronary occlusion, that in two local hospitals it has become an emergency-room item. From this standpoint, Schacter's results in experimental shock in dogs[6] seem applicable to humans.

I have had no opportunity of trying cholinesterase in radiation sickness, but it is worth mentioning that mice have been completely protected against 750r (the LD_{100}) of X-irradiation by giving them, three days previously, the amount of cholinesterase contained in 5 ml. of human plasma. This may be due to the known radiation resistance of mice sensitised by any foreign protein, but the matter needs exploration. Burn et al.[7] found a decrease in transport cholinesterase (called by them "pseudocholinesterase") of the intestinal wall of irradiated rats, and I regard this decrease as responsible for enhanced permeability of the intestinal wall and thus for the lethal proteosæmia which supervenes in these animals. It had previously been shown that in man the blood cholinesterase falls sharply after ordinary therapeutic irradiation.[8] From this it seems likely that in radiation sickness cholinesterase infusion will have the same effect as administration of terramycin or 'Chloresium,' which protect the animal by limiting absorption of cholinergic proteoses formed by coliform flora in the intestinal tract. Cholinesterase would also directly neutralise proteoses ("peptones") in the blood-stream. (Experimentally, it has been found that infusion of human plasma cholinesterase will cut short peptone shock in dogs or cats.)

When it was observed that, in cases where they induced remission in the myelosuppressive blood dyscrasias, terramycin, chloresium, or cortisone all raised the initially low blood cholinesterases characteristic of these conditions, a general concept evolved: it appeared that cholinesterase therapy would be useful only where (as in macrocytic anæmia, pemphigus, and surgical shock) the blood cholinesterase is depleted. But the observations at St. Bartholomew's Hospital on succinylcholine intoxication, as well as my own clinical experience, indicate a wider application. Some of the observed therapeutic effects, seen as they are in patients whose blood cholinesterase is normal or even raised, remain inexplicable. For example, a patient with generalised sarcoidosis, and another with ulcerative colitis, both in extremis following failure of adrenocorticotherapy, suddenly started to recover after a single intravenous injection of 2·5 ml. of a plasma cholinesterase concentrate (400 times the concentration of normal plasma

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1. Evans, F. T., Gray, P. W. S., Lehmann, H., Silk, E. *Lancet*, Oct. 4, 1952, p. 682.
2. Proewig, F. W. *Münch. med. Wschr.* 1950, 92, 1117.
3. Barnard, R. D. *N.Y. St. J. Med.* 1952, 52, 1253.
4. Barnard, R. D. *Med. Rec.* 1947, 160, 610.
5. Barnard, R. D., Mentha, J. *Science*, 1948, 107, 2773.
6. Schacter, R. J. *Amer. J. Physiol.* 1945, 143, 552.
7. Burn, J. H., Kordik, P., Mole, R. H. *Brit. J. Pharm.* 1952, 7, 5
8. Barnard, R. D. *Med. Rec.* 1948, 161, 350.

given only as a last resort and on no rational basis whatever. Furthermore, in 7 cases of severe, protracted, antihistamine-resistant penicillin urticaria the improvement following cholinesterase therapy was truly amazing. Likewise, single infusions of plasma cholinesterase have seemed instrumental in reversing cachectic trends in some patients with inoperable neoplastic disease.

Preliminary investigations, herein merely hinted at, have raised more questions than they have answered about the applicability of cholinesterase in treatment. It is indeed fortunate that a pharmacodynamically active preparation has finally been made available, so that investigators of the calibre of the St. Bartholomew's Hospital group may continue to elicit the answers needed.

Laurelton,
Long Island, N.Y. ROBERT D. BARNARD.

ANTIDIURETIC SUBSTANCE IN HUMAN SERUM

SIR,—The careful experiments of Dr. Hawker (Dec. 6) show that serum from normal and pregnant women is antidiuretic when injected intraperitoneally into rats. It is most improbable, however, that this property of serum is related in any way to the water exchange of the subject, for the following reasons:

(1) Ames and van Dyke[1] have shown that the antidiuretic action of sera may be much greater when given intraperitoneally than when given intravenously.

(2) Dicker and Ginsburg[2] have shown that the antidiuretic substance in rat serum is absent from rat plasma.

(3) Brun et al.[3] withdrew large volumes of blood from donors after fainting—one of the most powerful stimuli to the release of antidiuretic hormone (A.D.H.)—and transfused them into normal recipients. They made no statement about the titre of A.D.H. in the blood, but inspection of their figures shows that it must have been equivalent to about 0·01 milli-units (mU) of 'Pitressin' per ml.

(4) In normal subjects, an intravenous injection of 1 or 2 mU of pitressin at the height of water diuresis will reduce the urine flow. I have withdrawn blood from dehydrated normal male subjects, hydrated them, and injected each intravenously with his own serum an hour later, when the urine flow was rising. No antidiuretic effect was observed: the titre of A.D.H. in each serum was equivalent to less than 0·1 mU of pitressin per ml. Simultaneous assay by the intraperitoneal technique in rats, however, gave figures for the antidiuretic activity similar to those found by Dr. Hawker and by Lloyd and Lobotsky[4]—namely, about 2·0 mU of pitressin per ml. (These results not yet published.) There is no reason why this method should not be extended, withdrawing a pint of blood and injecting the serum into the donor or into a normal recipient.

Middlesex Hospital,
London, W.1. A. A. G. LEWIS.

DEATH AFTER ANÆSTHETIC WITH HYPOTENSION

SIR,—Dr. Bodman (Nov. 29) reports the death, following hypotensive anæsthesia, of a man who was found post mortem to have extensive carotid atheroma. In conclusion he observes that carotid disease, like coronary disease, may be "another hazard sent . . . to plague the anæsthetist." Accepting this sentiment, one may at least say that the patient imposes the hazard on the anæsthetist unwittingly, but can the reverse be maintained?

Consider what happened to this "fit man of 76."

For an operation calling for no muscular relaxation, and involving no immediate surgical risk, he was given in succession and over a short space of time 'Omnopon' and scopolamine, thiopentone, pethidine, tubocurarine, a 10% cocaine spray, gas and oxygen, and pentamethonium bromide; and four of these were given intravenously. After this his respiratory mechanism was paralysed and his blood-pressure was between 50 and 60 mm. Hg.

Clearly, many patients have circulatory disease which is undetectable, or undetected, before operation. And merely to give the surgeon a bloodless field, it seems unjustifiable to treat patients in this way.

Windsor, Berkshire. DOUGLAS BELFRAGE.

DIAGNOSIS OF BREECH PRESENTATION

SIR,—The clinical diagnosis of breech presentation is occasionally made difficult by the patient's obesity, or by her tendency to "guard" against the merest attempt to palpate her abdomen. In such circumstances, I have for some years used a simple procedure which I have found of considerable value and which I have not read of in any medical publication.

If, after making the usual examination, I am still uncertain whether a breech or a vertex occupies the upper pole of the uterus, I place my left hand against the right side of the patient's abdomen, just below the level of the fundus of the uterus, the palmar surface of the hand and fingers facing medially. I then ask the patient to turn on to her right side, still keeping my left hand in the position described. As she does so, gravity causes the vertex (or breech) to fall towards the examining hand. A flick of the fingers of the left hand will now ellicit ballottement if the vertex occupies the upper pole, and the round shape and hard consistence of the head will be easily appreciated. On the other hand, ballottement will not be possible if a breech occupies the upper pole, and the softer and less easily defined outline of the breech will be felt by the fingers.

I first made this observation some years ago when I was a house-surgeon, and I have found that little practice is necessary, even in otherwise difficult cases, to differentiate in this way between breech and vertex with reasonable certainty.

Apart from the fact that this simple test may reduce the number of requests for X-ray examination, it has the added virtue that it is reliable and depends upon nothing but the hands and the sensitivity of the fingers.

Dunfermline. R. G. WHITELAW.

TERRAMYCIN

SIR,—I refer to your annotation on this subject (Nov. 29). The paper by Dr. Finland and his colleagues is quoted as saying that doses of 0·25 g. six-hourly "give significant, continuous blood plasma concentrations." I have not been able to find this passage in the paper. Further, this dosage is totally inadequate for patients over 3 years of age.

Bliss et al.[1] have shown that terramycin is bacteriostatic in concentrations of 4 µg. per ml. for most susceptible organisms, and this is regarded by most workers as the minimal inhibitory concentration. Welch[2] found with a dosage of 0·25 g. six-hourly that the blood-serum assay levels in adults never exceeded 2 µg. per ml.

A series of 50 infants and children, under the care of Mr. A. B. Wallace in the burns unit in the Royal Hospital for Sick Children, Edinburgh, had 0·25 g. or more six-hourly, and the assay levels fell below 4 µg. per ml. in 24% of cases.[3]

As toxic effects you mention diarrhœa and stomatitis; but these do not occur in children even when the drug is given without the protection of a gelatin capsule.

We cannot support your statement that such toxic effects as occur are "minimised by milk," but we agree with Parsons and Wellman[4] that sodium bicarbonate gr. 10–20, twenty minutes before each dose, is the most effective "buffer."

You state that "remarkable alterations in the intestinal flora" occur during terramycin therapy. You do not mention *Streptococcus fæcalis*, *Bacterium coli*, proteus, *Pseudomonas pyocyanea*, or other normal fæcal

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1. Ames, R., van Dyke, H. B. *Endocrinology*, 1952, 50, 350.
2. Dicker, S. E., Ginsburg, M. *Brit. J. Pharmacol.* 1950, 5, 497.
3. Brun, C., Knudsen, E. O., Raaschou, R. *J. clin. Invest.* 1946, 25, 568.
4. Lloyd, C. W., Lobotsky, J. *J. clin. Endocrin.* 1950, 10, 318.

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1. Bliss, E. A., Warth, P. T., Chandler, C. A. *Ann. N.Y. Acad. Sci.* 1950, 53, 277.
2. Welch, H. *Ibid*, p. 253.
3. Ritchie, H. D., Wallace, A. B. *Antibiotics*, 1952, 2, 391.
4. Parsons, W. B. jun., Wellman, W. E. *Proc. Mayo Clin.* 1951, 26, 260.

bacteria as sensitive organisms, so may I ask against which organisms you conceive of the drug being active in producing this alteration?

The drug is said to have "no action at all on proteus and *Ps. aeruginosa* or in typhoid and salmonella infections." Hobby et al.[5] noted an action on *Salmonella typhi* and *Ps. pyocyanea*. Also Bliss et al.[1] found it effective against proteus, *Ps. aeruginosa*, and *S. typhi*, and against some strains of the latter two organisms it is active in very small concentrations.

There is considerable evidence that terramycin, for all its shortcomings, is at the moment the doyen of the large-bowel sterilising agents.[6] It is an important drug in the treatment of the infections of childhood, and is much less toxic for children than adults. Most authors have encountered reactions in 50% or more of adults treated; but in children they occur in less than half this proportion. In Finland's series of 87 adults the drug had to be withdrawn in 13%. We found this necessary in only 4% of our younger patients.

I do not believe that the drug should be dismissed as a poor relation of aureomycin or as a stand-by for penicillin, particularly in general practice (where the oral route is ideal) or in the children's hospital.

Liverpool School of Tropical Medicine. H. D. RITCHIE.

SIR,—You state that terramycin has no action at all on proteus and *Ps. aeruginosa*, or in typhoid and salmonella infections, mumps, measles, chickenpox, smallpox, malaria, and trichinosis. However, the inclusion of *Ps. aeruginosa* and typhoid and salmonella infections in this list is incorrect; for terramycin has been found to be effective against many strains of pseudomonas, particularly in urinary tract infections[7] because of its ability to attain high concentrations in the urine.

Favourable clinical results have also been obtained in typhoid and salmonella infections.[8–12] However, further investigations must be made before any final conclusion can be drawn regarding the rôle of terramycin in the treatment of these infections.

Pfizer Ltd., London, W.1. R. K. PHILLIPS
Director of medical services.

*** We tended, like Keefer,[13] to dismiss (perhaps too hastily) terramycin in the treatment of pseudomonas and salmonella infections, for favourable results have undoubtedly been achieved in some instances. But opinions are by no means unanimous and, as Dr. Phillips reasonably suggests, final judgment must await further investigations.

We regret that the reference to the statement about "*significant, continuous blood plasma concentrations*" was incorrect; the words were those of Welch,[2] to whose work Mr. Ritchie refers. The plasma levels attained (1–2 µg. per ml.) are none the less "significant and continuous"; for it does not necessarily follow that concentrations of a drug demonstrated to be bacteriostatic *in vitro* must invariably be achieved in the plasma before the drug can work. For example, Lyons[14] said of chloramphenicol that "the clinical response to treatment with this drug is often superior to that suggested by sensitivities as determined in vitro." Moreover, the data recorded by Bliss et al.[1] give no conclusive evidence for accepting the figure of 4 µg. per ml. "regarded by most workers as the minimal inhibitory concentration." For gram-positive cocci they cited 0·04–1·2 µg. per ml.; for gram-positive bacilli 0·01–0·5 µg. per ml.; and for gram-negative bacilli (about which we were reserved) 0·6–5·0 µg. per ml. for *S. typhi* and *Hæmophilus influenzæ*, and 3·1–100 µg. per ml. for pseudomonas and proteus.

Mr. Ritchie has been unfortunate in his experiences with milk as a means of reducing toxic effects. Herrell et al.[15] (and many clinicians and ward-sisters in this country) have had more encouraging results, while Parsons and Wellman,[4] whom Mr. Ritchie mentions as advocates of sodium bicarbonate, observed that "the use of milk, which allows maximum absorption, is simple and effective."

In the matter of the reactions of the common bowel organisms to terramycin, Baker and Pulaski[16] have demonstrated that terramycin will eliminate coliform bacteria from the fæces. Gram-positive cocci may be completely suppressed or may survive unchanged; *proteus, meanwhile, becomes dominant*.—ED. L.

Public Health

Tuberculin Matriculation or Mass Radiography?

WHICH is the more effective—continuous tuberculin testing of the whole population by the system described by Gedde-Dahl as "tuberculin matriculation,"[17] or mass radiography? Johansen and Hjort[18] have compared the two systems in the district of Gloppen on the West Coast of Norway, where tuberculin matriculation has been in operation since the autumn of 1943 and mass radiography since the autumn of 1950. The tuberculin (Pirquet) test was repeated every year among tuberculin-negative persons and those who had been vaccinated with B.C.G. Tuberculin matriculation was applied to a total of 5891 persons; mass radiography was applied to 3870—all over the age of 14. Only 3·9% of those eligible for tuberculin matriculation, and 19·6% of those eligible for mass radiography, did not undergo these tests. Neither method is foolproof, and each tended to show up the shortcomings of the other. Tuberculin matriculation proved useful in discovering and keeping under control convertors before they had developed radiologically demonstrable changes. Johansen and Hjort conclude that in their district both methods are necessary, and that their investigation has failed to show which is the more effective.

Infectious Diseases in England and Wales

Disease	Week ended Nov.				
	1	8	15	22	29*
Diphtheria	29	27	11	41	29
Dysentery	414	213	211	158	197
Encephalitis:					
Infective	1	4	2	3	4
Postinfectious ..	1	2	—	3	1
Food-poisoning.. ..	85	110	151	77	[illegible]
Measles, excluding rubella	11,229	11,264	12,035	12,134	11,791
Meningococcal infection	34	30	29	28	[illegible]
Ophthalmia neonatorum	38	34	29	35	[illegible]
Paratyphoid fever ..	7	2	5	8	[illegible]
Pneumonia, primary or influenzal	575	503	452	519	61
Poliomyelitis:					
Paralytic	65	51	82	62	[illegible]
Non-paralytic ..	21	36	22	21	21
Puerperal pyrexia ..	259	211	226	227	[illegible]
Scarlet fever	2099	1976	2065	2226	[illegible]
Smallpox	—	—	—	—	—
Typhoid fever	8	4	3	3	1
Whooping-cough ..	1456	1419	1780	1851	215

*Not including late returns.

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[5] Hobby, G. L., Lenert, T. F., Dougherty, N. *Ann. N.Y. Acad. Sci.* 1950, 53, 27.
[6] Baker, H. J., Pulaski, E. J. *Ibid*, 1950, 53, 324; Di Caprio, J. M., Rantz, L. A., *Arch. intern. Med.* 1950, 86, 649; Shaeffer, J. R., Pulaski, E. J. *U.S. Forces med. J.* 1950, 1, 1447; Dearing, W. H., Needham, G. M. *Proc. Mayo clin.* 1951, 26, 49; Pulaski, E. J., Artz, C. P., Reiss, E. *J. Amer. med. Ass.* 1952, 149, 40.
[7] Lissell, W. D., Fletcher, A. P. *Brit. med. J.* 1950, ii, 1190.
[8] Sayer, R. J., Michel, J. C., Moll, F. C., Kirby, W. M. M. *Amer. J. med. Sci.* 1951, 221, 256.
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[10] Benhamou, E., Sorrel, G., Sicard, Y. *Paris méd.* 1951, 41, 336.
[11] Kunstadter, R. H., Milzer, A., Kagan, B. M. *J. Pediat.* 1951, 39, 687.
[12] Ballrage, S. *Nord. Med.* 1951, 46, 1139.
[13] Keefer, C. S. *Ann. N.Y. Acad. Sci.* 1950, 53, 223.
[14] Lyons, C. *Ibid*, p. 360.
[15] Herrell, W. E., Hellman F. R., Wellman, W. E. *Ibid*, p. 448.
[16] Baker, H. J., Pulaski, E. J. *Ibid*, p. 324.
[17] Gedde-Dahl, T. *Amer. J. Hyg.* 1952, 56, 139; see leading article, *Lancet*, Nov. 8, 1952, p. 922.
[18] Johansen, A., Hjort, P. *Nord. Med.* Oct. 31, 1952, p. 1519.

Obituary

GERALD TYLER BURKE

C.I.E., M.D. Lond., F.R.C.P.

Lieut.-Colonel Burke, a former secretary of the Medical Council of India, died at Bexhill-on-Sea on Nov. 13 at the age of 70.

He was born in 1882, the son of an officer of the Army Pay Department. He studied medicine at St. Bartholomew's Hospital, taking the Conjoint diploma and the M.B. Lond. with honours in 1907. Two years later he entered the Indian Medical Service by competitive examination. During the first world war he served in East Africa and, after the Armistice, in Constantinople where he was in charge of the medical wards in large military hospitals. He was three times mentioned in despatches.

During a period of study leave in 1922 he obtained the M.D. and M.R.C.P., and he returned to India with the intention of specialising in medicine and medical education. On securing his transfer to the civil side of the I.M.S. he was posted to the United Provinces for duty. The wide experience he gained as a district medical officer in that vast and densely populated province made him proficient in general surgery, operative ophthalmology, and gynæcology, and broadened his clinical outlook, but it did not shake his determination to specialise in medicine, and in 1929 he was appointed to the chair of medicine at Lucknow University. He was elected F.R.C.P. in 1933. His painstaking methods, devotion to the interests of his patients, and kindly firmness with his students made him an ideal professor, and he was greatly beloved by both Europeans and Indians in Upper India.

In 1935 he was persuaded to accept appointment as secretary of the recently created All-India Medical Council, though he gave up his clinical post with reluctance. Despite the medico-political tension of that time Burke, as a transparently honest and fairminded man, was persona grata with official and non-official members alike. On his retirement in 1938, he was appointed C.I.E.

On his return to this country he was appointed to the standing medical board of the India Office, which, in 1947, became the Board of the Commonwealth Relations Office.

"During his nine years in that office," a colleague writes, "recruits to the civil and military services in India passed through his hands. The multitude of sick and disabled officers of the Indian Army who came before him at regular intervals after being invalided from the East also greatly appreciated his fatherly wisdom and gentle dealing."

Burke's first wife died in 1937, leaving a grown-up daughter. His second wife survives him with two small sons.

IAN EARLE McCRACKEN

M.D. Edin., B.Hy. Durh., D.P.H.

Dr. Ian McCracken, senior lecturer in public health at the London School of Hygiene and Tropical Medicine, died on Nov. 30 after a short illness.

He was a North-country man by birth and affection. Coming from the Scottish borders he knew and loved the lands around Melrose, Kelso, and Tweed. It was against this background that much of his research into country practice and the growth of the dispensary system was conducted.

Dr. McCracken's father was a well-known general practitioner in Newcastle, and he himself practised there independently for many years. Graduating in Edinburgh in 1924, he took his public-health qualification in the University of Durham at a much later date, when he had already acquired a wide reputation as a fine clinician and a wise family doctor. In 1937 his health, which had never been robust, broke down under the strain of a profession to which he gave himself heart and soul, and he was obliged to curtail his activities. He took up laboratory work in the public-health service, and in 1940 offered his services to the medical officer of health (Sir John Charles) for civil-defence duties. In this way he became more and more closely associated with the public-health department in Newcastle and, when Sir John Charles was appointed to the Ministry of Health, in 1944, Dr. McCracken succeeded him on a temporary basis.

At the end of the war his health again gave cause for anxiety, but after a period of rest and treatment he was able to join the staff of the London School of Hygiene as a part-time research-worker in the history of public medicine. In the course of time he assumed full-time duties, and he devoted himself without stint to the welfare of the school. Happily he was able to give his energies in full measure to his two abiding interests—the personal guidance of students in their work, and the study of medical history. Through his early death at the age of 52 Dr. McCracken leaves a wide circle of friends who mourn his loss; and many groups of students of the post-war years will remember him as a wise and kindly adviser, a scholar, and a friend.

J. M. M.

JOHN JAMES DUNCAN KING

D.Sc. Lond., Ph.D. Sheff., F.D.S. R.C.S.

Dr. King, whose death, at the age of 45, we have already announced, was the first director of the Medical Research Council's dental research unit.

He qualified L.D.S. R.C.S. from King's College Hospital, London in 1929, having received a certificate of honour in operative dental surgery in 1928. After holding a house-appointment at King's he spent two years as an assistant in private dental practice.

The trend of his future career was already evident when he took the diploma in public dentistry at the University College of Dundee in 1932. Soon afterwards he asked Lady Mellanby for an opportunity to study research methods under her guidance. With a M.R.C. grant he was appointed to the staff of the Sheffield University field laboratories where researches on nutrition and dental caries were then being carried out. His interest in the dental aspect of Sir Edward Mellanby's work on vitamin-A deficiency led him to study the gingival tissues; and he always retained his interest in paradontal diseases. Among other species he made use of ferrets, which was the first time these animals had been used for nutritional studies. He was awarded the degree of PH.D. of Sheffield University on the results of these and other investigations.

In 1938 he made a long and arduous series of observations on the incidence of dental caries in the Isle of Lewis, not only doing hundreds of mouth examinations but collecting useful information about the diets of the island children. His findings were briefly reported in our columns and later incorporated in a M.R.C. special report.

At the outbreak of the late war, while holding a Beit fellowship, Dr. King joined the Army Dental Corps and continued to investigate gingival diseases, particularly trench mouth. Full of ideas on this subject he returned to do experimental work in London. He studied the gingival tissues of ferrets, using a capillary microscope of his own design; and, as always, he constantly returned to the human subject to assess the possible practical importance of his findings.

In 1946 when the M.R.C. set up a dental research unit at King's College Hospital Medical School, King was the natural and almost inevitable choice as director. In 1948 he visited Trinidad and British Guiana to make a characteristic, careful survey of caries and paradontal diseases in the natives. He was elected a fellow of dental surgery of the Royal College of Surgeons in 1949. He was an active member of the M.R.C.'s dental research committee, and at the time of his death he was helping to prepare a report on a sugar and caries investigation sponsored by the committee.

H. N. G. writes: "King would not commit himself to any theories which had not been completely substantiated. No-one, as yet, has succeeded in completely solving any of the outstanding dental problems but it is certain that the pioneer work of Lady Mellanby, from which King's investigations stemmed into original fields, have paved the way to their ultimate solution. King's work throughout demonstrated the interaction of nutritional, mechanical, and infective factors in dental disease. In particular he was able to show how paradontal disease in animals could be induced by injury from salivary calculi and how bone-gnawing with retention of muscle attachments could, by friction, prevent tartar formation and the associated gingivitis. Recently he had made extensive studies of the reaction of the gingival tissues to 'Epanutin.'

"King's life was devoted to his work. He was a friendly, most likeable man, often outspoken and devoid of guile. He never had an easy time because it was difficult to arouse the interest of his colleagues and thus obtain all the coöperation he felt he needed. For years he had difficulty in attracting workers to dental research, but by his sincerity and doggedness he succeeded in building a most efficient unit."

ALBERT EDWARD WALKER

M.B.E., M.D. Edin.

Dr. Edward Walker was the last of the stalwarts of the medical profession in Huddersfield who flourished in the early years of this century—men like John Irving, Peter McGregor, Marshall, Porritt, and Robinson—and he has outlived all his contemporaries by many years. He died on Oct. 21 in his 90th year.

He was born at Golcar, a village on the outskirts of Huddersfield, built on the steep slopes of a spur of the Pennines. He went to school at Pannal College near Harrogate, and he studied medicine at Edinburgh University where he qualified in 1884, proceeding to his M.D. in 1892. He practised all his working life in Huddersfield, and from 1905 to 1922 he was physician to Huddersfield Royal Infirmary.

He also took an active part in the affairs of Huddersfield. Keenly interested in education, he was a member of the old school board and later of the education committee. He served on the public library and art gallery committees, and he was at one time a member of the board of governors of Almondbury Grammar School, and a governor of the Huddersfield Technical School. During the first world war he was secretary of the Huddersfield division of the British Medical Association, and in recognition of his work he was appointed M.B.E.

C. D. P.-S. writes: "Edward Walker's deafness cut him off from many interests in his later years, but his hobbies of walking and reading—history was his special subject—and the wireless kept him from mental rustiness, and he retained a remarkable youthfulness of spirit. His appearance seemed to change little with his advancing years; and he was mentally alert to the end of his life. Only two or three weeks before his death he was out and about, accompanied by his dog, a constant companion."

In 1893 Dr. Walker married Miss Ethel Learoyd, who died several years ago. He leaves a daughter and three sons, two of whom are doctors. Mr. Arnold Walker, F.R.C.O.G., is chairman of the Central Midwives' Board, and Dr. Geoffrey Walker is carrying on his father's practice in Huddersfield.

DUNSTAN BREWER

M.R.C.S., D.P.H.

Dr. Brewer, who was for twenty years medical officer of health for Swindon, died on Nov. 30 at the age of 77.

He was born in Kensington, the son of Henry William Brewer, and he was educated at St. Charles College, Notting Hill, University College, and St. Mary's Hospital, where he qualified in 1897. After holding an appointment as assistant medical officer at the Kensington Infirmary he joined the staff of the Metropolitan Asylums Board in 1902. Two years later he took the D.P.H., and in 1908 he was appointed medical inspector of schools to the West Riding county council.

In 1920 he became M.O.H. for Swindon and superintendent of the Victoria Hospital there. During the next twenty years, under his guidance, the public-health services of the town were greatly developed. On his retirement in 1940 the council thanked him for his long and outstanding service to the town, and the local education committee also met to record their appreciation of his work for the children of the borough. His colleagues presented him with a silver rose bowl.

R. P. C. writes: "Dunstan Brewer was known to all in the profession in Swindon, not only as M.O.H. but as one to whom we could go at any time with problems. He was always helpful to young men starting in general practice, and his dealings and speech were open and straight. As superintendent and chairman of the medical committee of the Victoria Hospital he encouraged a friendly spirit while getting business through without delay. At our clinical meetings he discussed technical subjects lucidly, and as a speaker he was clear-headed with a keen sense of humour. As M.O.H. for a neighbouring rural district, I found him a kindly and helpful colleague when epidemics affected both our areas. We all regretted losing him on his retirement."

Diary of the Week

DEC. 14 TO 20

Monday, 15th

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5 P.M. Dr. T. H. Whittington: Myopia, and Care and Treatment of Myopic Patient.

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5.30 P.M. Prof. E. C. Amoroso: Comparative Physiology.

Tuesday, 16th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. J. D. Boyd: Development of Heart in Relation to Congenital Heart-disease.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. G. B. Dowling: Tuberculosis of the Skin.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, W.1
5.30 P.M. Dr. Douglas Gordon: When the Electro-encephalogram Helps.

EUGENICS SOCIETY
5.30 P.M. (Burlington House, Piccadilly, W.1.) Prof. Roger Russell, PH.D.: Experimental Studies of Hereditary Influences on Animal Behaviour.

CHELSEA CLINICAL SOCIETY
8.30 P.M. (South Kensington Hotel, 41, Queensgate Terrace, S.W.7.) Mr. Basil Henriques, J.P., Dr. William Moodie: Juvenile Delinquency.

Wednesday, 17th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of Comparative Medicine.* Dr. R. Lovell, Dr. S. De Navasquez, Dr. J. B. Enticknap, Dr. Cuthbert Dukes: [illegible]
8.15 P.M. [illegible] tice. Dr. A. B. Davies, Dr. F. E. [illegible]: Fitness to Drive a Vehicle.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. C. D. Calnan: Treatment of Fungous Infections.

Thursday, 18th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. A. Hemingway: Dynamics of the Heart Beat.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Dermatology.* Dr. R. L. Waterfield: Observations on the Development of the L.E. Cell.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.30 P.M. (11, Chandos Street, W.1.) Radiography of the Vertebræ. Carcinoma of the Rectum. *Pyloric Stenosis.* (Film meeting.)

Friday, 19th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Epidemiology and Preventive Medicine.* Dr. F. E. Camps, Dr. D. Thomson: Acute Epiglottitis. Dr. W. C. Cockburn: Treatment of Whooping-cough with Antibiotics.

ROYAL EYE HOSPITAL
5.30 P.M. Mr. Howard Reed: Slit-lamp Appearances and their Diagnostic Value.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. G. B. Dowling: Tuberculosis of the Skin.

BIOCHEMICAL SOCIETY
2 P.M. (St. Bartholomew's Hospital Medical College, Charterhouse Square, E.C.1.) Scientific papers.

Saturday, 20th

CAMBRIDGE UNIVERSITY
10.15 A.M. (Addenbrooke's Hospital.) Postgraduate symposium on surgical diagnosis and minor surgery.

NUTRITION SOCIETY
10.15 A.M. (University Department of Biochemistry, Sheffield, 1.) Conference on the Rôle of Vitamins in Metabolic Processes.

Notes and News

CENTRAL MIDWIVES BOARD

In 1902 the Midwives Act first brought the registration of midwives under official control. Last week, on Dec. 3, the Central Midwives Board marked the fiftieth anniversary of this event by a dinner, held in the Apothecaries' Hall, London. Mr. Iain Macleod, in a brief speech before he returned to the House of Commons, paid tribute to Miss Elizabeth Greaves, who for twenty-seven years up till 1952 was the Ministry's representative on the board. He remarked also on the happy relations between the Ministry and the board, and wished that the Ministry's dealings with other professions were so constantly amicable. The National Health Service, he pointed out, had revealed a need for still more midwives. Sir John Charles, chief medical officer to the Ministry of Health, recalled that in 1878 William Farr had spoken of "the deep dark continuous stream of maternal mortality." Up till then the needs of the woman in labour had not been wholly ignored: from 1518 the Royal College of Physicians of London included midwifery in its curriculum (though "this must have been a Collegiate figment of the imagination"); and from 1829 the Society of Apothecaries ran two courses in midwifery. In 1878 a private member's Bill to regulate the practice of midwifery was introduced, but it failed. In 1902, however, Parliament acted. For nearly thirty years Sir Francis Champneys presided over the board, until his death in 1930. Sir John Charles noted with pleasure the steady growth in the representation of midwives on the board: whereas in 1902 no midwife was included, it now had 6. Sir John Charles was proposing The Board; and, in replying, Mr. Arnold Walker, its chairman, first spoke of the honour of holding the dinner in the Apothecaries' Hall, where the first steps towards statutory control of midwifery had been taken. He went on to express the hope that some day the maternity service would be controlled by a single hand. The municipal midwifery service introduced in 1936 had been, he said, very efficient and very happy; this was a remarkable tribute to local authorities throughout the land. Many, he suggested, might regret that municipal responsibility for the service had been ended by the National Health Service Act. Thanks to the system of "split" training, the midwifery service had never failed in the war years. The board was now experimenting with a system of training which linked the district more closely with the hospital. In conclusion, Mr. Walker presented an illuminated address to Miss Greaves. Prof. A. A. Moncrieff, vice-chairman of the board, welcomed the guests in cordial terms. Sir Wilson Jameson, who, as master of the Society of Apothecaries, was both guest and host, responded. It was 150 years, he said, since the society began its fight for midwifery. The Midwifery Profession was proposed by Sir Allen Daley; and in her reply, Miss N. B. Deane, president of the Royal College of Midwives, suggested that British midwives could make a still greater contribution to planning health services both nationally and internationally.

ROSE SIMMONDS MEMORIAL FUND

A fund has been opened in memory of the late Miss Rose Simmonds, one of the first dietitians in this country, to provide prizes or scholarships in dietetics. Prof. Dorothy S. Russell, F.R.C.P., Dr. W. G. Wimbush, and Mr. W. R. S. Ritchie, C.A., together with the chairman and treasurer of the British Dietetic Association, have agreed to act as trustees. Donations may be sent to the treasurer of the association, 251, Brompton Road, London, S.W.3.

WORLD-WIDE PLANS FOR BIRTH-CONTROL

A new international organisation for the study of methods of birth-control and the spread of information about them was formed in Bombay on Nov. 29 at the closing session of the third international conference of planned parenthood.[1] The organisation is to be known as the International Planned Parenthood Federation, and it will take the place of the present international committee on planned parenthood. Regional offices will be established in New York, London, and Bombay, and later in other parts of the world. For the time being, at any rate, the headquarters will be in London. The conference, which was attended by 400 delegates representing fourteen countries, elected as honorary presidents of the federation Mrs. Margaret Sanger, head of the Planned Parenthood Federation of the United States, and Lady Rama Rau, president of the Family Planning Association of India. One of the objects of the federation will be to press for the inclusion of family planning institutes in the national health programmes of all countries; and the conference recommended that every country should aim at making advice about birth-control available to 80% of its women in the next ten years.

THE ADDICTION AND THE MAN

Harold Maine has written an autobiographical account of his alcoholism and mental illness.[1] He is an American, a moderately successful professional writer who became alcoholic in his 'teens; and he describes, with considerable insight and literary ability, his unsettled early life and his failure to come to terms with a harsh situation. He became a chronic alcoholic, the black sheep of his family and the despair of his first and second wives. Both his marriages ended in divorce, and he sank to the depths of alcoholic degradation. In the attempt to get cured he sought hospital treatment in a variety of institutions, in most of which he found that the doctors were remote and indifferent and the attendants ignorant and systematically brutal. Despite all this he found a sense of kinship with his fellow-patients, and when his craving for drink had subsided he eventually became an attendant himself. Of the institutions in which he subsequently worked, a Veterans' hospital was the most appalling, and this at a time when the public was being led to believe that everything was being done for the mentally ill ex-Serviceman. Mr. Maine's story is the more convincing because he is evidently a man of wide sympathy and great tolerance, and he views even callous attendants and caste-conscious doctors as victims of a vicious system too vast for them to oppose. Like the public, whose dirty work they are doing, they have a deep need to persuade themselves that the mentally ill are getting the best possible treatment. When they fail in this they take refuge in the cynical saying "Once a nut, always a nut!": thus placing the patient in a subhuman category, and relieving their sense of guilt about their treatment of him. Despite the horrors, this book is rewarding because of the unconscious self-revelation of a man of great humanity and courage, endowed with pity for every human being except himself.

AN UNUSUAL VIEW OF SIERRA LEONE

Mr. Pearce Gervis was stationed in Sierra Leone during part of the war, and shortly after his arrival at Freetown he took the opportunity of pushing up-river and into the interior. By what was almost an accident he was adopted by a native village, and the villagers built him a fine hut. From there he went further inland. Mr. Gervis has a discerning eye and a pleasant style. In addition he is a photographer of quite unusual skill. The result is, for the general reader, a wholly satisfying travel book,[2] which is adorned by over sixty magnificent photographic studies.

This work is of considerable importance to the student of primitive medicine. References to the "Poro school"—the initiation school for young men—are frequent in works on this subject; but the rites are secret, and few authors attempt to give particulars. Certainly no white man has previously ever lived in the Poro. Mr. Gervis was fortunate in having been able to resuscitate from drowning a youth belonging to the village which had adopted him, and this led to his reluctant admission to a Poro school in the neighbourhood. He was in effect admitted as an assistant master in order to demonstrate the method—and was presented as a test with a youth who had been immersed almost, but fortunately not quite, beyond the point of resuscitation. This particular Poro school must have ranked high among similar institutions—almost like a public-school in England. The youths spent a considerable time in it—three years in the case of a chief's son—and they learned many things which would be useful in adult life. Mr. Gervis witnessed the operation of circumcision, which was performed in the early morning after a night spent in wild dancing, during which the subject danced till he became unconscious from exhaustion. He was then laid face downwards over a stream of very cold water, so that the sex organs were immersed in it until the morning. The anæsthetic effect seems to have been satisfactory. The actual operation was performed with a piece of broken poison-bottle, encrusted with the blood of many previous victims. The author was able to introduce some cleanliness and an antiseptic, and it is to be hoped that the deaths from sepsis which previously took

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1. *New York Times*, Nov. 30, 1952.

1. If a Man be Mad. London: Gollancz. 1952. Pp. 435. 15s.
2. Sierra Leone Story. London: Cassell. Pp. 240. 25s.

place have been much reduced in number. At another Poro school of a less ambitious nature the operation was carried out with a safety-razor blade.

In the course of his wanderings Mr. Gervis met "Dr. Ruth," a middle-aged British gynæcologist who had spent much of her life as an independent benefactor of the natives. Doctor Ruth eventually gained admission to a Susu Bundu initiation school for girls, and her account of the operation which is there performed is included in the book. This well-produced work is of unusual interest to the historian and the anthropologist.

University of Cambridge

On Nov. 29 the following degrees were conferred:

M.D.—P. H. Buxton, P. D. B. Davies, J. Perrin, D. G. Vulliamy, Lionel Wolman.

M.B., B.Chir.—*Nancy I. Cardno, J. H. Newton, Petrie M. Newton.

M.B.—* Svarna L. Bhatia.

* By proxy.

University of Dublin

On Dec. 4 at the school of physic, Trinity College, the following degrees were conferred:

M.D.—D. W. Montgomery.

M.B., B.Ch., B.A.O.—M. M. Berber, R. M. Bowman, H. W. Bridge, H. M. O. Brown, Margaret E. Charleton, D. D. Chesney, Leila L. Dyer, W. B. C. Fagan, J. C. H. Haythornthwaite, Ruth A. Helsby, Marie T. Hyde, Rupert Indar, G. M. Irvine, Sheila King, J. J. G. Kneafsey, M. C. Latham, Anna M. K. Little, K. W. H. B. McAlpine, O. R. McCarthy, M. A. McVicker, B. A. Montgomery, J. R. Polson, Mavis Sayers, Sarah B. Schwartzberg, C. A. H. Trench, Betty E. Wallace, R. G. B. Williamson.

Royal College of Physicians of London

Dr. D. A. K. Black will deliver the Goulstonian lectures on Tuesday and Thursday, Jan. 13 and 15, at the college, Pall Mall East, S.W.1. He will speak on Body-fluid Depletion. The Milroy lectures will be given by Dr. W. R. S. Doll on Tuesday and Thursday, Feb. 10 and 12, on Bronchial Carcinoma—Incidence and Ætiology. All four lectures are at 5 P.M.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Dec. 1, with Dr. Andrew Allison, the president, in the chair, the following were admitted fellows of faculty:

W. M. Dennison, J. C. Dick, Bernard Isaacs, Leo Schamroth, Marjory B. Snodgrass, D. G. C. Whyte.

Radioactive Substances Advisory Committee

Sir Charles Darwin, F.R.S., has been appointed chairman of this committee in succession to Sir Henry Dale, O.M., who has retired. Prof. G. R. Cameron, F.R.S., has been appointed a member of the committee.

First World Congress on Fertility and Sterility

This congress will be held from May 25 to 31 in New York. It is sponsored by the International Fertility Association with the coöperation of the American Society for the Study of Sterility. Further particulars may be had from the chairman of the local arrangements committee, 1160 Fifth Avenue, New York, 29, New York.

Symposium on Anticholinesterases

On March 27 and 28 at the Wellcome Research Institution, Euston Road, London, N.W.1, the British Pharmacological Society and the fine chemicals group of the Society of Chemical Industry are holding a symposium on this subject which will include discussions on chemical features which confer inhibition; mode of action in vitro; acute effects of the mode of action in vivo; chronic effects of the mode of action in vivo, including effects on man. Further particulars may be had from Mr. George Brownlee, D.SC., physiology department, King's College, London, W.C.2.

Presentation to Dr. R. J. Allison

On Nov. 27, the members of the past and present staff of the Milford Chest Hospital presented Dr. Allison, to mark his retirement, with a triple-speed record-player, a cheque, and an album containing the signatures of the contributors. He has been superintendent of the hospital since it was opened, nearly 25 years ago, as the Surrey County Sanatorium. Tributes were paid to him by Sir Geoffrey Todd, F.R.C.P. (on behalf of the South-West Metropolitan Regional Hospital Board), Dr. K. A. Soutar (Surrey County Council), Mr. J. T. Pyne (chairman of the hospital management committee), and Dr. A. S. Herington (deputy physician-superintendent of the hospital).

First International Congress of Physiotherapy

The first congress of the World Confederation for Physical Therapy is to be held in London from Sept. 7 to 12. Further particulars may be had from the press officer of the Chartered Society of Physiotherapy, Tavistock House (South), Tavistock Square, W.C.1.

Burns on Television

In the television series *Matters of Medicine* on Monday Dec. 15, at 9.30 P.M., there will be a programme on the Treatment of Burns.

CORRIGENDA: *Bovine Tuberculosis and Human Tuberculosis.*—In the two tables accompanying the letter by Mr. L. Pitcher, M.R.C.V.S. (Dec. 6) the words *per annum* were wrongly placed at the head of columns 3 and 6 in each table. The figures in these columns actually represent the *total* number of notifications of pulmonary tuberculosis in the years given in columns 2 and 5. The words *per annum* should have appeared above columns 4 and 7, which give the notifications per 100,000 population *per annum*.

Epidemic Hæmorrhagic Fever.—In the paper by Captain A. J. Rowe, in our issue of Nov. 15 (p. 980), the date of the first appearance of this disease among United Nations forces in Korea was given incorrectly. It should have been given as June, 1951.

Appointments

ANDREWS, G. S., M.D. Brist.: consultant pathologist, hospitals in the Newport, East Monmouthshire, and North Monmouthshire areas.

BEARD, A. J. W., M.D. Lond., D.A.: anæsthetist (consultant), National Heart Hospital, London.

JACOBS, H. B., F.R.C.S., D.O.M.S.: asst., ophthalmic outpatient department, Middlesex Hospital, London.

Leeds Regional Hospital Board:

DAVIDSON, WILLIAM, M.B. Glasg., D.P.H.: asst. chest physician (S.H.M.O.), York and Scarborough area.

HILL, R. L. T., M.B., B.SC. Glasg., D.M.R.D.: consultant in radiology, Bradford "A," Bingley, Keighley, Skipton, and Settle groups.

MCDOUGLE, H. A., M.B. Edin.: asst. anæsthetist (S.H.M.O.), Hull "A" and East Riding groups.

NAKIELNY, E. A., M.B. Polish School of Medicine, Edin.: asst. chest physician (S.H.M.O.), Hull area.

Welsh Regional Hospital Board:

EVANS, C. J., M.B. Lond., B.SC. Wales, F.R.C.S.: consultant thoracic surgeon, Glantawe, Mid-Glamorgan and West Wales H.M.C.S.

LLOYD, D. O., M.B. Lond., D.P.M.: asst. psychiatrist (S.H.M.O.), North Wales Hospital for Nervous and Mental Disorders, Denbigh.

LLOYD, G. H. T., M.D. Lond., M.R.C.P.: consultant physician, Clwyd and Deeside H.M.C. group.

PORCHER, H. I. H., M.D. Lond., D.P.H.: asst. psychiatrist (S.H.M.O.), Morgannwg Hospital, Bridgend.

WILLIAMS, O. G., M.D., B.SC. Lond., M.R.C.P.: consultant pathologist, hospitals in the Swansea and Llanelly areas.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

BULLOUGH.—On Dec. 1, at Hope Hospital, Salford, to Anna (née Cicognani), wife of Mr. A. S. Bullough, F.R.C.S.—a daughter (Irma).

DICKSON.—On Nov. 30, at Walton-on-Thames, to Evangeline (née Sladen), wife of Mr. John W. Dickson, F.R.C.S.—a daughter.

POULTON.—On Nov. 28, at Forest Gate Hospital, London, to Hel (née Iremonger), wife of Dr. E. Maclean Poulton—a son.

RUSSELL.—On Dec. 5, at Hartlepools Hospital, to Isabel, wife of Dr. Frank Russell—a son.

STEVENS.—On Dec. 2, at Oldchurch Hospital, Romford, to Ann, wife of Dr. J. D. Stevens—a son.

MARRIAGES

GIBB—FEETHAM.—On Nov. 8, at Oxford, William Eric Gibb, F.R. to Mary Edith Gertrude Feetham, M.B.

DEATHS

BREWER.—On Nov. 30, at Rockingham Rectory, Market Harborough, Dunstan Brewer, M.R.C.S., D.P.H.

MCCRACKEN.—On Nov. 30, Ian Earle McCracken, M.D. Edin., D.P.H., of Ladbroke Grove, London.

SQUIRE.—On Nov. 27, in Exmouth, Walter Perfect Squire, M.R.C. major, R.A.M.C. retd, aged 92.

THE AFFERENT-LOOP SYNDROME

BILIOUS REGURGITATION AFTER SUBTOTAL GASTRECTOMY AND ITS RELIEF

CHARLES A. WELLS
M.B. Lpool, F.R.C.S.
PROFESSOR OF SURGERY IN THE UNIVERSITY OF LIVERPOOL

I. W. MACPHEE
M.D. Glasg., F.R.C.S., F.R.C.S.E.
RESEARCH ASSISTANT, DEPARTMENT OF SURGERY, UNIVERSITY OF LIVERPOOL

AMONG the unpleasant symptoms following subtotal gastrectomy bilious regurgitation is one of the most common, most troublesome to the patient, least clearly differentiated, and easiest to cure. It is surprising that more attention has not been paid to this symptom as a distinct entity in the post-gastrectomy syndromes. Nausea, distension, sweating, and deficient absorption are manifestations of altered function, and, as all those who have tried to correct them are aware, present an exceedingly difficult problem in treatment; but bilious regurgitation has, in our experience, proved to be easily remedied, especially when severe.

In the many reports published on post-gastrectomy problems the frequency of bilious vomiting can be recognised, but it has rarely been differentiated from the other post-gastrectomy symptoms. Steinberg (1950) clearly recognised the syndrome of afferent-loop stasis, and Wells and Welbourn (1951), in a study of the mechanism of the various post-gastrectomy syndromes, first clearly defined the cause of this bilious vomiting, and devised a remedy which was subsequently found to differ but little from Steinberg's treatment.

Afferent Loop Stasis

MECHANISM

This is a problem in simple mechanics, a kink developing in the afferent loop of any of the gastrojejunal anastomoses. The condition does not therefore follow the Billroth-I type of gastrectomy. It is seen especially in the Finsterer-Lake type of antecolic *right-to-left* anastomosis associated with a Hofmeister valve. When the afferent loop is too long, the tendency to kinking is all the more pronounced (fig. 1*a*). The weight of a loaded colon, it has also been suggested, drags the afferent loop down and kinks it at its point of suspension from the lesser curvature of the stomach. More rarely a very short afferent loop is also liable to kink at its junction with the stomach (fig. 1*b*). This phenomenon is sometimes observed in the retrocolic Polya type of anastomosis; it rarely follows gastro-enterostomy and the older limited partial gastrectomy with Polya type of anastomosis. In these operations the afferent right-to-left loop is not carried so high and consequently does not kink when the upright posture is assumed. For this reason afferent-loop stasis is most commonly seen with the most radical gastric resections, and the modern type of operation is particularly liable to this complication. Conversely, afferent-loop stasis is much more infrequent after total gastric resections because the Roux-en-Y type of anastomosis does not lead to kinking of the afferent loop. The anastomosis of œsophagus to jejunum with entero-anastomosis is clearly immune from afferent-loop stasis.

Occasionally some other factor may contribute to this kinking (fig. 1); we observed it in 1 case when the afferent loop has become bound down by adhesions to the anterior parietal wall; in 1 case of gastrojejunocolic fistula (fig. 1*d*), and in 1 case after torsion of the afferent loop. This last condition has also been noted by Gaillard (1951) occurring twelve years after the original gastrectomy.

No matter what type of anastomosis may have been done, and no matter how extensive the gastric resection may have been, any cause whereby the afferent loop becomes kinked at its junction with the stomach leads to the typical symptoms of afferent-loop stasis. They must be clearly differentiated from symptoms arising from the efferent limb of the anastomosis.

CLINICAL FEATURES

Within an hour, and usually much less, after a meal the patient complains of a bitter taste in the mouth and the regurgitation of yellow, green, or brown bile *quite unmixed* with food. This, by itself, is almost pathognomonic of afferent-loop stasis. If the bilious vomiting be severe, food may finally be ejected, as the upset in motility spreads further down the gastro-intestinal canal. The vomiting of food, however, is always preceded by bilious regurgitation. This condition is so common in the first few weeks after gastrectomy that its occurrence should occasion no surprise. By the end of three months after operation, however, it should have subsided; and, if it has not, the true afferent-loop syndrome has probably become permanently established. Rarely the onset of bilious regurgitation is delayed for years after the gastrectomy.

The bilious regurgitation following a meal is often related to the ingestion of fatty foods. The passage of fat into the efferent limb of the jejunal loop is associated with an increased liberation of bile, which tends to accumulate in the almost closed afferent loop. The pressure and distension associated with increased motility to overcome the obstruction increase and are often associated with a feeling of fullness sometimes amounting to pain. This is very similar to efferent-loop spasm, but the patient with afferent-loop stasis is sometimes aware of the discomfort to the *right* of the midline. When the pressure in the afferent loop rises sufficiently high, the duodenal contents are suddenly liberated into the stomach and efferent jejunal limb, and some of the bile-stained fluid is regurgitated unmixed with food. The sudden relief of tension relieves the patient of his pain or discomfort, he suddenly becomes hungry again, and he may have another meal within fifteen minutes of the first.

Often, however, the pancreatic and biliary secretions may remain dammed up for a day or days. The patient then complains of continuous epigastric pain or dis-

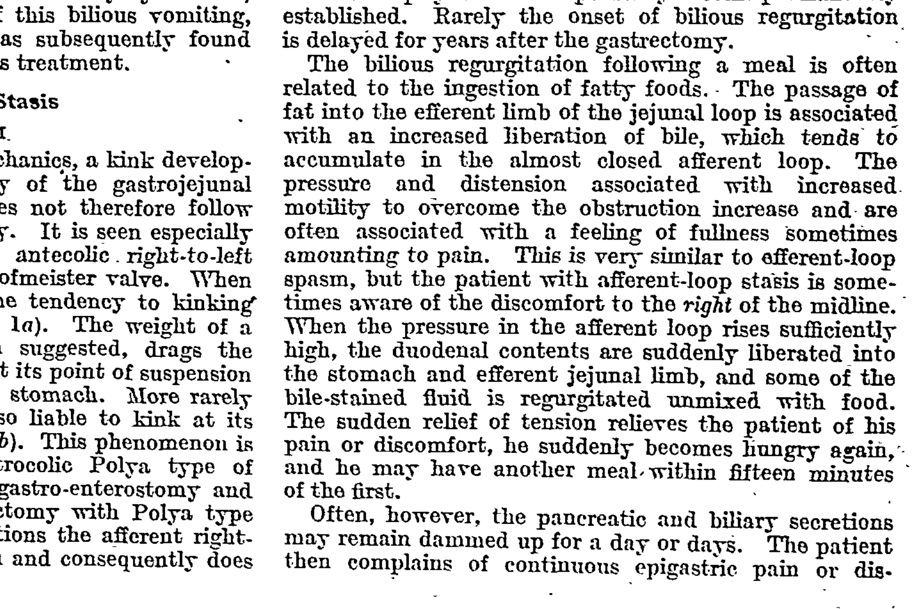


Fig. 1—Causes of obstruction of afferent loop: *a*, too long loop; *b*, short loop; *c*, kinking of retrocolic anastomosis; *d*, gastrojejunocolic fistula.

comfort, a permanent feeling of fullness, nausea, and anorexia, all made more severe by a meal. The stools are then bulky, pale, and offensive, and contain a high proportion of split fat. A slight icteric tinge of the conjunctiva may be detected. Such patients often volunteer the statement that they have a feeling of nervous depression during this stage. Quite suddenly, and not necessarily in direct relation to a meal, there may be a massive bilious vomit of 1 or 2 pints, associated with immediate relief of all the symptoms and then with a desire for food. Such patients with symptoms of splanchnic stimulation (nausea, feeling of fullness, and anorexia) are therefore very liable to eat too little food and, as the years pass, they become undernourished. Signs of hypovitaminosis, anæmia, and weight-loss may rapidly develop and increase the patient's misery. In the present series the incidence of malnutrition was much higher among patients with afferent-loop syndrome than in those without it.

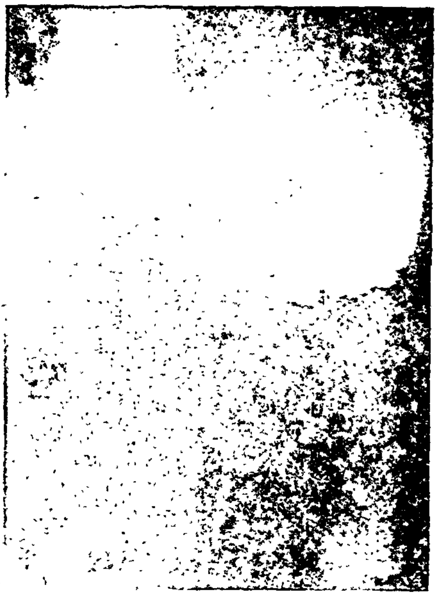


Fig. 2—Typical barium radiograph in afferent-loop stasis. Note absence of barium from afferent loop.

The retention of secretions within the afferent loop gives rise to some symptoms very similar to the efferent-loop syndrome. The excessive fullness after even a small meal, the nausea, and the anorexia are not due to the "small stomach" but to increased intestinal activity. In the efferent loop this seems to be due to hypermotility following the distending and stimulating effect of food (Wells and Welbourn 1951); in the afferent loop it is due to increased motor activity in a partly closed loop distended with secretions. Great care should be taken, however, to distinguish between the two syndromes. The efferent-limb syndromes are not amenable to the same surgical treatment as afferent-loop stasis with its semi-obstruction.

X-RAY APPEARANCES

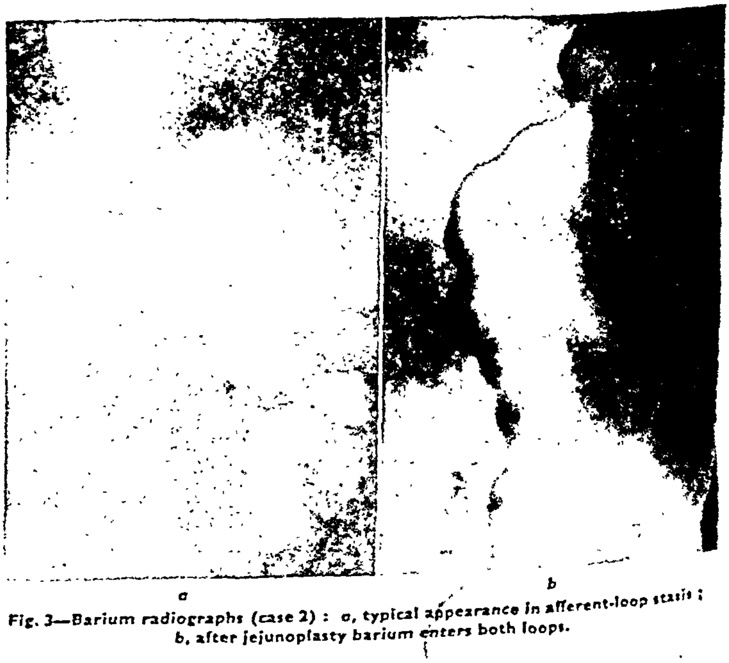
It is typical of the afferent-loop syndrome that the stomach remnant appears normal, and that barium passes rapidly and freely down the efferent limb. It is also typical that barium *does not enter the afferent loop* (fig. 2). The radiologist rarely comments on this, but in our experience it is an almost constant finding in afferent-loop stasis. On the other hand, the fact that barium *does not enter the afferent loop* does not necessarily mean that the condition is afferent-loop stasis.

After surgical reconstruction of the stoma to relieve the syndrome barium is often seen to enter the afferent loop. This is not associated with symptoms. Fig. 3 shows the appearance in case 2 before and after operation.

RELATION TO TYPE OF OPERATION

Goligher and Riley (1952), in a study of the post-gastrectomy syndromes, have pointed out that the type of anastomosis has little bearing on the occurrence of postprandial symptoms. As regards rapid emptying, efferent-limb symptoms, and malnutrition this has also been our experience. Radiography after a barium meal shows that a stomach without a pyloric sphincter empties rapidly, no matter what anastomosis may have been done. However, it is apparent that bilious regurgitation does not follow the Billroth-I type of gastrectomy, there being no afferent loop. Goligher and Riley also indicate that they have no recent experience of gastro-enterostomy or the related incidence of postprandial symptoms. We have had the good fortune recently to study the late results of vagal section and gastro-enterostomy in more than 40 patients. Owing to the courtesy of Mr. M. J. Bennett-Jones, we have had access to his case-records and operation notes on these patients. It is clear from this series that the immediate postprandial symptoms are not nearly so common after gastro-enterostomy as after gastrectomy, owing probably to the fact that afferent-loop stasis does not develop. The afferent loop in the ordinary posterior gastro-enterostomy is not suspended so high and is therefore less liable to acute angulation at the stoma. Provided the loop is in no way kinked as it passes upwards towards the mesocolon, the features of afferent-loop stasis should therefore not be encountered.

Capper (1952) has discussed the "early" symptoms which developed in 79 of 660 patients subjected to gastrectomy; 41 of them had bilious regurgitation after food, either with or without visceral symptoms, and were relieved when they lay down after a meal. In our view these patients undoubtedly had afferent-loop syndrome. As Butler (1951) has indicated in the same series, the early symptoms did not occur in the 102 patients who had undergone the Billroth-I type of gastrectomy. Further, if the patients with the syndrome lay down before a meal, bile-stained fluid could be aspirated from the stomach, allowing the patient thereafter to consume a larger meal. Again, the passage



a b

Fig. 3—Barium radiographs (case 2): *a*, typical appearance in afferent-loop stasis; *b*, after jejunoplasty barium enters both loops.

of a mercury-loaded bag into the stomach induced the symptoms; but, after aspiration of bile from the stomach, introduction of the bag did not induce the symptoms with the same weight of mercury. Butler and Capper next did 128 gastrectomies in which the stomach attachments along the lesser curvature were reconstituted (Capper 1951), whereupon the syndrome occurred in only 1% compared with 13% in 113 controls. They conclude that the non-occurrence of "dumping" in their second series was attributable to better suspension of the stomach. Conversely, they attribute the occurrence of "dumping" symptoms in general to an autonomic nervous disturbance set up by traction on the stomach. It appears to us that an afferent-loop element is evident in a high proportion of their first series, and that relative freedom from post-gastrectomy symptoms in the second series may well be attributed to the avoidance of afferent-loop stasis. Suspension of the stomach and afferent jejunal loop in the way they describe would have just this effect.

Pulvertaft (1952), in a careful follow-up study of 632 Polya-type gastrectomies done by the late A. H. Visick, reported 59·4% free from postprandial symptoms, 22·1% with regurgitation of bile, and 32·7% with "dumping" (visceral) symptoms. Of these two groups with postprandial symptoms 14·3% had both bilious regurgitation and visceral symptoms. As in Capper's (1951) series, therefore, about half of all the patients with early postprandial symptoms complained of bilious regurgitation, and of these about half had also the associated visceral symptoms commonly called "dumping" symptoms.

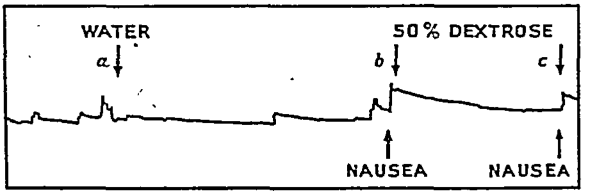


Fig. 4—Tracing from balloon in efferent loop, showing that intestinal spasm may be caused by hypertonic irritant.

Significance of Syndrome

Most observers consider that the symptoms of "dumping" are due to distension of the small gut as the food passes rapidly and in an undigested state from the stomach remnant. Muir (1949), Machella (1949, 1950), and Goligher and Riley (1952) have all reproduced the symptoms of epigastric fullness and nausea, sometimes associated with the other visceral and vasomotor symptoms of the whole "dumping syndrome," by distending the small bowel. This requires closer examination. The introduction of a balloon into the efferent limb is not necessarily associated with symptoms. If the distending force is applied slowly enough, the bowel may dilate slowly before the force, no contraction or spasm is produced, and therefore no symptoms are experienced. Fig. 4 shows the results of distending the small bowel *slowly* with water at *a* immediately after a peristaltic contraction: the pressure within the lumen of the bowel remains unchanged, the gut distending before the increased pressure. When, however, at *b* and *c* 50% dextrose is introduced in the same *very slow* manner, spasm follows, associated with all the visceral and vasomotor symptoms of the condition. As Welbourn (1951) has indicated, the specific cause of the symptoms under discussion is the hyperperistalsis which follows a rapidly induced distending force in the jejunum. Distension without hyperperistalsis is not effective.

INCIDENCE OF BILIOUS REGURGITATION

No. of patients	Free from symptoms	Symptoms		
		Mild	Moderate	Severe
293	240 (*81·9%*)	17 (*5·8%*)	5 (*1·7%*)	31 (*10·5%*)

When the symptoms occur only from activity in the efferent jejunal limb, Wells and Welbourn (1951) describe the condition as the "efferent-loop syndrome." This was formerly thought to be common. When, however, such symptoms are associated with bilious regurgitation, the distending force is clearly within the afferent loop, and it is at this site that the hypermotility arises. As already stated, such a condition appears in at least 50% of all cases of jejunal symptoms following the Polya types of gastrectomy. In fact the condition is probably very much commoner than this, but where bilious regurgitation is not in evidence the diagnosis is not so simple. The tracing in fig. 4 is from such a patient with postprandial epigastric fullness, nausea, weakness, and sweating, associated with considerable loss of weight after a Polya gastrectomy. There had never been any vomiting of bile or of food. The tracing indicates that his efferent jejunal limb was not unduly sensitive to hypertonic irritants, his response being little different from that of a normal person. Glazebrook (1952), in a study of the patterns of intestinal motility in cases of true "efferent-loop syndrome," demonstrates all the abnormal patterns usually encountered. Since this patient, therefore, had no abnormal sensitivity of the efferent jejunal limb, it was presumed that his symptoms were referable to a semi-closed afferent loop in spite of the absence of bilious regurgitation.

In our opinion this type of case is probably much commoner than heretofore believed. For this reason, when a patient has typical jejunal symptoms but does not show the patterns of efferent-loop hypermotility as described by Glazebrook, the afferent-loop syndrome in a forme fruste should be suspected. If the condition is severe, jejunoplasty is strongly recommended. After more complete analysis along the lines suggested here the incidence of true efferent-loop syndrome may prove to be much lower than was previously believed.

In our study of this problem we have excluded all operations done during and after November, 1951, and all gastrectomies done for conditions other than peptic ulcer. We have also excluded all patients who have not been followed up at short intervals each year. This leaves a residuum of 293 patients who form the basis of the current investigation. All patients who have had bilious regurgitation for more than six months after operation are included. The accompanying table shows that 53 patients fall into this category. Of these, 17 have been classified as having mild symptoms (less than one attack a month), 5 as having moderate symptoms (less than one attack a week), and 31 as having severe symptoms (more than one attack a week). Of the 31 patients with severe symptoms 16 have already been subjected to operation for relief of symptoms, and all are now totally relieved.

The present series contains some problem patients who have had their initial gastrectomy done elsewhere. An incidence of 18% in the whole series, however, indicates that the afferent-loop syndrome is distressingly common, and our experience has caused us to revise our concepts of the frequency of post-gastrectomy symptoms.

Treatment

Though a little bilious regurgitation is usual in the early weeks after gastrectomy, the condition usually subsides, and no treatment is required. Where bilious regurgitation persists, the need for operative treatment depends on the severity of the condition. Where it occurs on only a few occasions each month, and does not interfere with the patient's occupation or social activities, operation is not required. The avoidance of fatty foods will decrease the number of attacks, but then careful watch should be kept on nutrition. The "ulcer diet" after gastrectomy undoubtedly increases the frequency and severity of the attacks.

Jejunoplasty

This operation, first suggested by Steinberg in 1934 (Steinberg 1952), described by Hoag and Saunders (1941), and modified by Steinberg (1949), was suggested by Wells and Welbourn (1951) as a satisfactory method of relieving the obstruction to the afferent loop. The operation for this purpose has been described in detail by Steinberg (1949). As he originally described it, the operation was part of the initial subtotal gastrectomy and planned to enlarge the gastric reservoir. Steinberg (1952) has now done the operation on 255 patients with what he considers to be gratifying results. Included in this series are 25 cases where the jejunoplasty was done for a post-gastrectomy state. In all but two instances these patients have obtained complete relief from their symptoms. Steinberg believes that these two patients may never have had peptic ulcer at the outset. Fourteen post-gastrectomy cases have now been treated by us in this way, with immediate and satisfactory results. Illingworth (Muir 1949) has diverted the afferent-loop secretions away from the stoma by making an entero-anastomosis between the afferent and efferent limbs. This operation serves the same purpose but endangers the region of the stoma by subjecting it to gastric secretion unmixed with duodenal contents.

A brief description of some of the cases treated by jejunoplasty is appended here. Unless expressly stated, the gastrectomy was of the high subtotal type described by Wells and Brewer (1948) with an antecolic anastomosis of the Finsterer-Lake type and with a Hofmeister valve.

Case 1.—A man, aged 53, with a duodenal ulcer underwent subtotal gastrectomy in 1945. This was followed by severe bilious vomiting after meals and by abdominal pain. Jejunoplasty was done on Aug. 2, 1950. On Nov. 15, 1951, he had complete relief from bilious vomiting and pain and had gained 12 lb. in weight.

Case 2.—A woman, aged 46, who had had a duodenal ulcer for twenty years, underwent subtotal gastrectomy on March 8, 1950. This was followed by severe bilious regurgitation. When in good health she weighed 9 st. 4 lb., before operation she weighed 7 st. 12 lb., and after operation she weighed 7 st. 5 lb. Jejunoplasty was done on Feb. 27, 1951. On June 16, 1951, she had no bilious regurgitation, and had gained 1 st. 2 lb. in weight.

Rotation of Afferent Loop

In one instance, where the afferent loop was too short, a rotation of the afferent loop had taken place and the bowel was constricted by the tight mesentery of the efferent limb.

Case 3.—A man, aged 33, had undergone elsewhere on Feb. 7, 1950, gastro-enterostomy and vagotomy for duodenal ulcer. This was followed by frequent vomiting of food but not of bile. On Sept. 21, 1951, he underwent subtotal gastrectomy. Vomiting of food now ceased, but its place was taken by repeated postprandial bilious regurgitation. On Dec. 18 barium was noted to enter both limbs of the jejunum but remained in the afferent loop for three hours. On Jan. 4, 1952, the twist in the afferent loop was undone and jejunoplasty done. In June the patient reported complete relief from bilious regurgitation. He was then working hard at a heavy job and was still gaining weight.

Barium was seen to enter the afferent loop but not leave it. This evidence, though not appreciated at the time, indicated that the obstruction to the afferent loop was not due to the usual kinking at the junction with the lesser curvature of the stomach.

Retrocolic Anastomosis—Billroth-I Operation

This was the only case in the series of bilious regurgitation after retrocolic anastomosis (fig. 1c). The number of cases in which this operation was done, however, was very small. Because of the short afferent loop jejunoplasty was impossible. The anastomosis was converted into the Billroth-I type.

Case 4.—A man had a retrocolic Polya gastrectomy done for ulcer in 1948. This was followed by severe bilious vomiting three or four times a day. His weight fell from 10 st. 10 lb. to 7 st. He came again for operation on July 27, 1951. Because of the short afferent loop it was impossible to do a jejunoplasty. The anastomosis was converted to the Billroth-I type, and vagotomy was done. On Oct. 4, 1951, the patient still had bilious vomiting, along with food, but only about once every ten days. He was much improved, and now ate most foods. He weighed 8 st. 9 lb. His stools, formerly light in colour, were now dark. By Dec. 13, 1951, bilious vomiting and vomiting of food had ceased.

Colonic Implant

Moroney (1951) has described an operation in which a segment of transverse colon, 4–6 in. long, is implanted between the gastric remnant and the cut edge of the duodenum. Such an operation, if it allows a reservoir for food, holds considerable possibilities in the treatment of some of the post-gastrectomy syndromes. It has been so used in the present series to prevent efferent-loop symptoms, as in case 5, where both afferent-loop and efferent-loop symptoms were experienced by the patient. The anastomosis, being of the Billroth-I type, excludes the possibility of further afferent-loop symptoms.

Case 5.—A woman, who had had symptoms of duodenal ulcer for several years, underwent subtotal gastrectomy on Feb. 1, 1949. In August, 1949, she had lost over 1 st. in weight and now weighed 6 st. 6 lb. She had severe diarrhœa. A barium meal showed no abnormality of the stoma. On April 20, 1950, investigation showed fæcal fat 86% split, 14% unsplit. Blood-sugar curves showed hypoglycæmia at the end of 1 hour after a meal. The patient complained of bilious regurgitation, colicky abdominal pain, loss of weight, diarrhœa, and lack of energy, associated with almost continuous nausea after a meal. On Nov. 30, 1950, she weighed 7 st. $2\frac{1}{2}$ lb., and in May, 1952, 6 st. 7 lb. On June 18, 1952, a 4-in. colon implant was inserted between stomach and duodenum, after the previous partial gastrectomy had been undone. The postoperative course was very satisfactory, the patient remaining completely free from vomiting. On leaving hospital she weighed 6 st. On Aug. 1, 1952,

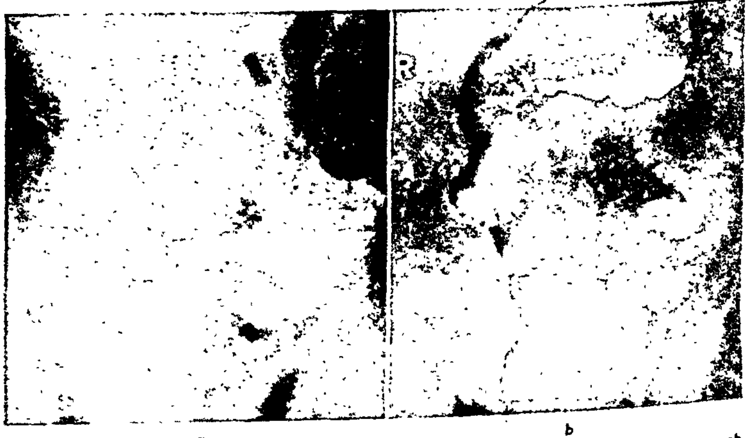


Fig. 5—Subtotal gastrectomy (case 6) : *a*, radiograph 3 hr. after barium meal (stomach is empty) ; *b*, after colonic implant, radiograph 3 hr. after barium meal (stomach not yet empty).

she was eating larger meals than ever before. She did not eat pastry and fried fish, because they induced nausea, but otherwise her diet was normal. She had no bilious vomiting and no diarrhœa, and her stools were of normal colour. She still had a feeling of faintness on exertion. Her hæmoglobin was 86% and weight 6 st. 11 lb.

This operation described by Moroney has also been utilised by us where a second gastrectomy has had to be done at a higher level in a patient who already has had symptoms of afferent-loop stasis.

Case 6.—A man, aged 64, had had epigastric pain and vomiting of food since 1942. In health he weighed 9 st. 3 lb. In April, 1951, partial gastrectomy was done elsewhere for gastric ulcer. After the operation he had bilious regurgitation and lost weight. A barium meal showed a large gastric remnant, and there was occult blood in his fæces. At operation on Feb. 12, 1952, it was found that only a third of his stomach had been removed at the previous operation. An adequate subtotal gastrectomy was now done and a 4-in. colon implant inserted between the cut end of the stomach and the duodenum. On June 27, 1952, he reported that he had no pain or vomiting and was eating all foods and taking moderately large meals, with no postprandial symptoms. He was gaining weight.

Fig. 5 shows barium radiographs of this patient at the end of three hours both before and after the colon-implant operation. A comparison indicates the considerable delay in complete gastric emptying after the Moroney type of operation.

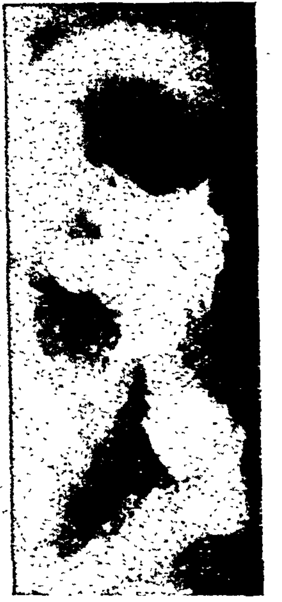


Fig. 6—Barium radiograph of only patient in present series who had symptoms due to afferent-loop reflux.

Afferent-loop Reflux

The study of barium-meal radiographs after gastrectomy shows that barium often passes backwards into the afferent loop. Owing to the nature of the operation it is seen most often in the left-to-right type of anastomosis—e.g., the Moynihan type (Ogilvie 1947). One of the reasons for advocating the Hofmeister type of valved anastomosis was specifically to avoid this reflux of food into the afferent loop. The tacit assumption, however, that the reflux of barium, and therefore of food, into the afferent loop is associated with symptoms has not been proved. This reflux occurs very commonly after gastro-enterostomy without causing symptoms. In the present cases of afferent-loop stasis the appearances after jejunoplasty indicate that barium now passes into the afferent loop, and yet no symptoms have been observed. Further, reflux is often observed after subtotal gastrectomy in symptomless cases. Forcheri (1951) has observed in a study of 50 cases that the reflux of food into the afferent loop does not cause symptoms. Goligher and Riley (1952) have also shown that the reflux of food and barium into the afferent loop is rarely associated with symptoms. The suggestions of Ogilvie (1935), Maingot (1948), and Mimpriss and Birt (1948) that reflux is a cause of symptoms cannot therefore be substantiated. Whatever merit the Hofmeister type of valve with right-to-left type of anastomosis may have, it cannot be supported *per se* as a prevention of "dumping" symptoms.

As Wells and Welbourn (1951) have indicated, the symptoms of afferent-loop reflux, when they do occur, are vomiting of *food mixed with bile*, associated with visceral symptoms. The syndrome is quite uncommon after the Finsterer-Lake type of gastrectomy with a Hofmeister valve. Indeed, only one true case of the condition has been observed in the present series (fig. 6). The vomiting of food and bile after the Billroth-I type of anastomosis is, of course, due to a different mechanism.

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HEALING POLYARTERITIS NODOSA

OBSERVATIONS ON THREE CASES AFTER A.C.T.H. AND ON ONE CASE AFTER SYMPATHECTOMY

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A HUNDRED years have passed since Rokitansky (1852) described a case in which he had found multiple small aneurysms on the visceral arteries at necropsy; Eppinger (1887) showed histologically that Rokitansky's case was an example of polyarteritis nodosa. Since then several hundred cases have been reported, and many cases now go unpublished. Recent reviews include those by Harris et al. (1939), Miller and Daley (1946), and Rose et al. (1950). It is our purpose to refer here only to some aspects of the disease which are relevant to its course and prognosis and particularly to the healing of its lesions.

It is salutary to recall that Kussmaul and Maier (1866) indicated the possibility of clinical diagnosis, the possible value of biopsy, and the possibility of recovery or intermission in polyarteritis nodosa. The diagnosis was made at the bedside in the second of their 2 cases, and muscle biopsy was performed; the patient himself drew attention to the similarity of his illness to that of the patient who had died of "periarteritis nodosa." When the paper was written he had shown no sign of active disease for several months.

Grant (1940) pointed out that one of the commonest misconceptions about polyarteritis nodosa is that it is invariably fatal, usually in a few months. He calculated that the average duration of the illness in most of the published cases was from four to six months, but that the average duration of 70 cases with adequately recorded histories was just over two years if account was taken of previous illnesses which could reasonably have been manifestations of polyarteritis. The duration of the disease may indeed sometimes be measured in years; remissions and even long intermissions may occur, and perhaps permanent recovery—although the occurrence of spontaneous intermissions makes it essential that reports of clinical recovery should be considered with reserve. "Recovery" had lasted more than one year in only 11 of the 20 cases of supposed recovery discussed by Klein (1949), and it is doubtful if the diagnosis of polyarteritis nodosa was justified in some of these cases; Klein's own second case was probably an example of the localised appendiceal arteritis which Plaut described in 1951. It is important to recognise also that healing of the vascular lesions does not necessarily imply recovery from the effects of the disease, for the patient whose arteritis has healed with fibrosis may yet die from interference with the blood-supply to vital structures.

Apparent recovery has taken place in polyarteritis nodosa after treatment with antisyphilitic drugs (Schmorl 1904, Spiro 1919), sulphonamides (Goldman et al. 1942), penicillin (White 1947), and penicillin and anti-histamine drugs (Sutherland 1948, Tomenius 1949); it is interesting that almost all these drugs have been suggested as a cause of the disease in other cases (Miller and Daley 1946). Before the recent introduction of cortisone and adrenocorticotropic hormone (A.C.T.H.) to therapeutic practice no treatment could be relied on to influence the course of the disease favourably. The ameliorating effect of adequate dosage with these hormones has been described in all the published cases thus treated (see Selye 1950, 1951a), except one (Brodthagen et al. 1951) in which the diagnosis is open to doubt. Although these drugs have been in use for too short a time for their value to be assessed properly, the regularity with which serial biopsies during treatment have shown healing of arteritic lesions, and with which relapses following withdrawal of the drugs have responded to their readministration, suggests that the improvement may be attributed to the treatment.

The remarkable healing of the lesions which may be seen after treatment with A.C.T.H. was demonstrated in 3 of the following cases of polyarteritis nodosa. Comparable healing was seen in the 4th case after sympathectomy for malignant hypertension.

Healing after Treatment with A.C.T.H.

THE FIRST CASE

Case 1.—Mrs. A, a housewife, born in 1903, had good health until January, 1950, when for two weeks she suffered from colic and severe bloody diarrhœa. In April, 1950, she had an attack of dizziness, followed by vomiting. High blood-pressure was diagnosed, and rest in bed was ordered. During the next two weeks neuritis developed in both arms. By July, 1950, the neuritis had subsided and she began to get about again; she felt exhausted and was troubled by vague retrosternal pain and by dyspnœa on exertion. Her condition deteriorated steadily, and she was admitted to the General Hospital on Nov. 9, 1950.

Condition on Admission

She was wasted and anxious. Her heart was enlarged; the apex-beat was in the fifth intercostal space, 2·5 cm. outside the midclavicular line, and the second sound was accentuated in the aortic area. Pulse regular (88 per min.); blood-pressure 240/130 mm. Hg. Retinal arteries thickened and tortuous; no papillœdema. Other systems normal. No fever.

Investigations

Urine: protein ++; occasional erythrocytes and hyaline and granular casts; sterile. Urea concentration 2·46 g. per 100 ml. of urine; blood-urea 28 mg. per 100 ml.; standard urea clearance 114%. Peripheral blood: erythrocytes 4,290,000 per c.mm.; Hb 10·2 g. per 100 ml.; leucocytes 13,500 per c.mm. (neutrophils 76%, eosinophils 1·5%, lymphocytes 9%, monocytes 13·5%); erythrocyte-sedimentation rate 38 mm. in one hour (Wintrobe). Basal metabolic rate +4%.

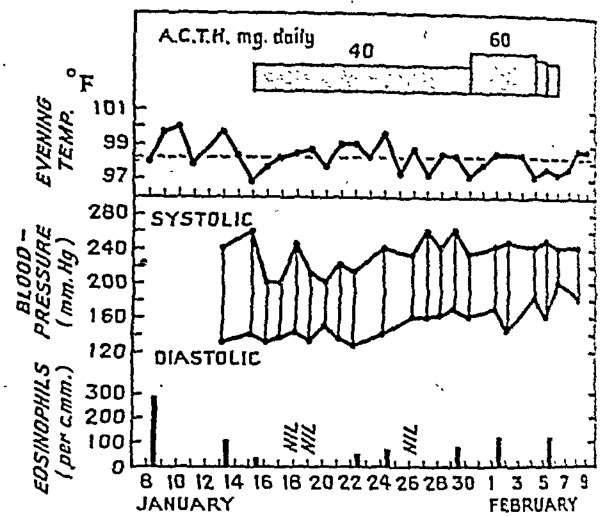

Fig. 1 (case 1)—Dosage of A.C.T.H., temperature, blood-pressure, and eosinophil-counts.

Progress

Two weeks after admission a remittent pyrexia began which never exceeded 101°F (38·3°C); the heart-rate corresponded to the temperature. The patient became listless and apathetic and sweated heavily at night. Aching precordial pain was present for hours at a time and was not affected by nitroglycerin. Repeated electrocardiograms showed only left ventricular preponderance. The blood-pressure did not vary significantly. Radiographs of the chest showed only cardiac enlargement. Serum-agglutination reactions for salmonella, brucella, and dysentery organisms were negative. The Paul-Bunnell test was negative. The urine remained sterile. No occult blood was found in the stools.

Dec. 5.—A course of hexamethonium bromide was started; the initial dose of 0·25 g. twice daily by mouth was gradually increased to 0·5 g. five times a day by *Dec. 12*. This drug had little effect on the blood-pressure and was withdrawn on *Dec. 15* because it caused severe nausea.

Jan. 1, 1951.—A painless expansile pulsatile swelling, 1 cm. in diameter, was noticed in the left cheek. The development of this aneurysm in association with the other clinical findings led to the diagnosis of polyarteritis nodosa, although biopsy of a pectoral muscle on *Jan. 3* showed no abnormality. On *Jan. 7* severe throbbing pain suddenly developed in the left forearm, the musculature of which immediately became swollen, hard, and pulsatile; a loud systolic bruit was heard, and it was considered that an aneurysm had burst. The arm returned to normal during the next two weeks.

The patient's general condition continued to worsen. On *Jan. 15* a course of A.C.T.H. (Armour) was started (fig. 1). Considerable subjective improvement followed, although pyrexia persisted and her weight fell from 49 to 45 kg. On *Jan. 22* an expansile pulsatile swelling with a loud systolic bruit was noted above the right clavicle; its size increased rapidly for two days until it measured 5 cm. in diameter. By *Jan. 30* it had become hard and non-pulsatile; the facial aneurysm had by now also hardened and ceased to pulsate.

Feb. 4.—Shortage of A.C.T.H. necessitated reduction of dosage, and treatment was stopped on *Feb. 6*; 995 mg. had been given intramuscularly in twenty-two days. The patient's condition did not alter appreciably after withdrawal of A.C.T.H. until *Feb. 23*, when she complained of generalised aching abdominal pain. This persisted until *Feb. 28*, when she suddenly collapsed with signs of internal hæmorrhage and died in a few minutes.

Necropsy Findings

Several hundred saccular aneurysms were found on visceral and parietal arteries; their diameter ranged from 0·1 to 5·5 cm. The largest included those which had been detected during life: one arising from the right inferior thyroid artery (5·5 cm.), one in the left cheek (2·5 cm.), and one in the muscles of the left forearm (2·5 cm.). The last-mentioned was surrounded by a large organising hæmatoma; an identical lesion in the right calf had not been observed before death. All the aneurysms were filled with adherent thrombus.

The peritoneal cavity contained more than 1300 ml. of blood which had tracked through the liver from one of several aneurysms surrounded by fibrous tissue in the vicinity of the porta hepatis. A second freshly ruptured aneurysm in the liver had given rise to a large subcapsular hæmatoma. The heart (340 g.) showed left ventricular hypertrophy, and the kidneys (combined weight 270 g.) had the appearances of hypertensive nephrosclerosis.

Histology

Lesions of polyarteritis nodosa were numerous in most organs and tissues. All the lesions showed advanced or complete healing by fibrosis; fibrinoid material had disappeared from all but a few vessels (fig. 2); lymphocytes and large mononuclears predominated in the rather scanty cellular exudate, and neutrophil polymorphs and eosinophils were rare or absent. Many of the affected vessels were occluded by organising thrombus, and some were recanalised. All the aneurysms examined had undergone thrombosis; a few fibroblasts had invaded the peripheral hyaline zone of the thrombus, but there was no effective organisation; in some instances the vascular lumen was separated from the peri-aneurysmal tissues only by a thin layer of unorganised thrombus and poorly consolidated fibrous tissue. Small hæmorrhages were common in the wall of the sacs, and there was often much blood pigment in the vicinity. Some of those peripheral nerves which were involved in the fibrosis round adjacent aneurysms showed minor degenerative changes in the myelin sheaths and axons; no arteritic lesions were found within the nerves. In addition to polyarteritic lesions, hypertensive arteriolosclerosis was present, particularly in the kidneys.

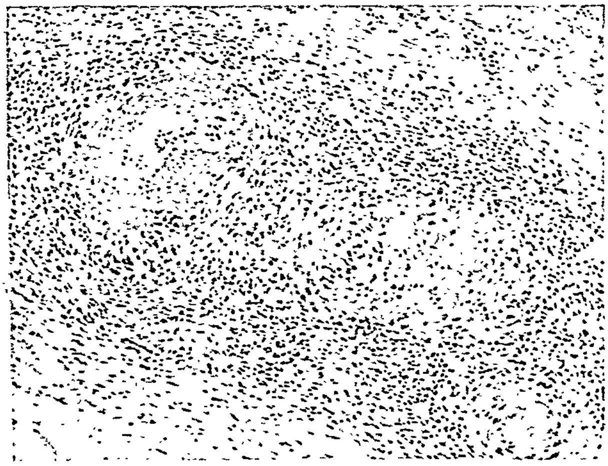

Fig. 2. (case 1)—Healing polyarteritic lesions, showing fibrosis and predominance of large mononuclears and fibroblasts in cellular reaction: remnants of fibrinoid are present in this lesion, which shows much less advanced healing than most of the lesions in this case. (Hæmatoxylin and eosin. × 96.)

THE SECOND CASE

Case 2.—Mr. B, a general labourer, born in 1929, had excellent health until the beginning of December, 1951, when his ankles were painful and swollen for three days. A few days later his calves became painful to touch, although they were not spontaneously sore. He began to feel ill and feverish. Thirst, polyuria, and nocturia developed. Within three weeks he was too ill to leave bed, and on Jan. 3, 1952, he was admitted to the General Hospital.

Condition on Admission

His temperature was 99·6°F (37·6°C). His calf muscles and right biceps brachii were very tender; the joints were normal, and some loss of power in the legs and right arm appeared to be due to muscular pain. There were no abnormal neurological findings, and the other systems were also normal. Blood-pressure 135/80 mm. Hg.

Investigations

Cerebrospinal fluid: normal pressure; two cells in 3 c.mm.; reducing substance 106 mg. per 100 ml.; protein 20 mg.; chloride (as NaCl) 690 mg.; Lange curve 1100000000; Wassermann reaction negative (0·5 ml. of C.S.F.). Urine: protein ++; sp. gr. 1·012–1·024; numerous erythrocytes; occasional epithelial and granular casts; sterile. Blood: packed-cell volume 47%; erythrocytes 5,060,000; Hb 14·1 g.; leucocytes 16,500 per c.mm. (neutrophils 86%, lymphocytes 9·5%, monocytes 4·5%); erythrocyte-sedimentation rate 14 mm. in one hour (Wintrobe). Serum Wassermann and Kahn reactions negative. Agglutination reactions for salmonella, brucella, dysentery, and leptospira organisms negative. Chest radiographs and electrocardiogram normal.

Progress

There was slight pyrexia throughout the illness. During January the patient's condition changed little. Two blood-cultures proved sterile. The blood picture altered gradually: the hæmoglobin fell to 10·4 g. per 100 ml. and the leucocytes to 9800 per c.mm. (neutrophils 76%, eosinophils 16%). Transient paræsthesiæ and weakness in the limbs were associated with local impairment of touch and pain sensation. He complained occasionally of pain in various large joints, which appeared normal on examination. Polyarteritis nodosa was suspected, and a muscle biopsy at the end of February showed typical lesions.

March 2.—He complained of "stinging" in the lower part of the abdomen; his temperature was 102°F (38·9°C) and there was tenderness in the hypogastrium and iliac fossæ. On *March 11* he coughed up a little blood-streaked mucopurulent sputum, which yielded a heavy growth of *Streptococcus viridans* and coagulase-positive *Staph. aureus;* cultures for tubercle bacilli were sterile. Chest radiographs remained normal, the cough was never severe, and hæmoptysis was not repeated.

March 14.—A course of A.C.T.H. (Armour) was started with a daily dose of 20 mg. given intravenously in 500 ml. of physiological saline solution over eight hours (fig. 3). On *March 18* severe melæna occurred, and the Hb decreased rapidly to 4·7 g. per 100 ml.; transfusion of 4 litres of blood restored it to 10·4 g. On *March 19* the dose of A.C.T.H. was changed to 30 mg. intramuscularly every six hours. On *March 26* a course of 300,000 units of penicillin intramuscularly twice a day was started. On *March 29* he developed sudden pain in the left arm, and a tender swelling was found occupying the bicipital groove; the pulses were normal, and no œdema developed.

Although there was no dramatic response to A.C.T.H., the patient felt better, and his general condition steadily improved. His blood-pressure remained normal. He had slight abdominal pain occasionally; there was no further melæna, and the blood-picture remained substantially unaltered. The course of A.C.T.H. ended on *April 1;* the total amount given was 1780 mg. in nineteen days. On *April 2*, while still receiving penicillin, he was wakened by severe pleuritic pain in the left side, and coughed up a little dark sputum. Pleural effusion developed rapidly on the left side, causing gross displacement of the mediastinum and severe respiratory distress in spite of repeated thoracenteses. The fluid was turbid and yellow, and contained 3·25 g. of protein per 100 ml.; cultures yielded a heavy pure growth of *Bacterium coli.* A course of streptomycin was started. On *April 3* aspiration of the effusion produced only 40 ml. of thick purple fluid:

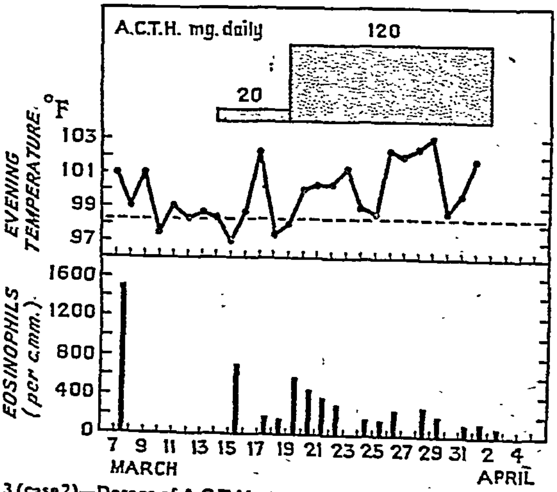

Fig. 3 (case 2)—Dosage of A.C.T.H., temperature, and eosinophil-counts.

The patient's condition deteriorated rapidly, and he died on April 3, forty hours after the onset of pain in the chest.

Necropsy Findings

The left pleural sac contained 1900 ml. of thin fibrinopurulent exudate, and the left lung was completely collapsed. The spleen (300 g.) was necrotic and sealed off from the general peritoneal cavity by fibrinous adhesions; its capsule had partly disintegrated, and a collection of thick purple pus was present between it and the diaphragm; a thoracentesis needle-track led into the abscess. The splenic artery and vein, left brachial artery, right axillary vein, prostatic plexus, and veins in the calf muscles were occluded by organising thrombus; there were no apparent prethrombotic changes in their walls. A few thrombosed aneurysms up to 1·0 cm. in diameter were present on visceral arteries. The kidneys (combined weight 440 g.) were large and congested. A few small infarcts of different ages were present in the kidneys and testes, and there were several small ulcers in the lower ileum. *Bact. coli* was isolated in pure culture from the spleen and pleural exudate.

Histology

Arteritic lesions were less numerous than in case 1; all showed advanced healing or were healed. Arterioles in the synovia of large joints and in many peripheral nerves were involved; demyelination and interstitial fibrosis were seen in the affected nerves. The thrombus in the splenic and brachial arteries and in the veins was organising; there was no underlying arteritis or phlebitis. The spleen was infarcted, and suppuration had developed at the margin of the infarcted tissue, where coliform bacilli were present. The ileal ulcers were healing: they appeared to have originated by confluence of focal areas of ischæmic necrosis. Many glomeruli showed epithelial crescents, capsular adhesions, and fibrinoid change; all the affected glomeruli were undergoing organisation, and healing was usually far advanced.

THE THIRD CASE

Case 3.—Miss C, housekeeper, born in 1891, had had nasal catarrh for many years and winter bronchitis since 1945. In October, 1949, asthmatic bronchospasm complicated bronchitis for the first time; penicillin relieved this attack of bronchitis but was not effective in a recurrence in April, 1950, which responded to streptomycin administered after a heavy growth of Friedländer's bacillus had been obtained from the sputum; lobelia and grindelia kept the spasm under control. A blood-count at that time showed red cells 5,270,000 per c.mm., Hb 14·7 g. per 100 ml., and leucocytes 8100 per c.mm. (neutrophils 68·3%, eosinophils 7%, lymphocytes 19·7%, monocytes 5%). A trace of protein and occasional hyaline casts were found in the urine, and the patient gave a history of polyuria and nocturia for many years. Asthmatic bronchitis recurred in August, 1951, and responded to penicillin, but neither penicillin nor streptomycin was effective in a severe attack in December, 1951. She was admitted to the General Hospital on Jan. 6, 1952.

Condition on Admission

The only abnormal clinical findings were the signs of chronic bronchitis with bronchospasm. Blood-pressure 130/80.

Investigations

Radiography showed evidence of chronic pansinusitis, although antral washings were clear on each side. A heavy growth of *Strep. viridans*, Friedländer's bacillus, and *Neisseria catarrhalis* was obtained from the washings and from sputum. Chest radiography showed emphysema and a little basal fibrosis. Vital capacity 2400 ml. Electrocardiogram normal. Serum Wassermann and Kahn reactions negative. Blood: erythrocytes 4,780,000; Hb 13·3 g. per 100 ml.; leucocytes 9400 (neutrophils 41·5%, eosinophils 39·5%, basophils 0·5%, lymphocytes 18%, monocytes 0·5%); erythrocyte-sedimentation rate 16 mm. in one hour (Wintrobe). Plasma-albumin 3·5 g. per 100 ml., plasma-globulin 3·2 g. Urine: no protein; occasional erythrocytes and hyaline and granular casts; sterile.

Progress

A week after admission the patient complained that she had had numbness and pins-and-needles in the hands and feet since *Jan. 1.* There were no objective neurological signs until *Jan. 26,* when loss of ankle-reflexes and weakness of dorsiflexion of the feet were observed. On *Jan. 28* a white-cell count showed leucocytes 17,500 per c.mm. (neutrophils 41·5%, eosinophils 42·5%). Polyarteritis nodosa was suspected, and a muscle biopsy on *Feb. 8* showed typical acute lesions with very numerous eosinophils. *Feb. 11*: weakness and sensory disturbances of neuritic type in hands and feet and wasting of the thenar muscles were present.

Feb. 12.—A course of A.C.T.H. (Armour) intramuscularly was started. There was slight subjective improvement in the neurological condition during the course but no alteration in the objective findings. Bronchospasm had begun to improve before A.C.T.H. was given and continued to do so. *Feb. 18*: plasma-albumin 4·2 g. per 100 ml., plasma-globulin 2·8 g.; the plasma-proteins subsequently varied little. On *March 7* A.C.T.H. was withdrawn; the total dose was 1695 mg. in twenty-five days. On *March 10* a muscle biopsy showed healing of polyarteritic lesions, with fibrosis and a cellular infiltration consisting predominantly of plasma cells, although eosinophils were still to be found. The biopsy wound healed rapidly. On *March 14* a blood-count showed red cells 4,400,000 per c.mm.; Hb 12·5 g. per 100 ml., and leucocytes 15,600 per c.mm. (neutrophils 85%, eosinophils 0·5%, lymphocytes 13%, monocytes 1·5%). On *March 16* the patient was discharged home. She had been afebrile throughout her stay in hospital; her blood-pressure had varied little and was 120/80 on discharge.

Subsequent Course

Her condition remained stationary for a few weeks. She felt well, although inconvenienced by pain and weakness in the limbs. Early in May she became increasingly dyspnœic on exertion and her ankles were swollen. On *June 7* she was readmitted to hospital in severe congestive heart-failure. Her heart was enlarged; the apex-beat was in the fifth interspace, 2·5 cm. outside the midclavicular line. Blood-pressure 130/110. Pulse regular and feeble, rate 110 per min. There was wasting of the small muscles of the hands and gross impairment of common sensation and kinæsthesia in hands and feet, with loss of the patellar and ankle reflexes. Blood-urea 190 mg. per 100 ml. Urine: protein +++; sp. gr. 1·008–1·015; numerous erythrocytes; occasional hyaline and granular casts. Blood: erythrocytes 3,710,000; Hb 11·3 g.; leucocytes 4900 (neutrophils 68%, eosinophils 0·5%, basophils 0·5%, lymphocytes 28·5%, monocytes 2·5%).

The patient's condition deteriorated in spite of treatment with digitalis and morphine, and she died suddenly on *June 29.* She had severe pain in the hands and feet during the last few weeks of her illness; the distribution and quality of pain never suggested myocardial ischæmia.

Necropsy Findings

The heart (400 g.) was enlarged; the left ventricle was hypertrophied, and both ventricles were dilated. There were small foci of myocardial fibrosis; no infarcts were seen, although the apical part of each ventricle contained organising thrombus. The superficial coronary arteries were patent and almost free from atheroma. The viscera showed chronic venous congestion, and there were serosal effusions and dependent œdema.

Histology

Lesions of polyarteritis nodosa were widespread; none was found in the lungs. All the lesions were apparently completely healed by fibrosis, and there was little or no cellular accumulation round them. No aneurysms were found. Many peripheral nerves showed patchy demyelination and interstitial fibrosis round obliterated arterioles. Healing glomerulitis identical with that in case 2 was present. There was considerable myocardial fibrosis, associated with arteritic lesions, and there were multiple small areas of fresh or organising infarction, particularly underlying the mural thrombus.

DISCUSSION

Reparative fibrosis of the vascular lesions is not uncommon in untreated polyarteritis nodosa. The remarkable feature of the three cases described above was that all the affected vessels which were seen showed advanced or complete healing, whereas in untreated cases healing lesions are outnumbered by those which show active destructive inflammation. As more than 120 blocks of tissue were examined histologically in each of the present cases, we believe that the absence of any lesions which were not healing may be considered to be representative of the state of the vasculature as a whole. Complete spontaneous healing of polyarteritis nodosa has seldom been reported; Pickert-Menke (1920), Manges and Baehr (1921), Arkin (1930, case 5), and Davson et al. (1948, case 13) described the only acceptable cases which we have been able to find. That the number of spontaneously healed cases has represented such a small proportion (considerably less than 1%) of the published cases of the disease seems to be evidence that healing in the present cases may be attributed to treatment with A.C.T.H. We have found no detailed accounts of pathological findings in other cases of polyarteritis nodosa treated with A.C.T.H., but post-mortem histological findings similar to ours have been described briefly in cases treated with cortisone (Engleman et al. 1950, Baggenstoss et al. 1951, Drury et al. 1951). Comparable healing of arteritic lesions in successive muscle biopsies during treatment with cortisone or with A.C.T.H. has been recorded by Carey et al. (1950), Selye (1950), and others.

Aneurysms, which were present only in cases 1 and 2, showed less organisation than non-aneurysmal lesions. Inadequate fibrosis of their walls and lack of effective organisation of the enclosed thrombus apparently predisposed to small hæmorrhages and consequent increase in size of the lesions by accretion to the thrombotic mass; in some instances massive hæmorrhage occurred, one of those in the liver in case 1 proving fatal because its situation precluded spontaneous arrest of bleeding. Aneurysms of identical structure and with the same liability to rupture are found in untreated polyarteritis nodosa, and it is unjustifiable to attribute their defective fibrosis in our cases to A.C.T.H., particularly since there was no apparent deficiency in the development of fibrosis of the non-aneurysmal lesions. Published observations on the effect of A.C.T.H. and cortisone on the formation of scar tissue are conflicting. Several workers have commented on the apparently normal healing of biopsy and other wounds in patients receiving large doses of these hormones (Carey et al. 1950, Slick et al. 1951), although Baxter, et al. (1951a) observed retardation of reparative fibrosis during treatment with A.C.T.H., and Baxter, et al. (1951b) described an inhibitory effect of cortisone on wound-healing in animals.

Ischæmic lesions were remarkably few in relation to the extent of the vascular involvement in our cases. The myocardial fibrosis and infarction in case 3 were clearly related to occlusive healing of arteritic lesions of the interstitial branches of the coronary arteries, and the patient's death from rapidly progressive myocardial failure was undoubtedly due to this consequence of polyarteritis nodosa. Visceral infarcts have been conspicuously numerous in spontaneously healed polyarteritis nodosa (Arkin 1930) and in some cortisone-treated cases (Baggenstoss et al. 1951). Meacham et al. (1951) suggested that vigorous hormone therapy might effect too rapid healing, with fibrous obliteration of the vessels, and so cause widespread infarction. Though this possibility deserves consideration, the findings in our cases indicate that this complication is not inevitable with the dosage used; however, as in case 3, even infarction of restricted extent may by its situation lead to death. Occlusive healing of the arteritic lesions may have been responsible for the gradual rise of the diastolic blood-pressure in case 1 (fig. 1) and for the development of arterial hypertension in case 3: when the latter patient left hospital after the course of A.C.T.H her blood-pressure was normal and her heart was not enlarged; twelve weeks later, when she was readmitted in heart-failure, the diastolic pressure was 110 mm. Hg, and left ventricular hypertrophy as well as dilatation contributed to the cardiac enlargement then present.

The widespread but by no means generalised glomerulitis in cases 2 and 3 was similar to that described by Davson et al. (1948) in non-hypertensive patients with polyarteritis nodosa and renal failure. Neither renal failure nor hypertension was observed in case 2, and renal failure was manifested in case 3 only by the high blood-urea level during the terminal phase of cardiac failure, to which it probably was essentially secondary. The total duration of illness in case 2 was four months, and urinary symptoms developed during the first month. It is difficult to estimate the duration of polyarteritis nodosa in case 3, in which death took place six months after the onset of neuritic symptoms; there was no good evidence that the asthmatic bronchitis and accompanying eosinophilia which began almost three years before her death were related to polyarteritis; the presence of some chronic renal disorder was indicated by the history of polyuria and the finding of proteinuria and casts two years before death, although histological examination did not show any lesion other than glomerulitis of the type commonly associated with polyarteritis nodosa. Healing of the glomerular lesions in these cases may also be attributable to A.C.T.H., for the glomerulitis of this disease is probably a manifestation of the same pathogenetic mechanism as that which underlies the development of the arteritis itself.

No beneficial effects of A.C.T.H. on the peripheral neuropathy were observed in these cases. In cases 1 and 2 the neuritic symptoms subsided before treatment began, and in case 3 the treatment brought no appreciable relief. In all 3 cases histological examination indicated that the nervous damage was secondary to vascular lesions.

None of the recognised side-effects of A.C.T.H. therapy was observed in cases 1 and 3. No serious disturbance of electrolyte balance was shown in any of the cases by frequently repeated chemical and electrocardiographic investigations. Case 2, however, requires further discussion in relation to possible complications of the treatment. The immediate cause of death in this case was respiratory embarrassment and toxæmia associated with subphrenic and pleural infection. In accordance with recorded experiences during treatment with A.C.T.H. or with cortisone (Derbes and Weiss 1951) the presence of serious sepsis was clinically latent before the fulminant development of the pleural effusion. Both the pleurisy and the subphrenic abscess had obviously lasted too long for either to have developed as a result of inadvertent misplacement of the thoracentesis needle. Probably the pleurisy developed by transphrenic spread of infection from the abscess complicating the suppurative splenitis, which had clearly developed as a complication of infarction due to thrombosis of the splenic artery, although the source of infection was obscure. Infection possibly took place during a bacteriæmia which, as the organism concerned was *Bact. coli*, may have originated in the intestinal ulceration. No angiitis underlay the thrombosis of the splenic and other large vessels; though thrombosis was possibly merely symptomatic of the patient's general condition, it may have developed as a direct complication of treatment with A.C.T.H. The effects of A.C.T.H. and cortisone on coagulation have been inconstant (Smith et al. 1950). Cosgriff et al. (1950) observed thrombosis or embolism in 11 of 175 patients treated with A.C.T.H.; their observations included thrombosis of the radial artery, venous thromboses, pulmonary embolism, and myocardial infarction; they suggested giving anticoagulants to patients under prolonged treatment with A.C.T.H. or with cortisone, particularly careful dosage being necessary because the hormones can induce unusual sensitivity to anticoagulants.

Healing after Sympathectomy

Case 4.—Mr. D, a market-gardener, born in 1898, had good health until January, 1950, when he developed bronchopneumonia, which responded slowly to penicillin. Convalescence was protracted, supposedly because of incipient heart-failure associated with swelling of the hands and feet, and he was away from work for seventeen weeks. Polyuria developed during this illness and became steadily severer during the rest of his life.

In February, 1951, he began to suffer from headache which within a few days became so severe and unremitting that he had to give up work. His blood-pressure, which was 150/80 mm. Hg when the headache began, rose rapidly. Early in May his sight became blurred; his vision soon amounted only to perception of light. He was admitted to the Queen Elizabeth Hospital, Birmingham, on June 16, 1951.

Condition on Admission

His heart was large, the apex-beat was in the fifth intercostal space in the anterior axillary line, a faint systolic murmur was heard at the apex, and the second sound was accentuated in the aortic area. Pulse regular (72 per min.). Blood-pressure 205/130. There was severe papillœdema, with retinal hæmorrhages and exudates. The other systems were normal.

Investigations

Urine: protein 2–3 g. per litre (Esbach); occasional erythrocytes and hyaline casts. Blood-urea 48 mg. per 100 ml.; urea clearance 103% of normal. Peripheral blood: erythrocytes 4,940,000 per c.mm.; Hb 13·8 g.; leucocytes 10,200. Electrocardiogram: left axis deviation. Blood-pressure ranged from 195/120 to 230/135.

Surgical Treatment (Mr. V. S. Brookes)

The clinical diagnosis was malignant essential hypertension. Although the patient was considered to be a poor subject for surgery, it was decided to carry out sympathectomy in view of the incapacitating headache and deteriorating vision. On *June 22* the left sympathetic chain (from the second thoracic to the second lumbar ganglion inclusive) and splanchnic nerves were removed. Headache was completely relieved, and the blood-pressure fell to 120/80; vision did not improve. As was expected, after the first-stage operation the blood-pressure gradually rose from 125/80 on *July 7* to 205/130 on *July 16*. On *July 17* the right sympathetic chain (from the second thoracic to the first lumbar ganglion inclusive), the splanchnic nerves, and part of the cœliac ganglion were resected. The operation and the first few hours afterwards were uneventful; the blood-pressure was 100/60. Twelve hours after the operation the patient collapsed; his respirations fell to 8 per min., his pulse was weak (80 per min.), and his blood-pressure rapidly became undeterminable; he died within a few minutes.

Necropsy Findings

The heart (500 g.) was much enlarged by left ventricular hypertrophy; the valves were normal. There was slight atheroma of the aorta and coronary arteries. The kidneys (combined weight 400 g.) contained a few cortical scars and small recent infarcts; their architecture was otherwise normal. A small firm dark-red nodule was present in one testis.

Histology

Polyarteritic lesions were numerous in various organs (fig. 4); healing was as advanced as in case 3, and no acute lesions were found. The nodule in the testis was a typical thrombosed polyarteritic aneurysm. Hypertensive arteriolo-sclerosis was also present, and there was fibrinoid necrosis of some afferent glomerular arterioles and glomeruli; the necrotic lesions were under [illegible]. Many other glomeruli showed healing; [illegible] with that in cases 2 and 3. Sclerosing granulomatous folliculitis was present in the spleen.

Operation specimen.—The finding of polyarteritic lesions in the necropsy material led to examination of serial sections of a ganglion obtained at the first operation. A small artery in the periganglionic tissue showed the typical appearances of acute polyarteritis nodosa with no evidence of healing.

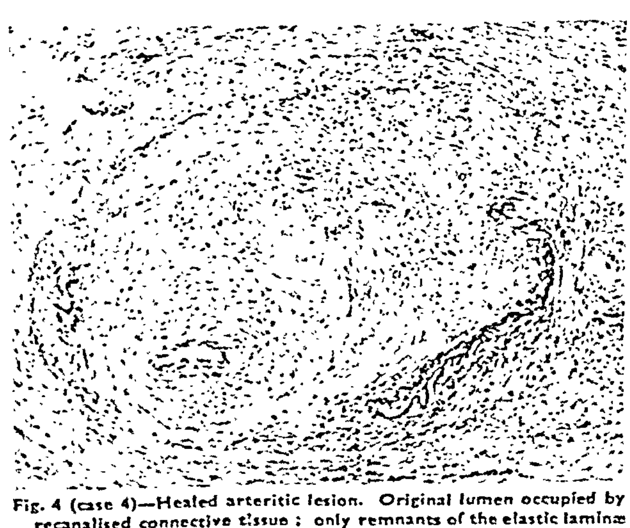

Fig. 4 (case 4)—Healed arteritic lesion. Original lumen occupied by recanalised connective tissue; only remnants of the elastic laminæ survive. (Weigert's elastic stain and carmalum. × 94.)

DISCUSSION

As only 17 pieces of tissue were examined microscopically in case 4, there were less adequate grounds than in the 3 cases treated with A.C.T.H. for assuming that the histological findings were representative of the vasculature as a whole. Nevertheless every one of the numerous lesions found showed advanced or complete healing, in contrast to the typical acute lesions in the surgical specimen obtained twenty-five days before death. Comparable healing of the glomerulitis and granulomatous splenic folliculitis (Ball and Davson 1949) of polyarteritis nodosa was also observed.

The history suggests that polyarteritis nodosa may have dated from the pneumonia, eighteen months before death, although the presenting manifestation of malignant hypertension developed only six months before death. Although Smith and Zeek (1947) suggested that arterial hypertension is the cause of polyarteritis nodosa, and although hypertension of the lesser circulation may cause lesions in the pulmonary arterial tree which are histologically indistinguishable from those of polyarteritis nodosa (Symmers 1952), there is no convincing evidence that hypertension causes this disease-entity. In the case under discussion malignant hypertension probably developed as a consequence of the arteritis. Nevertheless it is difficult to dissociate the healing of the arteritic lesions from the fall in blood-pressure maintained for two weeks after the first-stage sympathectomy, and it is relevant that the necrotic arteriolar lesions of malignant hypertension also showed evidence of repair. The mechanical strain imposed on a diseased vessel by severe hypertension could well prevent healing of established arteritis; a sustained fall in blood-pressure might break a vicious circle and allow other factors to operate in the establishment of healing. It may be significant in respect of this that one of us (W. St. C. S.) has observed that healing and healed lesions are relatively more numerous in those cases of polyarteritis nodosa in which arterial hypertension was absent or late in development, and that aneurysms are commonly more numerous and larger in cases in which hypertension was severe.

We know of only 1 published case in which surgical treatment for hypertension was undertaken in the presence of polyarteritis nodosa. Horne et al. (1950) reported the case of a man, aged 36, with malignant hypertension; splanchnicectomy was performed, and active polyarteritic lesions were said to be present in the resected tissue; six years later the patient was free from symptoms and his blood-pressure was normal.

Conclusions

Some tentative conclusions concerning the treatment of *polyarteritis nodosa* may be drawn from the 4 cases described here. Although 2 of the 3 patients treated with A.C.T.H. unquestionably died of polyarteritis nodosa, these 3 cases are important because an extended histological study post mortem revealed objective evidence of the remarkable extent to which the lesions of polyarteritis nodosa may heal by fibrosis under the influence of A.C.T.H. The paradoxical association of healing of the lesions and death is not remarkable in a disease which threatens every organ with the consequences of vascular occlusion.

It is this paradox which makes the therapeutic problem of polyarteritis nodosa particularly difficult; in many cases the lesions must already be widely disseminated by the time the diagnosis is made, and often the vasculature of vital organs will already have suffered such damage that no treatment will save the patient from disablement or death.

Our findings justify further trial of A.C.T.H. or cortisone therapy in polyarteritis nodosa. The possibly disastrous effects of obliterative healing of affected vessels in organs such as the heart and kidneys do not seem to us to be a contra-indication to treatment; the same effects might as readily develop if the patient survived long enough for healing to take place naturally. The risks are outweighed by the chance that even a small proportion of patients who would otherwise die of the disease may be cured by treatment instituted before potentially lethal damage has been done to the vasculature of vital organs. Accurate diagnosis at the earliest possible stage in the course of the illness is therefore of fundamental importance in relation to successful treatment. At the time of writing we have under observation cases of histologically confirmed polyarteritis nodosa which remain free from all evidence of disease a year or more after treatment with A.C.T.H. Such cases, however uncertain their ultimate outcome, are a further encouragement to persevere with this treatment.

The similar healing after sympathectomy in the fourth case was of particular interest. If lowering the blood-pressure in hypertensive patients with polyarteritis nodosa can cause healing of the arteritic lesions, better therapeutic results may possibly be obtained with A.C.T.H. or with cortisone if the hormone therapy is supplemented in such cases by antihypertensive treatment with drugs or by surgery. The case for such combined treatment is strengthened somewhat by the evidence that the lesions of polyarteritis nodosa may be most numerous in those cases in which arterial hypertension is present, and that hypertension appears to predispose not only to the formation of aneurysms but also, as in case 1, to their rupture. It must be remembered, however, that A.C.T.H. and cortisone may possibly cause or aggravate arterial hypertension, although the evidence is conflicting (Selye 1951b); whether in cases of polyarteritis nodosa this is a result of occlusive vascular healing or an effect of the hormone unrelated to its therapeutic activity, the risk is one which may well be thought worth taking in view of the prognosis of the untreated disease.

Summary

Four cases of polyarteritis nodosa are reported in which all the arteritic lesions showed advanced or complete healing.

Of the 3 patients treated with A.C.T.H., 2 died of complications of the disease, unavoidable in one case, and possibly due to arterial hypertension in the other; the treatment may have caused the death of the third patient.

In the fourth case the lesions healed after sympathectomy for malignant hypertension.

Antihypertensive measures may have a place as an adjuvant to hormone therapy in the treatment of hypertensive patients with polyarteritis nodosa.

We wish to thank Dr. J. M. Malins, Prof. A. P. Thomson, Dr. Clifford G. Parsons, and Mr. A. L. d'Abreu for allowing us to publish the clinical histories of cases 1, 2, 3, and 4 respectively; Dr. M. G. FitzGerald for his assistance at the necropsy in case 1; Dr. G. W. Thorpe and Dr. D. B. Brewer, who performed the necropsies in cases 3 and 4 respectively, for their coöperation; Dr. P. M. Moody for the diagrams: and Mr. Allan Ayres for the meticulous preparation of more than a thousand histological sections.

References at foot of next column

FATAL APPENDICITIS

THE DECLINE IN MORTALITY

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ON returning to civil practice after the war, I gained a clear impression that the prognosis of all types of emergency surgery within the abdomen had improved. Particularly in appendicitis did it appear that patients who might have died before 1939 were now getting well, and getting well quickly. The Registrar-General's (1950) figures show that in 1948 the number of deaths from appendicitis in England and Wales was less than half that in 1934. Whereas 3193 peoople died of appendicitis in 1934, only 1257 did so in 1948, and the decline in the mortality figures in the intervening years, though not evenly distributed, is progressive (fig. 1).

It does not necessarily follow from these figures that the prognosis has improved: they may only indicate that fewer people are falling sick with appendicitis, and, in spite of the decrease in the absolute numbers of deaths, the mortality-rate may be unchanged. Thus from the Registrar-General's figures alone it is not possible to say that the prognosis in appendicitis has altered at all since 1934. The figures do, however, show that appendicitis does not kill half as many people each year now as it did in 1934.

A second glance at fig. 1 leaves no room for complacency even in this fact when, in this day and age, in England and Wales, more than 100 persons die every month from appendicitis. This eminently treatable condition still deals death on too large a scale, particularly in this country where the surgical services are

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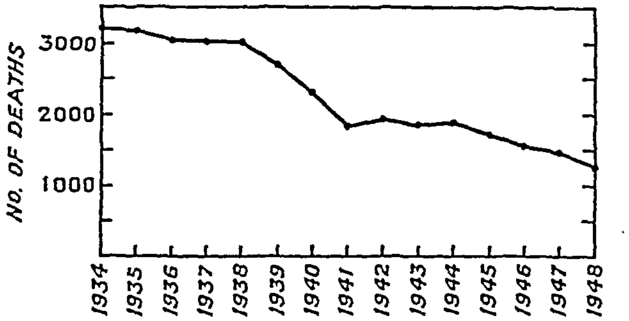

Fig. 1—Registrar-General's figures 1934–48 showing decline in numbers dying annually in England and Wales of appendicitis.

minutely and expensively organised. More than half the people who die are under 45 years of age, bread-winners, mothers of families, children, adolescents, and young adults. The treatment is too effective, the operation is too safe, and the outcome should be too certain, for these figures to be satisfactory.

INVESTIGATION

In 1946, on my appointment to a hospital where a large proportion of the emergency surgical work of a great city had been done by a skilled staff for the preceding eighteen years, it became my special interest over the next four years to observe the types of cases in which appendicitis was still fatal. From the well-kept hospital records generously provided for me by my surgical colleagues, and the industry of the office staff, all the cases of appendicitis over three different four-year periods were reviewed.

The organisation of the hospital lent itself to such an investigation. The long tradition of emergency surgical work had produced finely balanced units, each of 100 beds, each looked after by two surgeons, a registrar, and a house-surgeon. The pathological and X-ray departments were coöperative. The nurses, both in the operating-theatre and in the wards, accepted emergency surgery as one of their chief duties. The presence of almost the same surgeons for the greater part of the time under review made for the easy grouping of the cases of appendicitis into a classification based on the severity of the inflammation, since there was uniformity of description of the organ at operation. Most of the operations were done personally by the consultant staff; those done by junior officers were under close supervision.

There was also uniformity of treatment throughout the years, and the basic attack on the acutely inflamed appendix altered little. Details changed, but the surgical principle that an acutely inflamed appendix should be removed at the earliest possible moment after diagnosis, unless there was some overriding reason why this should not be done, was strictly observed.

The periods selected were 1934–37, 1940–43, and 1947–50. In 1934–37 most of the modern advances in general surgical technique were in use. The significance of fluid and salt balance, and the importance of giving parenteral saline solution when the intake by mouth was inadequate, had been generally accepted in the hospital. The importance also of early diagnosis and treatment, and of the time when operation might not be advisable and observation of a palpable lump might be the best course, were equally in the minds of the experienced surgeons responsible for the care of these patients.

In 1940–43 the new factor was the advent of chemotherapy, the new drugs being used in the treatment of the worst cases of appendicitis.

In 1947–50 there were two new factors: (1) antibiotics, and (2) the use of stomach suction, or decompression of the small bowel, in the treatment of peritonitis.

In all the periods the first and most important factor in treatment was the skilled and practised use of proven surgical principles. The other advances—chemotherapy, antibiotics, and bowel decompression—were adjuncts, albeit useful, to good surgery. Never is it suggested that they can purchase indulgences for ill-conceived or badly performed operations.

OPERATIVE TECHNIQUE

Technique remained remarkably constant not only through the years but also among the different surgeons. The standard approach to the appendix was through a muscle-splitting incision in the right iliac fossa. The appendix was removed, except when it was not easily available in an abscess. Most abscesses were treated by drainage only, but even here the appendix was removed if it presented. Whenever the appendix was removed, it was routine practice to crush and tie the base. The stump of the removed appendix was embedded in the cæcal wall. If for any reason it could not be embedded, a drainage tube was placed down to it. Gentleness in handling all the tissues, particularly the intestines, was practised assiduously to prevent postoperative ileus. Drainage tubes were often used in 1934–37; there was a general tendency to drain only the very worst cases in 1940–43; while 1947–50 occupies a middle position in this respect. In all the periods there was a greater tendency to drain children's abdomens.

In 1940–43 chemotherapy, though begun, was not general; nor was it standardised. Many different chemotherapeutic drugs were given by mouth, parenterally, and intraperitoneally, and the same surgeon did not always use the same method.

In 1947–50 the use of antibiotics, either alone or with chemotherapy, was general in cases complicated by any type of peritonitis or abscess.

CLASSIFICATION OF CASES

A simple classification according to the surgeons' findings at operation was used. Appendicitis being progressive, some easily recognisable milestones along the march of the inflamed appendix from simple acute inflammation affecting only the appendix to perforation with general peritonitis were taken to divide the cases into categories.

Group I includes all those cases where, at operation, the surgeon found that the inflammation was confined

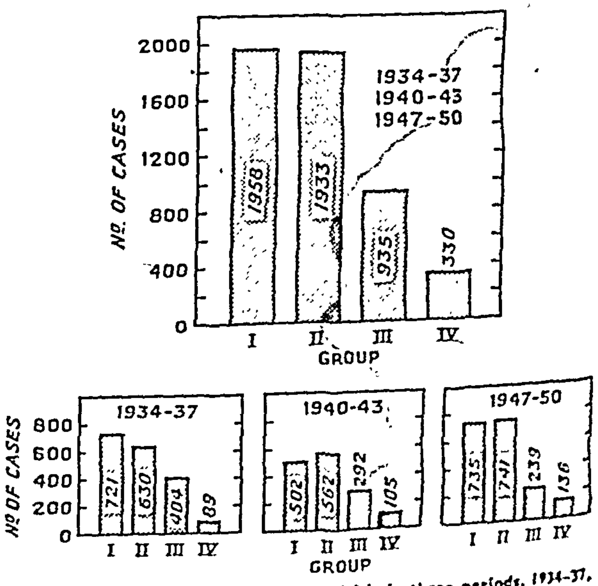

Fig. 2—Analysis of 5156 cases of appendicitis in three periods, 1934–37, 1940–43, and 1947–50, as a whole and separately. Numerals on histograms show numbers of cases.

ANALYSIS OF CASES INVESTIGATED

Year	Group I		Group II		Group III		Group IV		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1934 ..	201	1	152	3	97	11	25	8	475	23
1935 ..	206	1	168	5	106	12	21	8	501	26
1936 ..	148	0	138	8	98	14	24	5	408	27
1937 ..	166	1	172	6	103	7	19	11	460	25
Total 1934–37	721	3	630	22	404	44	89	32	1844	101
1940 ..	129	0	124	5	78	5	26	6	357	16
1941 ..	128	2	121	2	61	6	25	8	335	18
1942 ..	147	0	171	5	68	2	31	11	417	18
1943 ..	98	0	146	4	85	5	23	3	352	12
Total 1940–43	502	2	562	16	292	18	105	28	1461	64
1947 ..	165	0	200	2	80	10	47	10	492	22
1948 ..	159	1	216	1	80	2	48	2	503	6
1949 ..	207	1	200	1	58	3	28	2	493	7
1950 ..	204	0	125	1	21	4	13	2	363	7
Total 1947–50	735	2	741	5	239	19	136	16	1851	42
Grand total ..	1958	7	1946	43	935	81	330	76	5156	207

to the appendix wall and there was no visible spread to the peritoneum of the right iliac fossa.

Group II includes the cases where the inflammation had spread from the appendix to the right iliac fossa, and the beginnings of a spreading peritonitis were present.

Group III includes the cases where an abscess had formed in relation to the acutely inflamed appendix. These cases are among those which are not operated on, and consequently the diagnosis was made on the history and the presence of a firm and tender lump in the right iliac fossa or palpable on rectal examination. In a few cases at operation an unsuspected abscess was found in what had been diagnosed as a group-I or a group-II case. The term appendix abscess in all cases refers to primary appendix abscess and not to residual abscess developing after removal of the appendix.

Group IV includes those cases where there was acute appendicitis with general peritonitis. This was the smallest group numerically, but at all times this group carried the highest mortality-rate.

The numbers of cases in each group are indicated in fig. 2 and the accompanying table.

Only undoubted cases of acute inflammation were dealt with. If there was any doubt on this point, the case was excluded from the series. In the examination of the case-notes the nomenclature was usually found to be simple and self-explanatory. The group of cases labelled miscellaneously "subacute appendicitis," "obstructive appendicitis," "recurrent appendicitis," "interim appendicectomy," &c., were closely examined, and most could firmly be excluded on the surgeons' notes, as not being of acute inflammatory origin.

It was recognised at the outset that the whole purpose of the inquiry would be nullified if the classification of the cases was not accurate. It can be stated that all the 5156 cases recorded were truly cases of appendicitis.

RESULTS

In 1934–37, when the main attack on the acutely inflamed appendix depended, for its effectiveness, on surgical technique alone, 1844 patients with acute appendicitis were admitted to the hospital, and of these 101 died, giving a mortality-rate of 5·4%.

In 1940–43, when chemotherapy was beginning to be used to supplement surgery, there were 1461 patients, and of these 64 died, giving a mortality-rate of 4·3%.

In 1947–50, when to surgery and the wider use of chemotherapy there were added antibiotic drugs and decompression of the small bowel, there were 1851 patients with acute appendicitis, of whom 42 died, giving a mortality-rate of 2·3%.

It has already been shown from the Registrar-General's figures that fewer people die of appendicitis in England and Wales now than died in 1934, and that the decrease through the years has been progressive (fig. 1). The hospital figures now show that the mortality-rate in a large modern general hospital has also decreased in the period under review, and that the prognosis for acute appendicitis is at least twice as good now as it was in 1934.

Thus the figures are complementary, the one series supporting the other to indicate that both in absolute numbers (Registrar-General) and in mortality-rate (hospital) there has been a great improvement in the prognosis in acute appendicitis.

Now the hospital figures, unlike the Registrar-General's, can be broken down and examined by dividing the cases into their groups according to the severity of the inflammation, using the simple classification (described above) based on the surgeons' findings at operation.

Group I

Cases where the inflammation was confined to the appendix wall, accounted for a little more than a third of the total in each period The figures were remarkably constant, being 39% in 1934–37, 36% in 1940–43, and 39% in 1947–50.

The mortality-rate for group I is also constant, varying by only 0·1% in the three periods. In 1934–37 there were 3 deaths in 721 cases, giving a mortality-rate of 0·4%; in 1940–43 there were 2 deaths in 502 cases, giving a mortality-rate of 0·4%; and in 1947–50 there were 2 deaths in 735 cases, giving a mortality-rate of 0·3%. Thus in a total of 1958 cases of acute appendicitis in this group there were 7 deaths, giving a mortality-rate of 0·35%.

This is a very significant figure since it represents the true mortality-rate from appendicitis as distinct from the mortality-rate of appendicitis complicated by peritonitis. This figure of 0·35% has remained constant since 1934, unaffected by any advance in surgery in this hospital, technical or therapeutic.

Of the 7 deaths in this group 6 were due to pulmonary embolism, and the 7th took place on the operating-table from the patient's reaction to the anæsthetic. All these deaths were unforeseeable tragedies, not any more related to appendicitis than to any other abdominal operation. The figure 0·35% must be near the irreducible minimum, not only for appendicitis but also for any abdominal operation under present conditions.

Of the dead patients 5 were women and 2 men. One was aged 23; 2 were in their thirties, and the remaining 4 were in their fifties.

Thus in this group of nearly 2000 cases not 1 patient *died of appendicitis* or even the complications special to appendicitis. There were no deaths among children and adolescents, who made up a third of the group.

Group II

Here the inflammation, though not necessarily localised to the right iliac fossa, was still limited. This practical grouping may not be microscopically accurate, yet it is a workable measure indicating the next extension from group I. There were 1933 of these patients, of whom 43 died. As with group I, the proportion of these cases in each period corresponded closely, being about a third of the total cases.

In 1934–37 there were 630 patients and 22 died, giving a mortality-rate of 3·5%; in 1940–43, there were 562 patients, of whom 16 died, giving a mortality-rate of 2·8%; and in 1947–50 there were 741 patients, of whom 5 died, giving a mortality-rate of 0·7%. This reduction is tremendously worth while. The mortality-rate of group II has been brought down to the same region as that of group I.

A further interesting fact comes out of the hospital records. In group II the average time of the patient's stay in hospital was reduced by three days over the total period under review. In 1934–37 the average stay was eighteen days, whereas in 1947–50 it was fifteen days. To give some indication of what this means, a reduction of three days in the stay in hospital of 741 patients is a saving of 8892 meals, quite apart from their other needs. A general freeing of beds and services makes way for other emergencies, the supply of which seems inexhaustible.

It must be accepted that in the years 1947–50 there was much improvement in the prognosis for cases of appendicitis with peritonitis which had just begun to spread from the right iliac fossa. The mortality-rate was reduced, and so was the average stay in hospital.

Group III

There were 935 patients who had appendicitis complicated by an abscess, and 81 of them died. In 1934–37 there were 404 patients, of whom 44 died, giving a mortality-rate of 10·8%; in 1940–43 there were 292 patients, of whom 18 died, giving a mortality-rate of 6·1%; and in 1947–50 there were 239 patients, of whom 19 died, giving a mortality-rate of 7·9%. In group III there has not been much improvement over the whole period: the difference between 10·8% and 7·9% is not statistically significant. There is need for improvement here. This is a surprising finding, since the prognosis in appendicitis when a tender palpable lump appears in the right iliac fossa is generally held to be good. The surgeon tends to be pleased when he finds a lump. The figures indicate that a different attitude might well be adopted towards this dangerous condition. Here is a veritable surgical wolf in sheep's clothing. The reason why it had such a good reputation in the past is discussed below.

Since group III is more than twice as large as the other death-dealing group, general peritonitis (935 cases against 330), a reduction of its mortality-rate would do more than an equal reduction in any other group to reduce the general mortality-rate for appendicitis. Although there is a larger percentage mortality-rate with general peritonitis, the absolute figures show that more people die of appendix abscess. It is stated above that 81 patients died of appendix abscess in the whole period under review. In the same period 76 died of general peritonitis.

Group IV

In this group, where general peritonitis complicated appendicitis, there were 330 patients, of whom 76 died, an appalling over-all mortality-rate of 23%, but one which has improved through the years. In 1934–37 there were 32 deaths in 89 cases, a mortality-rate of 36%; in 1940–43 there were 28 deaths in 105 cases, a mortality-rate of 27%; and in 1947–50, with all the modern surgical advances up to 1950 at the disposal of the surgeons, there were 136 patients, of whom 16 died, giving a mortality-rate of 12% (fig. 2). Thus group IV, dangerous and difficult though it may be, has shown a response to modern treatment. The mortality-rate has been reduced to a third of the 1934–37 figures. In addition the average stay in hospital was shortened from twenty-nine days in 1934–37 to twenty-four days in 1947–50.

DISCUSSION

There has been a progressive decrease in the mortality-rate from appendicitis since 1934. From the results of the present investigation it is possible to indicate which types of appendicitis have an improved outlook.

Where the inflammation is limited to the appendix and surgical treatment is promptly applied, the mortality-rate approaches the bare irreducible minimum for abdominal operations generally, and has been steady at this figure since at least 1934. If all the cases were operated on at this phase, the problem would almost be solved so far as appendicitis was concerned. The mortality-rate remaining applies to abdominal operations generally and not specifically to appendicitis.

I suggest that, to emphasise the importance of the removal of the appendix in the early stage of appendicitis, such terms as "expectant treatment" and "conservative treatment" of appendicitis should never be used, and this for several reasons. It must be agreed that the treatment of appendicitis in group I is appendicectomy, because when the inflammation is limited to the appendix wall the mortality-rate cited above can hardly be improved on by any form of non-operative treatment. If these figures mean anything, they mean that there should be no such thing as the conservative treatment of *appendicitis*, since the conservative treatment, when it is applied, is directed at the associated peritonitis, which is a different matter. It may or may not be desirable to apply conservative treatment to the associated peritonitis, but it is almost never justifiable, in the light of the above-mentioned figures, to deny operation to *appendicitis without peritonitis*. Yet, if we continue to talk about the conservative treatment of appendicitis, doctors may feel it to be reasonable, under conditions where arrangements for appendicectomy, though available and adequate, are difficult to fix up, to treat early appendicitis conservatively and to await the outcome, hoping either for resolution of the inflammation or abscess formation; which is the same as converting group-I cases with a superb prognosis into group-III or even group-IV cases with the bad prognosis indicated above. If we more accurately talk about the conservative treatment of peritonitis, there is no doubt that patients under conservative treatment should be in hospital; such dangers could not normally be faced in a private house. To restrict the term to its more correct usage would underline the seriousness of the position whenever conservative treatment is even considered. It may lead to more group-I cases coming to operation and fewer patients entering hospital with peritonitis. In 1947–50, 1 in 5 of all the patients operated on for acute appendicitis had either an abscess or general peritonitis.

In group II, where the inflammation was limited to the appendix and the peritoneum of the right iliac fossa, where there was local peritonitis not amounting to abscess formation, the advent of chemotherapy, antibiotics, and decompression of the small bowel has reduced the previously considerable mortality-rate to levels approaching those in group I. If groups I and II are considered together for 1947–50, there were 1476 cases with 7 deaths, giving a mortality-rate of 0·5%. The combined mortality-rate for group III and group IV in the same period was 9·3%.

Consideration of group III and group IV is very important because here we can find where the new advances in surgery have been effective and where they have not. The death-rate from appendix abscess has not greatly altered since 1934. In 1947–50 the presence of a tender lump in the right iliac fossa, associated with a history of appendicitis, carried with it almost as high a mortality-rate as did proved diffuse peritonitis. It was not always so. In the earlier periods diffuse peritonitis was a much more lethal complication of appendicitis than was appendix abscess. Advances in surgery have reduced the dangers of diffuse peritonitis while leaving untouched those of appendix abscess. It seems that, in the past, surgeons were content to accept a mortality-rate of about 8% for appendix abscess, because it contrasted favourably with that of about 36% for diffuse peritonitis. In those days, if a diffuse peritonitis localised into an abscess, the prognosis was improved greatly, and it was a favourable sign to feel a lump in the right iliac fossa. It was from those days, long fled, that appendix abscess derived its good reputation. But now, when the mortality-rates are 12% for diffuse peritonitis and 7·9% for appendix abscess, the difference in prognosis is hardly statistically significant. The satisfaction when a tender lump becomes palpable in the right iliac fossa should give way to sterner feelings. It should be realised that a condition is present which accounts for more deaths than does any other type of appendicitis, that no impression has been made on these figures since 1934, and that this sign does not now warrant any clinical complacency. Rather should it be considered that the lump in the right iliac fossa signifies the hard core of the death-rate from appendicitis, and an improvement in the outlook of this condition would do more than anything to reduce the general mortality-rate from appendicitis, which, being more than 100 a month in England and Wales, is in greater need of attention than other and more publicised methods of dying.

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CONGENITAL ABSENCE OF THE COMMON BILE-DUCT

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CONGENITAL obliteration of the biliary tract is rare and usually fatal. The published cases have been fully reviewed by Ladd (1935), Ladd and Gross (1940, 1941), and Gray et al. (1948), and surgical intervention has been successful apparently in only 21 cases up to 1949.

Pathology.—One or more parts of the external biliary tract are either absent or exist as fine fibrous threads. Various abnormalities have been reported—e.g., the gall-bladder may be present but does not communicate with the ducts; or the gall-bladder may communicate direct with the duodenum, but there are no hepatic ducts.

Diagnosis.—There is no absolute rule for the diagnosis of congenital obliteration of the biliary tract, because some cases so diagnosed have cleared up spontaneously without operation, and it is assumed that they may have been caused by inspissated bile. Woolley (1948) says: "I believe we can conclude that we must be chary in reaching a diagnosis of congenital atresia of the biliary tract and depend upon a history of progressive jaundice for at least three months." Hæmolytic and infective conditions having been excluded, the diagnosis must be confirmed by laparotomy; otherwise the condition is fatal within the first year.

Treatment depends on the presence of at least one hepatic duct. 8 of the successful cases have followed the anastomosis of the gall-bladder to the stomach, 6 that of the gall-bladder to the duodenum, and 1 that of the gall-bladder to the jejunum. Choledochoduodenostomy and hepaticodochoduodenostomy account for the remaining 6.

CASE-RECORD

A boy, aged 3 months, was first seen on Oct. 25, 1947, with a history of increasing jaundice since birth. He appeared otherwise well, and had been born at full term. Delivery had been normal, and the baby was bottle-fed. He was an only child. Nothing relevant was found in the parents' histories. A Kahn test on the mother's blood was negative.

On admission the baby weighed 12 lb., and was well nourished but deeply jaundiced. No other abnormality was found. A blood-count was normal. The blood belonged to group A, and was rhesus-positive. The urine contained bile, and the fæces were white. Congenital atresia of the biliary tract was diagnosed and laparotomy was done five days after admission.

At operation under open ether the liver was found to extend two finger-breadths below the costal margin. The gall-bladder was 2 in. long and $^1/_2$ in. across; on aspiration it was found to contain bile. A common bile-duct could not be identified, so the gall-bladder was anastomosed to the pyloric antrum over a rubber tube with a double row of fine catgut sutures.

Postoperative recovery was uneventful. The stools became coloured within two days, and the urine cleared more slowly. The tube was passed in five days, and the jaundice cleared in six weeks. The child was discharged six weeks later, well and gaining weight, his weight then being 11 lb. 5 oz.

Subsequent progress was that of a normal child, apart from a small ventral hernia which is decreasing in size. In 1949 a cholecystogram showed no concentration of dye in the region of the liver. In 1951 barium-meal radiography showed no regurgitation into the gall-bladder, but traces of the meal could be seen in the gall-bladder area in the straight film.

COMMENT

The absence of any concentration of dye in the cholecystogram, and the presence of flecks of barium in the gall-bladder area after a barium meal, seem to establish the diagnosis of congenital obliteration of the biliary duct cured by cholecystogastrostomy.

Our thanks are due to Sister D. Fishwick, of the children's department, for her skilful postoperative care.

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THE TREATMENT OF PNEUMOCOCCAL MENINGITIS SINCE THE INTRODUCTION OF PENICILLIN

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No condition better reflects the advances in the field of antibiotic therapy during the last fifteen years than pneumococcal meningitis. Until 1936 this disease was almost always fatal. During the following two years a few cases were treated with type-specific rabbit antipneumococcal serum; but this was soon to be supplemented by sulphanilamide, and in turn by sulphapyridine, and eventually superseded by them. Hence, the specific antiserum treatment of pneumococcal meningitis will never be evaluated in its true perspective.

In 1940 Coleman reviewed in this journal the treatment since the introduction of 'M & B 693' (sulphapyridine) and concluded that the mortality-rate had been reduced from nearly 100 to 35%. This is in accord with Steele and Gottlieb's (1941) recovery-rate of 57% and Finland's (1938) 60% survival-rate. Waring and Weinstein (1948), reviewing published reports, placed the recovery-rate with sulphonamides at about 30%.

We report here the results in 31 cases of pneumococcal meningitis treated at the Presbyterian Hospital, New York, since the introduction of penicillin. The series is unselected, except that in all but one of them the invading pneumococcus has been isolated from the cerebrospinal

TABLE I—AGE-INCIDENCE OF PNEUMOCOCCAL MENINGITIS

Age-incidence (yr.)	No. of patients	
0–1	13	15 aged less than 2 years
1–2	2	
2–20	0	
20–30	2	16 aged more than 20
30–40	5	
40–50	1	
50–60	4	
60 or more	4	
Total	31	

fluid (C.S.F.) and typed. The period covered is from 1944 to 1950. Of the 31 patients 30 received intrathecal as well as intramuscular penicillin; 27 received sulphonamides also; 7 received the appropriate antiserum; 2 were given aureomycin; and 1 received streptomycin in addition to penicillin. In 4 cases simple mastoidectomy was also performed. This combined therapy makes it impossible to assess statistically the value of penicillin therapy alone. Jackson (1950) indicates the superiority of combined therapy; and Waring and Weinstein (1948), from an analysis of the literature, suggest that it is of greater value.

In the present series there were 3 deaths and a recovery-rate of 90%. The 3 deaths took place within twenty-four hours of the start of treatment, and if such cases were excluded, as was done by Smith et al. (1946), the recovery-rate would be 100%. If this is compared with the cure-rate of 43% where penicillin alone was used and that of 62% where combined therapy was used (Waring and Weinstein 1948), it can be concluded that every effective therapeutic measure should be used in the treatment of this severe infection.

CLINICAL AND BACTERIOLOGICAL FINDINGS

Table I shows that half the patients were under two years old, and the rest over twenty. This preponderance in the first two years of life is well recognised as a reflection of the frequency of middle-ear disease at that age. It is therefore surprising to note that only 1 of the 15 children had attributable ear disease, compared with 7 of the 16 adults.

TABLE II—ORIGIN OF PNEUMOCOCCAL MENINGITIS

Origin of infection	No. of cases
Respiratory Tract:	
Bronchopneumonia	7
Upper respiratory tract	5
Nasal septectomy	2
Nasal polypectomy	1
Trauma to posterior pharyngeal wall	1
Total	16 (*50%*)
Ear	8 (*26%*)
Sinus	2 *
Primary	5 (*16%*)
Total	31

* One case due to multiple face and skull fractures.

Length of Illness before Admission to Hospital

In 1 case the illness began when the patient was already in hospital recovering from nasal septectomy. At the other extreme, 1 patient was not admitted until six days after the onset. On the average the interval between onset and admission was two days.

Origin of Infection

In half the cases the respiratory tract harboured the infecting organism (table II). Aural infection was the origin in 8 (26%) of the cases; and, surprisingly, only 1 of these 8 patients was a child, though the series contained equal numbers of children and adults. The 5 cases of primary pneumococcal meningitis represent a fairly large proportion (16%) in which an original focus of infection was excluded beyond reasonable doubt.

Pneumococcal Types

The serological typing of pneumococci shows a wide scatter (table III), but, in accord with previous reports, half of them are seen to belong to the first eight types. In 1 case the type was established as that of type 1 by a polysaccharide precipitation test of the C.S.F. This was the only case in which the actual offending pneumococcus was not isolated.

Blood-cultures

Blood-cultures were made in 27 of the 31 cases, and a pneumococcus of the same type as in the C.S.F. was recovered in 11 cases (41%). Of these 11 cases in which a septicæmia was demonstrable, positive cultures of the same type of pneumococcus were also obtained from the nose, throat, ear, or mastoid in 9 cases (table IV). These 9 cases thus yielded the organism from the original focus, blood, and C.S.F. simultaneously. Only 1 of these 9 patients died—a male diabetic, aged 53, with bilateral bronchopneumonia *and bilateral otitis media.* Type-2 pneumococci were isolated from his upper respiratory tract, left ear, blood, and C.S.F. He died after his initial dose of penicillin.

TABLE III—SEROLOGICAL TYPES OF PNEUMOCOCCI ISOLATED

Serological type	No. of children	No. of adults
1	2	2*
2	—	1
3	—	3
4	2	2
5	—	—
6	1	—
7	1	1
8	—	1
9	3	1
10	1	1
12	1	—
14	2	—
19	—	1
20	1	1
21	—	1
23	—	1
34	1	—

* One type determined by polysaccharide precipitation test.

Return to Normal Temperature

In the 28 recoveries the temperature returned to normal and stayed normal on about the eighth day in hospital. This figure did not change during the years, despite the increasing dose of penicillin.

PENICILLIN THERAPY

During 1944–50 the dosage of intramuscular penicillin altered considerably, climbing steadily from the average of 200,000 units daily in 1944–45 to 1,600,000 units daily in 1950 (table V). The average length of treatment did not alter; it remained fifteen days throughout these years. Intrathecal penicillin was given for an average of seven days, with daily injections of 15,000–50,000 units, usually about 25,000 units. The intrathecal dose remained steady throughout the years and did not follow the climbing intramuscular dosage. Infants tolerated the intrathecal dose of 50,000 units of penicillin with no ill effects, and there were no residual neurological lesions.

It seems that the dangers of intrathecal penicillin have been overemphasised in the literature: in

TABLE IV—RELATION OF BLOOD-CULTURES TO OTHER CULTURES

Blood-culture	Nose and throat positive	Ear and mastoid positive
Positive *	8	1
Negative	3	1

* Altogether there were 11 positive blood-cultures. The 2 positive blood-cultures not recorded here had negative nose and ear cultures.

so serious a disease early sterilisation of the C.S.F. outweighs any doubtful complications due to penicillin. In this series early sterilisation of the C.S.F. was accomplished in 27 of the 28 recoveries. In 23 of the cases pneumococci were not recoverable from the C.S.F. at the second lumbar puncture twenty-four hours after admission, whereas in 4 other cases sterilisation of the C.S.F. was accomplished within forty-eight hours of admission.

In the 1 case in which positive C.S.F. cultures persisted for a month the C.S.F. culture reverted to positive on each of three occasions in which the intrathecal penicillin was stopped (see figure).

Enough reports on the treatment of pneumococcal meningitis have been published to show two grossly divergent views on the use of intrathecal penicillin. Advocates of only intramuscular penicillin emphasise the toxic reactions to intrathecal penicillin; many such examples have been published. But in the present series there were no toxic reactions, even when 50,000 units were given intrathecally to infants under two years old. The crystalline preparations of today need give no anxiety to the clinician compared with the anxieties of the undertreated case.

Dowling et al. (1949) considered intrathecal injections unnecessary if massive intramuscular therapy is maintained. Using 1,000,000 units of penicillin every two hours they reported a fatality-rate of 36%, excluding patients who died within twenty-four hours.

Compare with this the results obtained with the use of intrathecal plus intramuscular penicillin. Smith et al. (1946) reduced their mortality-rate to 10%. They emphasised the value of free access of adequate penicillin to all parts of the C.S.F. pathways, and its maintenance there for an adequate length of time. It has been said that their results are not representative, because most of their patients were adults and treated by a highly skilled team. Such criticism cannot be levelled against the present series, in which half the patients were under two years old, and none was admitted to a special neurosurgical unit. Even so, the recovery-rate is 100%.

TABLE V—INCREASE OF DAILY INTRAMUSCULAR PENICILLIN DOSAGE THROUGH THE YEARS

Year	Dosage (units)
1944 1945	200,000
1946	600,000
1947	700,000
1948	800,000
1949	1,500,000
1950	1,600,000

The controversy about intrathecal penicillin may be summarised as follows:

(1) The results of therapy in cases treated with intramuscular penicillin only have not surpassed the results in the present series.

(2) No damage to the central nervous system from intrathecal penicillin has been observed in the present series.

(3) Intrathecal penicillin can exert a beneficial effect on meningitis.

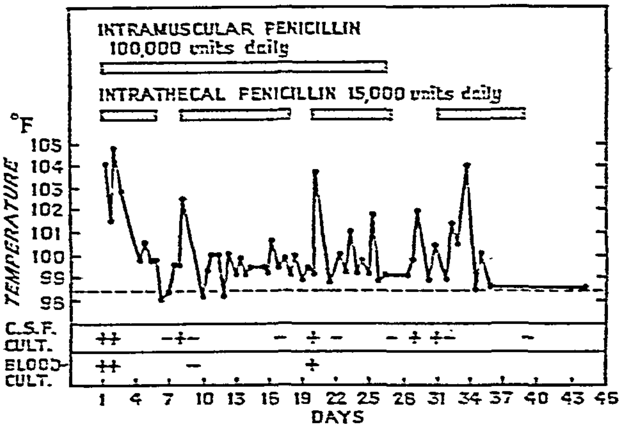

Chart of woman, aged 61, with type-9 pneumococcal meningitis following pneumonia of left lower lobe, showing that, whenever intrathecal penicillin was withheld, C.S.F. cultures reverted to positive.

For pneumococcal meningitis it is recommended that intramuscular penicillin be given in a dose of 2,000,000–4,000,000 units daily for two weeks, and that intrathecal penicillin in doses not to exceed 25,000 units dissolved in 10 ml. of physiological saline solution be given daily until definite improvement is noted. The preliminary observations of Lepper and Dowling (1951) suggest that the addition of aureomycin to this regimen increases the mortality-rate; so this combination is probably contraindicated. These workers treated alternate cases with penicillin and with penicillin plus aureomycin. Their mortality-rate in the penicillin-treated group was 30%, compared with 79% in the penicillin-aureomycin group. Further, recovery seemed to be slower in the penicillin-aureomycin group, as judged by the return of temperature to normal and by decrease in the number of leucocytes in the C.S.F. Since aureomycin alone can cure pneumococcal meningitis, it is probable that penicillin and aureomycin are mutually antagonistic in combination. This may well be a function of the differing modes of action of the two drugs, penicillin being bactericidal, whereas aureomycin is chiefly bacteriostatic.

DEATHS AND COMPLICATIONS

As already stated, there were 3 deaths.

In the case already described, meningitis complicated bilateral bronchopneumonia and otitis media in a diabetic. He died after the initial penicillin injection, and so cannot really be called a penicillin failure. He would probably have died in any case.

Another patient who died was a woman of 39, whose meningitis complicated severe injuries sustained in an automobile accident. There were multiple fractures of the skull and face, and there was serosanguinous discharge from eyes and nose. She died twenty-four hours after admission.

The third death was that of an infant aged 10 weeks, who died sixteen hours after admission. His meningitis followed an infection of the upper respiratory tract.

In the 28 patients who recovered there were no complications from either the meningitis or the penicillin. In 4 cases a simple mastoidectomy was done, in each case within three days of admission.

SUMMARY

In 1944–50, 31 cases of proven pneumococcal meningitis were treated with penicillin at the Presbyterian Hospital, New York. In 5 cases the pneumococcal meningitis was primary.

The daily dosage of intramuscular penicillin increased from 200,000 to 1,600,000 units.

The value of intrathecal penicillin is emphasised.

If 3 deaths within twenty-four hours of the start of treatment are excluded, the recovery-rate was 100%.

We are indebted to Dr. Yale Kneeland, jun., and to Dr. H. M. Rose for their helpful advice, and to Dr. D. Larson for performing the polysaccharide precipitation test.

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GOWN FOR INCONTINENT PATIENTS

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ALL enlightened hospitals aim at keeping their elderly patients active as far as possible, but a few who are too weak or apathetic even to sit up in a chair must spend their days lying motionless in bed, doubly incontinent and having to be fed. Each of these irremediably bedridden patients constitutes a serious nursing problem; some of them develop the habit of contaminating their hands with their excreta, and this may necessitate a complete change of bed-linen several times a day.

A simple modification of the ordinary hospital nightgown has been devised to prevent these patients' hands becoming soiled. The gown is easy to make and to fix; it can be laundered with the rest of the bed-linen; it keeps the patient warmer than the short gown that incontinent people usually wear in hospital; and it does not alter the appearance of the bed. It allows the patient to move the arms freely and to be propped up in bed when necessary. The object is not to restrain bodily movement but to prevent access of the patient's hands to the perineum. The gown is put forward as a useful development in nursing management and not as a substitute for full collaboration between nurse, doctor, and physiotherapist in the task of rehabilitation, which is the best approach to the problem of incontinence.

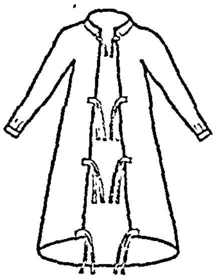

Fig. 1—Modified gown, showing position of tapes.

DESCRIPTION

A very large and strong long gown, with long sleeves, is opened completely down the front and its edges hemmed. Tapes are attached to tie at the neck 1½ in. below the usual neck-line and at three points on each side of this new opening (fig. 1). The gown is put on back to front, over the usual short gown. The top tapes are then tied behind the neck, but the rest of the gown is spread out over the patient, and the other three pairs of tapes are tied to the bedstead on each side, the first of these being high enough to prevent the patient inserting an arm below the gown (fig. 2). The lower edge of the gown should extend well below the knees. Finally, the patient is covered with sheet and blankets in the usual way.

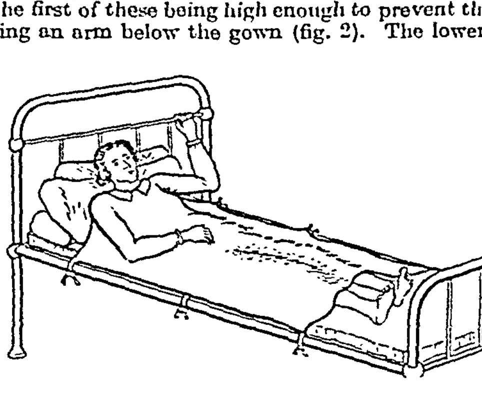

Fig. 2—How the gown is worn in bed.

No difficulties have been encountered in the use of this gown. It makes the patient feel much warmer as well as keeping the hands clean. It is also an exceedingly useful adjunct to the Brocklehurst bed (Brocklehurst 1951), designed for the same type of patient.

We are grateful for the encouragement and advice of Prof. Stanley Alstead.

REFERENCE

Brocklehurst, J. C. (1951) Incontinence in Old People. Edinburgh.

Preliminary Communication

THE BACTERIOLOGY OF CHRONIC BRONCHITIS

PERHAPS the most striking feature of the published reports on the bacteriology of chronic bronchitis is the great variety of organisms that can be isolated from th sputum in this disease, as described, for example, b Marshall[1] and Southwell.[2] In fact it seems true to say tha all the organisms commonly found in the upper respirator tract are frequent inhabitants of the bronchi in chroni bronchitis. In addition to noting this variety of organisms, Howell [3] pointed out that the predominant organis in any given case of chronic bronchitis may sho considerable variations over comparatively short interval of time. For example, *Neisseria catarrhalis* might predominate in the sputum of a patient on one occasio while a week or two later the predominant organis might have changed to, say, Friedländer's bacillus, whic in turn might be superseded later by the origina *N. catarrhalis* or even by some other organism. Th purpose of this communication is to draw attention to a phenomenon which has come to light as a result of a investigation into the variations described by Howell.

It seemed possible that the apparent variations in th predominant organisms might in fact be due to irregula distribution of the organisms throughout the sputum so that if single cultures only were made the predominan organism might well be determined largely by chanc according to the portion of sputum cultured. *Preliminary* investigations showed that in many cases the distribution of organisms in the sputum was in fact far from regular, and a more detailed study has indicated that the organisms that are distributed most irregularly are those which often seem to be responsible for the infective element of the disease.

VARIATION IN THE DISTRIBUTION OF ORGANISMS WITHIN A SINGLE SPECIMEN OF SPUTUM IN CHRONIC BRONCHITIS

Culture no.	Pus or mucus	Percentage of colonies in each culture			
		H. influenzæ	*Strep. viridans*	Non-hæmolytic strepto-coccus	*N. catarrhalis*
1	P	99	1	0	0
2	P	0	50	45	5
3	P	99	1	0	0
4	P	0	56	24	20
5	M	0	79	19	2

DIFFERENTIAL COLONY COUNTING

In order to determine the amount of variation in the distribution of organisms within a specimen of sputum, a system of "differential colony counting" has been developed. This is applied to cultures made from several different parts of the sputum, the parts being selected by a random sampling method. The relative numbers of the colonies of each type of bacterium present are determined by counting a total of 300 to 500 colonies on each culture plate. The counting is simplified by using a modification of an electric counter devised by Dr. W. D. Linsell. This counter and full details of the counting technique will be described elsewhere.

Initially cultures were made from some thirty parts of each sputum specimen, but it has been shown that, with the random sampling technique employed, this number may be reduced to five. Findings for a single specimen of sputum in which extreme variations are present are shown in the table. This specimen consisted of about 1 ml. of mucus with a lump of pus embedded in it. It was washed in physiological saline solution before cultures were made, in order to minimise risk of salivary contamination. It may be concluded, therefore, that no explanation other than uneven distribution of the organisms within the sputum itself can account for the variations observed.

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[1] Marshall, G. *Practitioner*, 1931, *126*, 59.
[2] Southwell, N. *Brit. J. industr. Med.* 1946, *3*, 75.
[3] Howell, T. H. Chronic Bronchitis. London, 1951; p. 61.

RESULTS

Sputa from 44 cases of chronic bronchitis have now been investigated by this technique; and detailed results will be published in due course. The following is a summary of the main findings:

(1) The organisms which show the most frequent and startling variations are *Hæmophilus influenzæ* and the pneumococcus. Variations have also been observed with *Staphylococcus aureus*. In some cases, especially those with more acute infections, these organisms may be distributed evenly throughout the sputum.

(2) The variations are not necessarily related to the presence or absence of pus. The table shows the results of four cultures from purulent parts of one specimen of sputum. *H. influenzæ* was present in only two cultures. In other mucopurulent sputa this organism has been found in large numbers in cultures from some of the mucoid parts and has been absent from purulent parts.

(3) The relative numbers of such organisms as *Streptococcus viridans*, non-hæmolytic streptococci, and *N. catarrhalis* throughout any specimen of sputum are fairly constant, suggesting that these organisms have colonised the bronchial tree in a regular manner. This constancy is usually also apparent if comparisons are made between consecutively produced specimens of sputum or specimens obtained on consecutive days, whereas the appearance of *H. influenzæ* and pneumococci may be quite irregular in different sputum samples. The relative proportions of the "stable flora" reflect closely those of the same organisms in cultures of throat swabs from the same patient.

EFFECT OF CHEMOTHERAPY

In addition to the purely bacteriological studies, the clinical and bacteriological response to chemotherapy in 6 patients with chronic bronchitis has now been studied in detail. In all cases the sputum contained a mixture of several different organisms. In 4 cases *H. influenzæ* or pneumococci or both organisms were present, each showing a considerable degree of variation in its distribution in the sputum. In the remaining 2 cases *H. influenzæ* was distributed evenly throughout the sputum. Chemotherapy designed to eliminate these two organisms produced a significant improvement in each case, even though the stable flora—e.g., *Strep. viridans* and non-hæmolytic streptococci—remained unchanged or returned soon after treatment was stopped. In those patients who later relapsed it was found that *H. influenzæ* or pneumococci had reappeared in the sputum. It seems likely, therefore, that these two organisms will prove to be the most important pathogens in chronic bronchitis with secondary infection.

FURTHER WORK

Studies of this kind are continuing in order to establish which organisms are of importance and which may be ignored in the chemotherapy of chronic bronchitis. In routine bacteriological laboratories the need is also apparent for a method of liquefying sputum without destruction of the organisms it contains, so that a homogeneous suspension can be obtained from which only one culture need be made. Such a method has been developed, and is at present being tested in this laboratory by Mr. G. A. Rawlins, who will report on his work in due course.

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M.D. Camb.
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Medical Societies

ROYAL SOCIETY OF MEDICINE

Chronic Otitis Media

THE section of otology of the Royal Society of Medicine, under the chairmanship of Air Vice-Marshal E. D. D. DICKSON, president of the section, discussed chronic otitis media at a meeting on Dec. 5.

Mr. F. McGUCKIN said that one of the common misconceptions about chronic otitis media was that it was always secondary to manifest otitis media: this was not always so. A patient would put up with a discharging ear for many years before seeking advice, and we must ask ourselves why he should consult the otologist after, say, fifteen years. What was the main trouble? Was it discharge or deafness or discomfort? The patient should be told as soon as possible of the best results that treatment could achieve. Could he expect a dry ear, a safe ear, an ear with which he could hear, or what? He would be disappointed if he did not know what to expect. He should also know, when an operation was advised, whether it was being done to stop the discharge or to give him a safe ear. Chronic otitis media was always a potentially erosive disease, which might spread locally to the facial nerve or the inner ear, or intracranially. In the latter case the patient was probably "ill," in the former probably not. Mr. McGuckin recognised three categories of chronic suppurative otitis media. The first he called the "accessible" group, in which there was a perforation with an exposed promontory (on the inner wall of the middle ear); in the second, or "inaccessible," group, cholesteatoma or granulations were present; a third group was "uncertain" and carried with it all the hopes of the first group and all the fears of the second. Experience and time were necessary before an ear could be transferred from the uncertain group to one of the other categories. The accessible cases required only minor interference, with mopping of the ear and antibiotics; but the inaccessible ones must be treated by some means that would make them accessible, and this always meant some form of surgery. In long-standing cases surgery included the excision of nutritionally defective tissue, either soft or bony; but operation was only one stage in the treatment, and postoperatively the patient was transferred to the minor-treatment group.

Mr. J. ANGELL JAMES said that chronic otitis media always arose from an acute infection of the middle ear. Three months could be taken as the dividing-line. He also classified his cases into three groups. In the first there was a healed perforation; and syringeing, diving, sudden nose-blowing, and pressure changes should be avoided in these cases. In the second group there was a patent perforation, through which recurrent discharge could occur. Here there was a risk to the inner ear from exposure to noise, and to the middle ear from dust in the external meatus. Any primary focus of infection in the nose should be removed—infected sinuses, deviations of the nasal septum, adenoids, and, rarely, neoplasms in the nasopharynx. The third group had an active discharge, more or less continuous but perhaps with slight remissions. Here the aim must be to preserve function. Again, any primary cause of infection must be removed, the threat of dangerous complications warded off, and steps taken to relieve the pain and discharge.

If an intracranial extension was present, operation would be necessary, and surgery was also indicated in the case of cholesteatosis and polypi. Under these circumstances X-ray examination may help to demonstrate bony destruction. Discussing the cause of polypi, Mr. Angell James said that he had felt for some time that aural polypi may have an allergic basis, but it had not yet been possible to demonstrate an eosinophilic reaction in them. When complications were not imminent and cholesteatosis and polypi were absent, conservative treatment could be adopted. The organisms should be identified and their sensitivity to the antibiotics tested. The appropriate antibiotic was then used, preferably in powder form unless the discharge was very profuse or the meatus stenosed (lactose was a suitable base). Careful toilet was an essential preliminary. A dry ear should now be attained after 90% of mastoid operations, so that we could recommend the operation more often than in the past.

Mr. Gavin Livingstone said that the decision whether to operate or whether to continue with conservative treatment was always a difficult one. Chronic otitis media was common in poorer people, and careful cleansing was very important and should be done daily if possible. But the working man could not easily attend hospital every day, and therefore he rarely came to the otologist until his deafness had increased or complications had arisen. Suction was an ideal method of cleaning the ear, and it should be carried out under skilled supervision; but syringeing could be done by less experienced people. Mr. Livingstone distinguished a further three groups of chronic otitis media. The first was the "safe" ear with a mucoid discharge: the postnasal space must be kept healthy, sinusitis must not be overlooked, and septic foci in the nose and mouth must be removed, particularly bad teeth. The second group he called the "mastoid" group, where the discharge was persistent and unpleasant and the hearing was greatly affected. Infections in the attic formed the third group. Whatever surgery was indicated in chronic otitis media, the guiding factor in each case was the particular pathological lesion present. This must be removed entirely, and the aim must be to produce a safe, hearing, and dry ear.

Air Vice-Marshal Dickson agreed with Mr. Livingstone about the importance of trained people treating these ears. It should not be left to the patient.

Mr. A. Tumarkin discussed the evolution of mastoid surgery, and compared his own operation of permeatal atticotomy with the techniques of Lempert, Popper, and others. He emphasised the association between chronic otitis media and the poorly pneumatised mastoid. He felt that "frustration of pneumatisation" occurred because air was unable to circulate in the pneumatic system. The cause was to be found in the nose—or, more specifically, in nasal catarrh. Chronic nasal catarrh was a disease of the whole upper respiratory tract, and led to blockage of the eustachian tube. Diamant (an otologist) and Dahlberg (a statistician) had recently revived Cheatle's theory which attributed the type of pneumatic system to inherited characters. They denied the importance of environmental factors such as eustachian block. Acceptance of their theory, thought Mr. Tumarkin, would paralyse any further research into this aspect of the problem.

Mr. T. B. Layton thought that all cases of chronic otitis media were due to a primary inflammation. There should be no new cases nowadays. The primary organisms were present for the first six weeks of infection; secondary organisms appeared after eight weeks. The infection was then chronic, and therefore mastoid infection should be cleared up between the sixth and eighth weeks. The three-month borderline which Mr. Angell James had suggested was too long. He agreed with Mr. Tumarkin in doubting the hereditary nature of the dense mastoid, but he felt that failure of pneumatisation was caused by an osteitis resulting from minor non-suppurative attacks of otitis media.

Mr. R. Scott Stevenson thought that too many radical mastoid operations had been done before the first world war. Between the wars we had tended to over-emphasise the importance of conservatism; and he wondered whether we were not now tending to swing again towards too much radical surgery. He agreed with Mr. Livingstone that skilled supervision was the ideal to be aimed at in conservative treatment, but he could not accept Air Vice-Marshal Dickson's suggestion that the patient should never be allowed to carry out his own aural toilet—sometimes he had to.

Mr. S. W. Allinson said that 90% of the children that he saw breathed through their mouths and could not blow their noses gently, one nostril at a time. He thought that many cases of the "catarrhal" type of chronic otitis media would settle down if the patients were taught to do this properly.

Mr. Terence Cawthorne said that 70% of cases of chronic otitis media in children cleared up with regular daily treatment. In the Services, Banham and others had shown that a similar or greater proportion would clear up in this way; and Johnston had shown the same for civilians in factory clinics. Surgery was needed for the 20 or 30% that failed to respond to conservative treatment. Recent work on chronic otitis media had given prominence to the teaching of Cheatle that anatomy determined pathology. All these cases started as acute infections: if the mastoid was cellular, acute mastoiditis resulted; if it was acellular, the infection would "tend to lapse into chronicity."

Mr. McGuckin said that chronic infection might sometimes be discovered by accident and that this insidious type was sometimes missed. Coliform organisms were present in about two-thirds of his cases.

Mr. James agreed with Mr. Tumarkin's views on the acellular mastoid in so far as he was convinced that it was acquired and not inherited. When patients with chronic otitis media were examined radiologically, one was amazed how often there was a cellular mastoid on one side and an acellular one on the other. He believed that there was some inherent characteristic in the lining of the middle-ear cleft which was responsible for pneumatisation. Failure of pneumatisation resulted from acute otitis media and could be compared with the changes sometimes seen in the paranasal sinuses, particularly the maxillary antrum.

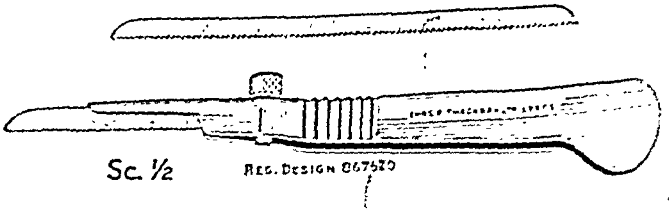
New Inventions

A NEW SURGICAL SAW

There has long been a need for a light-weight general-purpose saw for smooth, easy, and accurate cutting of bone or metal. The saw illustrated can cut bone or steel equally well and uses interchangeable miniature hacksaw blades $^1/_4$ in. wide. These blades cost very little and are available in two types—standard and high-speed steel. The latter are most suitable for sawing stainless steel but are slightly thicker than the standard blades.

The handle is of very simple construction, being made of stainless-steel sheet pressed to a shape which enables it to be held comfortably in the hand. The length of the exposed saw can be easily adjusted by means of the milled-head screw, which clamps the saw blade in position. The blade being reversible, the teeth can be faced to cut on either forward or backward strokes.

The saw was evolved for the accurate shaping and morticing of bone grafts in plastic surgery, where it has been well tried. It should find a wider field of usefulness



in other types of bone surgery, since the blade is always sharp and is not blunted by cutting bone or steel. No special sterilising precautions are necessary.

The saw is made by Chas. F. Thackray Ltd., 10 Park Street, Leeds.

Plastic Surgeon,
Frenchay Hospital,
Bristol

D. C. Bodenham
M.B. Brist., F.R.C.S.E.

Reviews of Books

Hamey the Stranger

John J. Keevil. London: Bles. 1952. Pp. 192. 21s.

The Royal College of Physicians of London owes much to Baldwin Hamey, son of the subject of this book; for he was one of its chief benefactors. He and his father were both confirmed letter-writers; and their letters, mostly in Latin, are in the archives of the college and the University of Leiden. Dr. Keevil, former library keeper of the college, has drawn on these letters in compiling this biography.

Baldwin Hamey the elder—Hamey the Stranger—was born at Bruges in 1568, the year in which Roman Catholic Spain sentenced to death, as heretics, all the inhabitants of the Netherlands. Things became so bad that in 1584, or soon after, the Hamey family migrated to Leiden, where Baldwin received his university education, first in philosophy and letters, and later in medicine. Through the influence of his teacher, Joannes Heurnius, he was appointed, two years after qualifying, as physician to the Czar of Russia; and found himself plunged into a world of murder and intrigue, where the vast figures of Czar Fedor, Boris Godunow, and the rest of the Godunow family moved in a drama much larger than life. Elizabethan England, to which Hamey soon fled with his promised wife, Sarah Oeils, must have seemed tame in comparison; and indeed the book partakes of the anticlimax. His graphic account of the Essex rebellion, and his own courage in various plague, smallpox, and typhus epidemics, stand out; but much space has to be given, unfortunately, to his struggle to persuade the college to examine him and give him an English diploma. It was achieved at last, but not without some undeserved humiliation for him. His son Baldwin, whose life is to form the subject of a second volume, *The Stranger's Son*, became M.D. of both Leiden and Oxford, as well as a fellow of the college.

This first tale is well told and worth reading, and we look forward to the second.

Surgery of the Chest

A Handbook of Operative Surgery. Julian Johnson, M.D., D.SC., professor of surgery, school of medicine and graduate school of medicine, University of Pennsylvania. Charles K. Kirby, M.D., associate professor of surgery, school of medicine, University of Pennsylvania. Chicago: Year Book Publishers. London: Interscience Publishers. 1952. Pp. 387. 68s.

The authors set out to provide an atlas of thoracic operations, and have adopted the general pattern of a page of illustrations to a page of text. The book is straightforward and easy to read and understand, since the illustrations are clear and precise. For anyone likely to become interested in thoracic work it gives a very good idea of the scope of the subject.

Almost every routine thoracic operation is described briefly and illustrated from the technical aspect, and the reader is given the choice of studying the operation of lobectomy in the supine, lateral, and prone positions, with special reference to the important anatomy of the lung root. In addition, such unhappy incidents as hæmorrhage from the aorta are considered, with the appropriate method for dealing with them. There is little to criticise, though it is strange that an elaborate plastic form of treatment should be described for cardiospasm in preference to the more simple Heller's type which is hardly mentioned. These clear descriptions and the apparent simplicity of modern heart operations should not, however, encourage the inexperienced surgeon to embark on them, thinking they are necessarily easy.

There is an attractive lack of pretension about this well-produced and well-illustrated book.

Microbial Growth and its Inhibition

First International Symposium on Chemical Microbiology. World Health Organisation Monograph Series No. 10. Geneva: World Health Organisation. 1952. Pp. 285. 15s.

In June, 1951, an international symposium was held in Rome on chemical microbiology, with particular reference to antibiotics and the various problems concerned with their inhibition of bacterial growth. It was organised by the Instituto Superiore di Sanità in collaboration with the Council for the Coördination of International Congresses of Medical Sciences and the World Health Organisation. The papers, read by leading specialists, have now been published in book form.

They cover a wide range, including the origin and nature of drug-resistance in bacteria, vitamin-B-group substances in bacterial metabolism; the liberation of nucleic acid when cells are heated, penicillin-fermentation, the chemistry of terramycin, antibiotics against fungi and antibiotics as stimulants of animal growth, the biological standardisation of antibiotic preparations, the lag-phase in bacterial growth, and similar subjects. The papers are mostly short reviews of subjects in which the authors were particularly interested, but the references are chosen with discrimination.

Each of the articles thus presents the considered opinion of a well-known authority. They are lucid and easy to read, and so should stimulate those working on chemical microbiology, and inform those not conversant with this field of research.

Refresher Course for General Practitioners

By various authors; reprinted from the *British Medical Journal.* London: British Medical Association. 1952. Pp. 486. 25s.

This volume is a "first collection" of articles which appeared in the *British Medical Journal* under their present title between October, 1949, and December, 1950. Their publication in book form should be welcome to many practitioners, whether or not they read them as they came out. The authors, drawn from many hospitals and teaching centres in London, the provinces, and beyond, have maintained a remarkably high level not only in the content but in the presentation of their matter. The articles are informed, readable and to the point, and well calculated either to supplement the reader's knowledge of the subject or to stimulate him to consider it afresh. They are illustrated where necessary with diagrams and photographs, well reproduced. The subjects of the 55 articles, though all relevant to general practice, cover no defined field and are arranged in no logical order. This makes for easy reading, but the random selection limits the usefulness of the book for reference.

Metabolism of Protein Constituents in the Mammalian Body

S. J. Bach, PH.D., F.R.I.C., department of physiology, University of Bristol. Oxford: Clarendon Press. 1952. Pp. 272. 40s.

In this book Dr. Bach has confined himself to a review of our knowledge of some aspects of the metabolism of alanine, glycine, serine, threonine, valine, leucine, isoleucine, methionine, cysteine, and cystine. There are sections on the formation and reactions in vivo of hæm pigments, bile pigments, porphyrins, uric acid, glutathione, and other metabolites; and an interesting account of cystinuria is included. The nutritional value and use of these amino-acids for glycogen formation are considered, and there is an exhaustive account (about 53 pages) of "biological methylation." On this subject Dr. Bach is evidently a scholar, and his review—including as it does references to pathological consequences, in man and other species, of deficiencies in methylating processes—could hardly be bettered.

In other respects, the book is less satisfactory, for in spite of the many references to original papers the treatment of some subjects is scrappy and inadequate. Thus the account of conjugated bile acids is inaccurate, and would not do for a student's textbook: and Dr. Bach does not mention the recent work of Friedman and Byers on the excretion of uric acid by dalmatian dogs. Again his references to detoxication do not include any to the work, or to the comprehensive review, of R. T. Williams. It is disturbing to find major deficiencies of this kind in a learned monograph.

Nevertheless, the book does contain some valuable surveys, especially of recent work with isotopes, and it should be useful to the biochemist and the (appropriately critical) advanced student.

Précis de Mycologie

M. LANGERON, Chef de la Section de Mycologie de l'Institut de Parasitologie de la Faculté de Médecine de Paris. 2nd ed. Revised and enlarged by R. VANBREUSEGHEM. Paris: Masson. 1952. Pp. 701. Fr. 5400.

THIS book, when first published in 1945, proved so popular with microbiologists, and particularly with medical mycologists, that the edition was quickly exhausted. Work on the second edition, which began immediately, was interrupted by the death of Dr. Langeron in 1950, and it was eventually completed by his former pupil, Dr. Vanbreuseghem.

The new book is in three sections: general mycology, technique, and medical mycology. The section on general mycology, representing the entire original book except for the descriptions of technical methods and a chapter on fungus diseases, has largely been rewritten with many additions; but it retains all those features which made the first edition so valuable. Descriptions of mycological technique, scattered throughout the text in the first edition, have been collected together in a comprehensive section on laboratory methods. The section on fungus diseases by Dr. Vanbreuseghem is entirely new and replaces the single chapter on mycoses in the first edition. In it the diseases are arranged in alphabetical order and the descriptions follow the plan adopted by nearly all textbooks on medical mycology. This section, which makes the book more attractive to the general medical reader, could with advantage be expanded in a future edition.

Anurie bei Chromoproteinurie (Hämolyseniere, Crush-Niere)

HANS U. ZOLLINGER. Stuttgart: Georg Thieme. 1952. Pp. 138. DM. 14.70.

THE author of this monograph has been interested for many years in the problem of the pathogenesis of the renal lesion associated with myolysis or with hæmolysis, primarily from the viewpoint of the pathologist.

In this study, however, he includes a good account of the clinical aspects of this syndrome, dealing briefly with the signs and symptoms and the mechanism involved in their production, the course, and the prognosis. The section on treatment is not so well balanced, dealing mainly with paravertebral block and decapsulation—therapeutic measures now largely abandoned. High-calorie, low-nitrogen diet is mentioned very briefly but without reference to Borst: avoidance of overhydration and electrolyte intolerance is stressed and there is a brief mention of dialysis methods.

It is, however, the sections dealing with the anatomy and pathogenesis of hæmoglobinuric or myoglobinuric nephrosis that the interested reader will find of most value; here Professor Zollinger speaks as an expert. He has surveyed in detail 55 cases of this condition coming to necropsy in Zürich in ten years (from roughly 17,000 necropsies). They include groups with hæmolysis due to mismatched transfusion, bad conservation of blood, or sensitisation; post-transfusion cases associated with pregnancy, operation, or infection; a group due to exogenous hæmolytic agents such as chlorate and soap; a group with muscle necrosis due to crush, carbon monoxide poisoning, or electrical accidents; one case of burns; and a final group of miscellaneous cases. Illustrative case-histories are given. The pathological findings are given in considerable detail and are well illustrated. A full discussion of pathogenesis reviewing the blockage, ischæmic, and toxic theories leads the author to the conclusion that this is a syndrome of multiple factors. There are 486 references, most of which are recent; and, unlike many monographs with large bibliographies, the references are used critically.

This will be standard reading on the subject for a long time.

After-Treatment (4th ed. London. Oxford: Blackwell Scientific Publications. 1952. Pp. 338. 30*s*.).—Mr. H. J. B. Atkins has thoroughly revised this popular book on the care of patients after operations, which he designed for general practitioners, house-officers, ward sisters, and dressers. Methods in surgery change quickly and are often ephemeral; but this book successfully reflects current views and practice, and the author has used discretion, judgment, and experience in presenting his subject. He has deliberately excluded all descriptions of technique—for such things as spinal puncture, the making of plasters, and so on—holding that these practical procedures can only be learnt at the bedside. Though there is much to be said for this point of view, it is nevertheless helpful for a resident to be able to refresh his mind with the important practical details and pitfalls of these small operations. He will need a small practical book to supplement this excellent guide to after-treatment.

Child Health. *The Practitioner Handbooks* (2nd ed. London: Eyre & Spottiswoode. 1952. Pp. 264. 21*s*.).—This, like the first edition, consists of 22 chapters, each written by a different authority, and covers many subjects not dealt with in textbooks of pædiatrics or public health. There is a section on feeding, and a good chapter on the control of common fevers, by Dr. C. M. Smith; but in general the book aims to give an account of the public-health services available in this country, rather than guidance to the practitioner on the application by himself of preventive medicine. For this edition Prof. Alan Moncrieff and Dr. W. A. R. Thomson, the editors have revised all the chapters. No new subjects have been added, however, and it is disappointing to find no mention of the problems of homeless children, which have aroused much interest recently, and which led to the Children Act of 1948. Nevertheless, this is the most up-to-date book on the subject of child health in this country, and it will continue to be a valuable guide to all concerned with the medical care of children.

New Dictionary of Psychology (London: Vision Press & Peter Owen. 1952. Pp. 364. 35*s*.).—He is a brave man who sets out to define psychological terms; so many writers use them with different meanings. This compilation by Philip Lawrence Harriman is useful but far from complete, and too many not so important American psychologists are listed at the expense of other nationalities. One American is listed merely because he was the first that ever burst into print in U.S.A. with *Mental Hygiene* as the title of a book; Lord Kelvin appears as "William Thomson Kelvin" instead of "William Thomson"; and Napoleon is included for opposing phrenology. Moreover some of the definitions sound wholly incorrect to English ears; but this may be due to American usage, for this book has been made and printed in America and had an English title-page stuck on to it. But there can be no such excuse for the statement that *lapsus calami* is a "psychoanalytic term referring to the unconscious wish for a disaster."

Permeability of Natural Membranes (2nd ed. Cambridge: University Press. 1952. Pp. 365. 30*s*.).—The first edition of the book was sold out within a year and it has been accepted as a standard work in its own field. Since 1943, however, there has been a considerable shift of emphasis in our whole way of thinking about the distribution of ions and other substances across natural membranes; the properties of the membranes themselves are less emphasised, and more importance is attached to active processes of ion extrusion which are linked to cell metabolism. Moreover, active cell processes probably prevent any formal thermodynamic equilibrium of the type treated in chapter III. It is obvious from their candid preface to the new edition that Mr. Hugh Davson, D.SC., and Prof. J. F. Danielli, D.SC., the authors, recognise the need for a more complete revision than they have in fact been able to make: "reprinting of this book with a few minor additions" is an accurate description of what has been done. The "minor additions" consist of a paragraph at the end of most of the chapters, giving references to work up to 1950. The book remains an authoritative summary of the older work in this field, but we hope that the authors will not be content to leave it at that, but will proceed to a full discussion of the subject, with a critical survey of the results of isotope studies and the effect of cell metabolism on the distribution of ions.

THE LANCET

LONDON: SATURDAY, DEC. 20, 1952

College of General Practitioners

As a Christmas present this year our profession is to be given a new college. When the suggestion came up, some of us hinted that, having several colleges already, we should prefer something rather different[1]; but Mr. Willink's committee has decided that a good useful College of General Practitioners is what we really need. The committee was a strong one[2]; its decision was unanimous; the college is all wrapped up and waiting for us; and there is therefore no point in thinking any more about possible alternatives. Some of these were theoretically preferable, but it may well be true that nothing short of a college would now serve the purposes that so many of us have at heart. Certainly, in its report published in this week's *British Medical Journal*, the committee has explained very convincingly why the project that failed 107 years ago must now be realised, and it is able to give a clear account of the functions proposed for the new college, of the initial structure, and of the stages by which the founders will gradually transform themselves into a representative academic organisation.

The purpose of the college is to work towards a renaissance of general practice, and its promoters declare that general practitioners, in the future as in the past, ought to be "good doctors practising medicine in their own right." They regard general practice as "fundamentally as important as the specialties."

> The general practitioner, they say, "must be prepared to assume some degree of responsibility in any and every illness, in people of all ages, over long periods of time; he must play his part in preventive medicine; and he must help in many social difficulties. His deliberate aim should be to achieve breadth of vision rather than great depth in any particular sphere. It is from him that patients first seek advice; to him they should have direct and continuous access; it is his duty to coördinate their whole medical care, to ensure that this is of the highest possible quality, to interpret his patients' needs to specialists and hospitals, and to interpret the specialists' opinions back to them. . . . His medical responsibilities are widespread and he must be equal to them; and the social problems with which he has to deal are widespread too."

On this basis, and on the broad definition of a general practitioner as a doctor "who does not limit his practice to a particular field of medicine or surgery," it is held that general practice embraces the work of many doctors in institutions, such as schools, factories, and prisons, and of general-duty officers in various services, military and otherwise. Hence, in selecting its foundation members, the college will be catholic in its range though eclectic in its insistence on experience or enthusiasm and on a financial act of faith. From New Year's day applications for foundation membership will be acceptable from doctors whose names appear in the Medical Register and who have one of the following qualifications:

1. Twenty years in general practice, or its equivalent as a general medical officer (with primary charge of patients) in a school, factory, or other institution, in H.M. Forces, Colonial Medical Service, Merchant Navy, &c.
2. Five years in general practice (or its equivalent) and an undertaking to accept postgraduate instruction for 3 days (or a corresponding number of hours) each year, or for $5^{1}/_{2}$ days every two years.
3. Five years in general practice (or its equivalent) and the possession of a higher postgraduate medical degree or diploma.

For foundation members the entrance fee will be ten guineas. Doctors who have not yet completed five years in general practice, and newly qualified men and women who contemplate entering general practice, are invited to join as foundation associates on payment of one guinea.[3] The foundation council of the college, which will receive these applications, will at first consist of the 10 members of the Willink Committee who are in general practice. In the New Year, after a circular letter has been sent to practitioners who are known or believed to be actively interested, this council will be enlarged to 21 and will proceed to draft provisional by-laws dealing, inter alia, with qualifications for ordinary membership and fellowship of the college. At a general meeting sometime in 1953, at which the by-laws will be presented, it will retire in favour of a new council; and at a second general meeting in 1954 the whole council will again retire and the constitution and by-laws will once more be re-examined.

So much for the machinery: what is the college going to be and do? It is to be "the headquarters of general practice in Great Britain"; it is to be "academic and educational, not political"; and, in supplementing (not competing with) the work of existing bodies, it is to provide "leadership of practitioners by practitioners." This leadership is to be both central and peripheral, and "one of the early duties of the college will be to establish regional faculties in the university cities and other large centres of population." In seeking the development of general practice on suitable lines it will consider and correlate the conclusions and proposals of the various committees and bodies that have concerned themselves with general practice and will plan and pursue an agreed policy. This will include encouragement of (1) the entry of practitioners into hospitals for more consultation and closer contact with specialists, (2) the restoration or establishment of general-practitioner beds where this is for the benefit of patients, and (3) direct access for all practitioners to laboratory and radiographic facilities; and the college will want its members to play their part in the development of health centres and clinics. Emphasis is rightly laid on the need to give medical students more understanding of practice, and it is thought that more liaisons could be arranged between medical schools and individual practitioners, on the lines of what has already been done successfully in several places.[4] To doctors newly entering practice advice on equipment might usefully be offered: "young men and women will be able to come to the college for help—perhaps as associates in their postgraduate year—to an academic home of their own, with a staff specially interested and experienced in their problems." The college might also have a contribution to make over trainee assistantships; and it would of course want to play a big part, with the universities and the British Postgraduate Medical Federation, in the arrangement of lectures and refresher courses for doctors established in practice, as well as perhaps sponsoring special lectures and exchanges of visits with colleagues overseas. The report pays close attention also to the possibilities of research by practitioners and speaks of a college research organisation which could aid individual doctors and study groups by advice or analysis of data: "ideas which arise from the problems of practitioners in their surgeries and in their patients' homes will, perhaps, become the inspiration of important and widespread investigations." In concluding their account of the functions that need to be performed, the writers add a statement on examinations, hypothetical and actual:

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[1] *Lancet*, 1951, ii, 1071.

[2] The members were: The Rt. Hon. Henry Willink, Q.C. (chairman); Dr. G. F. Abercrombie; Prof. Ian Aird, F.R.C.S.; Dr. G. O. Barber; Mr. John Beattie, F.R.C.O.G.; Dr. D. M. Hughes; Dr. J. H. Hunt (hon. secretary); Sir Wilson Jameson, F.R.C.P.; Prof. J. M. Mackintosh, F.R.C.P.; Sir Heneage Ogilvie, F.R.C.S.; Dr. R. J. F. H. Pinsent; Dr. A. Talbot Rogers; Dr. F. M. Rose; Dr. Richard Scott; Dr. J. D. Simpson; and Dr. J. C. Young.

[3] Forms of application for foundation membership and associateship may be had from the secretary of the College of General Practitioners at 14, Black Friars Lane, Queen Victoria Street, London, E.C.4. The Society of Apothecaries is allowing the college the use of this address and has also offered accommodation for meetings.

> "A college should be able, before long, to improve the quality—the art and the skill—of general practice by setting a high standard and by encouraging and helping general practitioners to reach and maintain it, in the same way that the Royal Colleges have raised and maintained the standard of specialised practice. If, in the course of time, a diploma is to be granted by a College of General Practitioners it will in no way interfere with the present qualifying examinations. For those who have been long in practice it will probably be obtainable by election; but if for younger men and women an examination is to be held, later on, this will be in breadth rather than in depth, and only in those subjects which are of particular interest and importance to general practitioners in their daily work. It will always be only one of several portals of entry into the college."

Meanwhile it is believed that the very existence of a college will raise the status and enhance the prestige of the general practitioner among medical students, specialists, and the public.

We share that belief. At the same time it seems right to say that Mr. WILLINK and his associates would have made an even stronger case for their college had they emphasised the remoteness of much of present-day practice from what they lay down as ideal. In admiring their summary of what a family doctor should be, it would be wrong to forget that, as the years of this century have gone by, fewer and fewer practitioners have managed to coördinate the whole medical care of individual patients, let alone families. No doubt it is for diplomatic reasons that the list of 167 references excludes the Collings report,[5] but the main conclusion of that major document is among the strongest arguments in favour of what is now being undertaken. "The over-all state of general practice," said Dr. COLLINGS, "is bad and still deteriorating. The deterioration will continue until such time as the province and function of the general practitioner is clearly defined, objective standards of practice are established, and steps are taken to see that these standards are attained and maintained." The practitioner of today, COLLINGS held, is living *on* the tradition of the 19th-century family doctor; but, except in a minority of practices—most of them in the countryside—he has ceased either to be, or to follow the ideal of, the family doctor. All observers agree that this process has been going on for a very long time, and those of us who seriously want it to be reversed must be deeply thankful to see at last the beginning of a movement within the profession which may prove capable of reversing it. Only from within the profession can this sort of salvation begin; for it is simply not true that all our failures to do the best possible work arise from inevitable circumstance or the errors of politicians. In their penetrating study of the present situation of the profession, LEWIS and MAUDE[6] say bluntly:

> ". . . too many doctors are using the difficulties of the N.H.S. as an excuse for their own unwillingness to render the devoted service which a true profession demands of its practitioners. There are too many doctors who, without the excuse of an excessive list of patients, still rush through their cases with a minimum of time and trouble. There is not, despite all the superficial excuses which are adduced, the slightest real justification for being content to receive sick patients, year after year, in dirty and untidy consulting-rooms. . . . Finally, a doctor who acquiesces in a general agreement to pass on *all* but the simplest routine cases to a *hospital or a* specialist is deliberately leaving unused, and therefore allowing to decay, most of the fruits of a long and intensive training; he is wasting time and public money."

As the Willink Committee truly remark, "if a doctor is discouraged, there is no branch of medicine in which he can deteriorate more rapidly"; and no task is more urgent than to tackle the discouragement evident in so many practitioners and the sources from which it springs. The backing of all of us is needed for what the founders of this new college rightly term their "sincere attempt . . . to improve the efficiency and good name of general practice." We regard the foundation of the college as a powerful psychological fillip for a group of men and women too many of whom have lost heart; and we hope the day will soon come when the specialist will be spared the embarrassment of hearing some equally able colleague describe himself as "only a G.P." Specialist and practitioner alike, we shall do well to keep in mind always LEWIS and MAUDE's conclusion that the main strength of the profession lies in "the confidence of ordinary folk in the doctor's surgery."

Hepatitis

OUR knowledge of the viruses which affect man is still rudimentary; and we know particularly little about virus carriers. The new technique of tissue culture of the poliomyelitis virus has given new zest to work on this disease. Unfortunately this technique is not practicable with hepatitis viruses. These viruses probably multiply in fertile hen's eggs; but they do not give rise to pathognomonic lesions in them, nor do they reproduce themselves in sufficient quantity to provide an antigen for serological tests. The only way to be certain that the virus has grown in the eggs or is present in any form in man and his environment is to inoculate other people with the suspected material. Much can be learnt, however, from accurate observation of the behaviour of the disease, as CAPPS and his colleagues[7] [8] in Chicago have lately shown.

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[4] *Lancet*, 1952, i, 495; *Ibid*, Aug. 30, 1952, p. 415.

[5] Collings, J. S. *Ibid*, 1950, i, 555.

[6] Lewis, R., Maude, A. Professional People. London: Phoenix House. 1952. Pp. 284. 15s.

[7] Capps, R. B., Bennett, A. M., Stokes, J. *Arch. intern. Med.* 1952, 89, 6.

[8] Bennett, A. M., Capps, R. B., Drake, M. E., Ettinger, R. A., Mills, E. H., Stokes, J. *Ibid*, 90, 37.

Asked to investigate jaundice in some nurses in an orphanage for infants and children under 3 years of age, they found that hepatitis had been endemic among the nurses for ten years, during which time 72 cases had been recognised. The source of their infection proved to be the infants and children in whom jaundice did not appear and hepatitis was not suspected.[8] Most of the affected nurses had been on duty on certain floors of the institution; and the clinical disease ceased to appear among them a few months after proper arrangements had been made for hand-washing and instructions given on personal hygiene and cleanliness. CAPPS and his associates [2] agree that in infants and young children the clinical picture of infectious hepatitis is relatively non-specific, and only those with clearly positive reactions to at least three different liver-function tests for four weeks or longer were accepted as having the disease; in most cases lassitude, gastro-intestinal disturbances, and hepatomegaly were also present. The validity of the diagnosis was thought to be confirmed by a positive result with a skin-test antigen made from infectious hepatitis virus grown in fertile hen's egg and inactivated by ultraviolet light.[9] Of 42 children who had a clinically recognised illness during twenty-two months of study, only 1 developed bilirubinæmia. The American workers admit they were applying strict criteria, and a very large number of other children classed as doubtful or asymptomatic showed some positive reactions for hepatitis. Isolation of suspected children had no effect in controlling the spread of the disease, presumably because so many infections were not clinically detectable at the onset; also some infants were incubating the disease when admitted. In over one-third of the children with clinical disease symptoms persisted for several months, and in these a positive skin test developed late—another example of tardy immunity to virus infection in very young people. The virus was recovered from the stools of 2 children who had been ill for five and fifteen months. CAPPS and his colleagues suggest that these 2 children were carrying the virus all this time; but reinfection or recent ingestion of the virus might have occurred in this orphanage. The minimum incubation period seemed to be 11–12 days—a shorter period than that usually reckoned for adults. Whether persistent infections with infectious hepatitis virus in childhood are common is still uncertain; but CAPPS et al.[7] raise the question whether the syndrome of infantile diarrhœa may occasionally be produced by this virus. In April, 1950, an epidemic of "infantile diarrhœa" broke out in the institution. Of the 14 affected infants, 12 gave positive skin tests two to three weeks after the onset of this illness (no tests were made before the onset).

Should an epidemic among infants and children be terminated? Perhaps it is well that they should develop immunity in early life if the disease is harmless to them; but can we be sure of this—especially in those with persistent symptoms. Several workers have described severe infectious hepatitis in young children. WYLIE and EDMUNDS,[10] for example, reported that of 12 cases in a London children's hospital, 2 had a delayed recovery, 4 had compensated cirrhosis, and 6 died eleven days to five years after onset with acute yellow atrophy or subacute necrosis plus multiple nodular hyperplasia. Several years ago STOKES and NEEFE [11] and HAVENS and PAUL [12] showed that gamma-globulin could be used to stop epidemics of infectious hepatitis in communities of children, and more recently STOKES et al.[13] have reported observations suggesting that, by some mechanism not yet understood, a single dose of gamma-globulin gave protection for five to nine months despite continued intimate exposure to continuing cases in uninoculated contacts.

When these methods fail, what have we to offer to the patient, young or old, to aid rapid recovery and prevent chronic hepatitis? Most clinicians agree that at present the best they can advise is bed rest and a palatable diet, with plenty of protein and carbohydrate and such fat as the patient can tolerate (though some think that there is a tendency to overwork the tired liver with too much protein). The new antibiotics do not appear to affect the acute process; but possibly in some instances coma or chronic hepatic disease may be controlled by inactivating the intestinal flora. Every new vitamin has been advocated in turn, and B_{12} is no exception. In a rough comparison between one diet with high protein, high carbohydrate, and moderate fat content, supplemented by multiple vitamins and brewer's yeast, and a second diet with high protein, high carbohydrate, and moderate fat content and the addition of 30 µg. of vitamin B_{12} by mouth for five days, the latter seemed to promote a more rapid return to normal appetite and liver size.[14] Further trial should perhaps be made of vitamin B_{12}, and also of cortisone and A.C.T.H.[15] which are known to increase appetite and consequently deposition of glycogen in the liver.

Radium Poisoning

THE dangers of ingesting radium or mesothorium are now recognised. This was not always so; and for a time after the first world war these substances were sometimes treated with a casualness that in retrospect seems shocking. 30 of the survivors from that light-hearted time have been sought out by a distinguished team from Boston and New York who describe in great detail the condition of these patients.[16] Now that the few radioactive elements found in the earth's crust are being supplemented by man-made materials, it is important to chronicle all the information that can be gathered about the long-term effects of radiation on the body.

A few of the patients in this American study were chemists or physicists working with radium or mesothorium; but most were engaged, in girlhood, in painting luminous dials. The risks of this occupation were made clear by H. S. MARTLAND as long ago as 1925. Luminous paint consists of zinc sulphide and a source of alpha particles, which may be either radium or mesothorium or a mixture of the two. Alpha particles striking the zinc sulphide emit flashes of light—a principle now used in scintillation counters for detecting and measuring sources of radioactivity. The mixture was applied to the dial by a paint-brush; and in order to obtain a fine point the girls used to moisten the brush between their lips, thereby ingesting substantial amounts of the radioactive material. In other instances radium or radium-mesothorium mixtures were taken medicinally. 5 patients in the series had consumed commercial nostrums containing radium and mesothorium, for the relief of such varied complaints as backache, low blood-pressure, arthritis, and thyrotoxicosis. Others had been given supposedly pure radium by injection as treatment for arthritis or lymphadenoma, or to aid recovery from pneumonia. Whatever the source, the material absorbed usually consisted of a mixture of radium and mesothorium, in proportions difficult to determine retrospectively. These two isotopes are treated identically by the body; but their decay products behave very differently. Radium, like calcium and strontium, is deposited in the inorganic lattice of bone. Its decay products also remain in the inorganic lattice, apart from the gas, radon, which is excreted in the breath (thereby providing the best method of diagnosing radium poisoning). Mesothorium, too, is deposited in the inorganic lattice of bone; but one of its decay products, radiothorium, tends to settle in the organic matrix of bone and possibly also in the soft tissues. This is especially dangerous since the alpha particles are then in a position to do more damage than they could, with their very limited range of action, when locked up in the less active parts of bone. Moreover, each atom of mesothorium retained in the body gives off, by successive transmutation, five alpha particles—about twice as many as the average for each fixed radium atom. Ingenious physical tests have shown the presence of mesothorium in patients previously thought to have been suffering from pure radium poisoning.

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[9] Henle, G., Drake, M., Henle, W., Stokes, J. *Proc. Soc. exp. Biol., N.Y.* 1950, 73, 603.

[10] Wylie, W. G., Edmunds, M. E. *Lancet*, 1949, ii, 553.

[11] Stokes, J., Neefe, J. R. *J. Amer. med. Ass.* 1945, 127, 144.

[12] Havens, W. P., Paul, J. *Ibid*, 129, 270.

[13] Stokes, J., Farquhar, J. A., Drake, M. E., Capps, R. B., Ward, C. S., Kitts, A. W. *Ibid*, 1951, 147, 714.

[14] Campbell, R. E., Print, F. W. *Amer. J. med. Sci.* 1952, 224, 252.

[15] Rifkin, H., Mark, L. J., Hammerman, D. J., Blumenthal, M. J., Weiss, A., Weingarten, B. *Arch. intern. Med.* 1952, 89, 32.

[16] Aub, J. C., Evans, R. D., Hempelmann, L. H., Martland, H. S. *Medicine, Baltimore*, 1952, 31, 221.

The clinical effects of radium-mesothorium poisoning are now reasonably well understood. The girls using the luminous paint remained free of symptoms until they had been working for one or more years; and symptoms might not appear until one to seven years after the last contact with the paint. The early manifestations were of two types: on the one hand rapid dental decay, followed by loss of teeth and necrosis of the jaw; and on the other hand progressive anæmia with leucopenia and thrombocytopenia. Those who escaped the anæmia, which was always lethal, were liable to the late consequences of having radioactive substances fixed in the bones. These again were of two types: either localised areas of necrosis in any of the bones, often with pathological fractures; or malignant tumours, derived either from the elements of bone (osteogenic sarcoma) or from neighbouring tissues (carcinoma of the nasal sinuses, fibrosarcoma of joints). The bone necroses have not themselves proved fatal, and there is even some indication that partial recovery may occur with time; all the late deaths have been due to malignant tumours. The syndrome of radium-mesothorium poisoning clearly depends on the chemical nature of the elements, which determines the localisation in bones, and on the type of radiation, which determines the amount of damage. Alpha particles, being most easily arrested in the tissues, do most damage per unit of radiation. The radium-mesothorium syndrome may be contrasted with the effects of an atomic-bomb explosion—although this would be complicated by the effects of blast and heat. HEMPELMANN et al.[17] have described what happened to 10 people who were accidentally exposed some years ago to a short intense outburst of fast neutrons and gamma radiation. About a week after exposure those affected developed severe constitutional symptoms with high fever, loss of weight, and gastro-intestinal disturbances; in addition there was gross damage to the more exposed areas of skin. One survivor developed bilateral cataracts three to five years after exposure. In those most severely affected all elements of the peripheral blood were impaired. The neutron bombardment induced radioactivity in elements already present in the body; but this induced radioactivity was thought to be insufficient to cause symptoms.

Exposure to external sources of radiation clearly has quite different effects from exposure to radioactive materials within the body. Basically radiations seem to act on tissues always in much the same way—by arresting mitosis they kill cells—but the clinical picture is diverse, since there are so many variables. Clinicians must be alert to the possibility of radiation damage in patients with unusual syndromes who have been exposed—even in the distant past—to radioactive materials.

Annotations

NO JUNIOR STAFF

To be fruitful the human mind must have time to pause and think. In England now we live lives in which there is little pausing and presumably less thinking. Routine housekeeping chores nowadays whittle down the spare time of most professional men and women in their homes; and even in hospital, as Dr. Ursula Paterson points out on p. 1225, the senior specialist cannot always hand over routine chores to a junior, for often there are no juniors to accept the charge.

A year ago, and again last April, we drew attention to this serious deficit in house-officers.[18] The hospitals most severely affected are mainly in the north, and in the periphery of the regions. Young men who want to specialise, or even young men who want to hear of a good opportunity in general practice, do better to stick to the central teaching hospitals of the region than to lose themselves in outlying parts, where they are apt to be overlooked. Young married men, returning from national service, are already anxious to find their places and settle down: they are in no mood to banish themselves from their homes for six months or a year to seek experience in a hospital which has slender links with a teaching unit. Yet these non-teaching hospitals, between them, deal with the bulk of the patients in the country; and in them, as Dr. Paterson points out, operating-lists are having to be curtailed because there are not the housemen, registrars, or junior anæsthetists to support the work of the surgeon.

It is not possible to say at present how great the deficit is, but this time last year the Manchester Regional Board alone had 157 unfilled vacancies among 570 junior medical posts. Registrars, senior house-officers, and house-officers were all needed, and the deficiency in the last two grades amounted to nearly a third of the total complement. Because their staffs are smaller, the small hospitals suffer more: a deficit of one where the whole staff is only three puts a heavy load on the two appointed. Prof. W. H. Wynn (p. 1225) forecasts a total deficit of 573 juniors in England and Wales next year for posts approved under the Medical Act of 1950, and a surplus in Scotland—available, as he says, for export—of 142. He points out that in teaching hospitals at present there is one resident to 15 beds; in non-teaching hospitals one to 103 beds.

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[17] Hempelmann, L. H., Lisco, H., Hoffman, J. G. *Ann. intern. Med.* 1952, 36, 279.

[18] *Lancet*, 1951, ii, 973; *Ibid*, 1952, i, 705.

The compulsory year in hospital before registration, which comes into force next year, will doubtless make some difference, but it is generally doubted whether it will end the difficulty. The suggestion has been made that general practitioners could be engaged on a part-time basis to do what is needed; but these doctors, specialists in their own field, should not be expected to deputise for juniors, or to further burden their too-full lives with the routine tasks of their 'prentice days; and they cannot be continuously on call to deal with emergencies, or to give suddenly needed anæsthetics. Their services, too, are relatively (and justifiably) expensive.

A partial solution which we advocated a year ago still seems to us sound, and has already been accepted, at any rate in principle, in organising the nursing staffs of regional hospitals. If each of the outlying hospitals of a region was more closely affiliated to a teaching hospital, young doctors could take posts in such hospitals feeling that they were to some extent sponsored by their parent hospitals—which indeed might take the trouble to mantain special links with them by means of case-conferences, medical meetings, or other devices. Compared with residents in a teaching hospital these juniors would be getting in some ways better experience—more responsibility and a greater diversity of patients. Professor Wynn has two further suggestions to offer: that more use should be made of the hundreds of registrars who will never reach consultant status; and that the period of conscription should be reduced, for doctors, to a year, with the proviso that the second year should be spent in hospital. The Forces, however, have their own staffing difficulties; and to them the young doctor is much more valuable in his second than in his first year of service.

We agree with Professor Wynn that the civilian problem is urgent and requires serious discussion.

ANTHRAX

THE increase in anthrax among farm animals during the past few months was recently the subject of a question in the House of Commons,[1] and the danger of increased risk to man must of course be considered, even if this is not great. There are always a few cases of anthrax among animals in this country; and with the increase in imports of feeding-stuffs, notably bone-meal, it was likely that the incidence should rise. It has, in fact, been rising steadily for some months; in June, 31 new outbreaks were reported among animals, in July 90, in August 123, in September 170, in October 185, and in November a further 209; in all there have been 1051 outbreaks among animals in Great Britain since the beginning of this year. There is no reason to suppose at present that this has meant any increase in the incidence among humans.

Human anthrax is uncommon in Great Britain, though there is always a slight incidence among workers in the bone and hide trades; and dockers, knackers, and agricultural workers may all come into contact with infection at times. The Chief Inspector of Factories, in his report for 1950,[2] mentions that there were 36 cases in that year (with no deaths), as against 21 in 1949. Laboratory workers and students handling stained films of anthrax need to be reminded from time to time that staining does not kill the spores of this organism, and that there is risk in handling such slides. This warning should be given specially to technicians in commercial laboratories who are interested in imported foodstuffs, and making a special study just now of anthrax. These workers may be handling anthrax cultures for the first time, and may not be fully familiar with the precautions necessary for safety. Contamination with live anthrax from stained slides is a risk which must be taken seriously, and those handling cultures should be scrupulous in avoiding contamination of their cuffs, or any other part of their clothing, and in leaving their white coats behind them in the laboratory when they go to meals. The hazards of a bacteriologist's life are sufficient, without adding to them unnecessarily.[3]

The present increased infection among animals certainly derives from feeding-stuffs; but the bones of a single infected animal may contaminate a large quantity of material, and bacteriologists can only report on samples: if these happen to be negative it does not necessarily mean that the main bulk is free from anthrax spores. A negative result thus gives no grounds for a feeling of security. Doctors consulted about macules or vesicles, especially on the hands or face, should have anthrax in mind *at present*, and inquire into the recent history.

LOCAL CHEMOTHERAPY FOR TUBERCULOUS EMPYEMA

WIDER use of pneumothorax therapy and wider employment of chemotherapy and other methods are resulting in a diminishing incidence of tuberculous empyema. Pneumothorax, however, may still give rise to empyema, which occasionally also arises spontaneously. Furthermore, collections of tuberculous pus in the chest sometimes form after major operations—for example, in the Semb space after thoracoplasty, in extrapleural pneumothoraces, and even after plombage or resection. Aspiration and local chemotherapy are of value in treating some of these cases; but often pleurectomy, or surgical intervention to obliterate the infected space, proves necessary.

The substances injected with the object of thinning or sterilising the pus have included 20% sodium *p*-aminosalicylate, thiosemicarbazone, and chloroazodin; streptokinase and streptodornase have also been employed. Streptomycin, applied locally, has proved somewhat disappointing; this is partly because its action is hampered by hydrolytic products of the protein in the pus, and partly because empyema fluid has a neutral or slightly acid reaction (pH 6·8–7·0) whereas streptomycin acts best in a slightly alkaline medium (pH $\geq$ 7·8). This second difficulty has been overcome to some extent by alkalinising the pus; this is rinsed with 2–4% sodium bicarbonate solution or $^1/_{20}$ *N* sodium hydroxide solution buffered with $^1/_{20}$ *M* borax solution, or else a 25% sodium citrate solution is instilled daily. In most cases the increase in pH is only transient; but Posternak [4] maintained a pH of approximately 7·5 by injecting 2·5–4% polyvinyl alcohol buffered with 0·1% borax solution; and this gel also appeared to delay the absorption of streptomycin.

The use of a buffered gel as a vehicle has been further investigated by Ståhle [5] in Sweden. A previous observation by Berkman et al.[6] that 'Cellophane' membranes placed in an aqueous solution of 50 µg. streptomycin per ml. adsorbed up to 30% of the drug suggested that a depot effect in the empyema space might be obtained with streptomycin bound to substances of high molecular weight. Ståhle dispenses with intramuscular streptomycin in his technique: after preliminary aspiration through the second intercostal space anteriorly with a long needle (the patient lying horizontally) the pleura is thoroughly rinsed with normal saline solution ; 300 ml. of the vehicle is then instilled, and 0·5–1·0 g. streptomycin or dihydrostreptomycin is instilled either daily or on alternate days. Comparative experiments revealed, however, that with physiological saline as the vehicle the concentration of streptomycin, even with a daily dose of 1 g., remained surprisingly low, dropping from 2500 µg. per ml. to 50–100 µg. per ml. after forty-eight to seventy-two hours. With a 1% solution of sodium carboxymethyl cellulose ('Cellugel I') as the vehicle, the level was maintained at 500–600 µg. per ml. for about seven days, after which it slowly dropped to 400 µg. per ml. ; the same dose of dihydrostreptomycin yielded an even higher concentration. The pH of the pleural fluid when this gel was used remained about 6·8–7·0—no higher than that when 0·9% sodium chloride was employed—but the same gel, buffered with disodium phosphate (named 'Cellugel II'), maintained a pH of 7·8–8·0 during the whole ten-day period of treatment. (The gel was withdrawn and renewed at ten-day intervals.) Ståhle concludes that dihydrostreptomycin given in cellugel II in doses of 1 g. every second day ought to give a therapeutically optimal effect in the local treatment of tuberculous empyema.

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[1] See *Lancet*, Dec. 6, 1952, p. 1128.

[2] Report of the Chief Inspector of Factories for the Year 1950. H.M. Stationery Office; p. 140.

[3] See *Lancet*, Dec. 13, 1952, p. 1165.

[4] Posternak, D. *Schweiz. Z. Tuberk.* 1948, 5, 122.

[5] Ståhle, I. *Amer. Rev. Tuberc.* 1952, 66, 271, 285.

[6] Berkman, S., Housewright, R. D., Henry, R. J. *J. Immunol.* 1949, 60, 349.

The number of cases treated by Ståhle is small—only 8 in all, including 2 of the extrapleural type—but his results were encouraging. In all but one the result was satisfactory ; 2 which failed to respond to cellugel I later responded to the buffered solution, cellugel II. Before the treatment was terminated the pleural contents, when withdrawn, had to be grossly clear and less in amount than the solution injected ten days previously—that is, the tendency towards absorption had to predominate. In 7 of Ståhle's cases these criteria were fulfilled in ten to ninety (average thirty-six) days ; 1 patient with a persistent bronchopleural fistula failed to respond to the treatment. Ståhle obtained his most satisfactory results in cases of acute recent empyema ; chronic empyemata also responded, but he admits that " secondary surgical treatment is often required to close the pleural space." No ill effects were noted from the alkalinisation or from the cellulose gel itself. The main points are that an optimum pH of 7·8 can be achieved by using a buffered cellulose gel, which has the additional virtue of maintaining the effective chemotherapeutic agent at a high level in the empyema space ; and that in the pleural cavity, and probably elsewhere, dihydrostreptomycin is more effective locally than streptomycin.

HEALTH NEEDS OF THE GOLD COAST

ONE of the first acts of the new responsible government of the Gold Coast was to obtain the services of a commission of inquiry into the health needs of the colony. The commission reported last July[1] ; and the government have already issued a statement[2] in which they approve of the general policies of the commission and accept the majority of its recommendations. So the people have reason to look forward to a period of steady growth in their health services.

An introductory chapter shows that out of a total population of just over 4 million only 574 children are likely to pass the school-certificate examination in 1952, and that by 1960 this figure will have risen only to 1057. Comprehending the dependence of health on education, the commission have realistically fashioned their recommendations according to this educational background.

Malaria, tuberculosis, yaws, trypanosomiasis, leprosy, onchocerciasis, ankylostomiasis, schistosomiasis, and venereal diseases each presents important medical problems. The nutrition of large numbers of the people is unsatisfactory—from the Gold Coast indeed came the first descriptions of kwashiorkor. Ignorance of mother-craft is widespread throughout the colony ; and there are only 152 registered medical practitioners, of whom 89 are in government service. The government have accepted the proposal that the establishment be increased during the next five years to 150. Gold Coast students at present training in this country are too few to fill future vacancies, and overseas recruitment must continue. The number of medical students from the colony is not likely to reach even 20 a year ; and to start a school for such small numbers would be uneconomical. The government will make every endeavour to find places at medical schools in the United Kingdom for all studer qualified to enter and likely to be successful.

An important development is the recommendation f setting up 43 new health centres. These should buildings or groups of buildings suitably equipped a staffed to treat minor illnesses, to offer a limited materni and child-welfare service, and to instruct the local co munity in matters of health and hygiene. In gener the curative aspect of medicine should receive le emphasis than the preventive aspect ; and successf treatment should be a means of gaining the confiden of the people and of securing their coöperation in pr ventive and educational measures. These new heal centres will be under the general supervision of medic officers and will be integrated with the hospital service The person in direct charge of each, with the title clinic superintendent, will be a nurse of proven capacit who has been specially trained for the work. His sta will consist of at least a midwife and a sanitary inspector and it is hoped that in time trained health visitors wi be added. The government has accepted this recon mendation, but states it may not be possible to buil more than 10 centres in any one year.

At present there are 949 nurses on the register : 59 of these, mostly men, are in government service. Th commission consider that to provide normal replacement for these, and to staff new hospitals and extensions, a annual output of 150–175 nurses will be necessary. Thi is based on a ratio of 1 nurse to 2·5 beds. A majo problem, to which no clear-cut solution is offered, is the provision of a suitable number of sister-tutors. Equally important is the training of health visitors, who are needed to supervise the midwives and extend their work. There is a recommendation that the School of Hygiene at Accra should train 12 a year.

Much space is devoted to the question of providing an adequate water-supply. Comprehensive schemes involving a capital expenditure of £3½ million are recommended. This covers both piped supplies to the larger municipalities and the sinking of wells and the development of other small supplies. The principle that the supply of wholesome water should be paid for by the consumer is recognised.

Much of the report is taken up with administrative measures for reorganisation of the medical department. The distinctions between government and municipal functions in health matters are clearly set out. Means for the integration of the government medical services with those maintained by the mining companies are suggested, and a senior medical officer will be appointed for special duty in the mining areas. The recent government policy of assisting financially the work of medical missions is endorsed. In these matters, as in all else, the report provides precise guidance for all charged in any way with responsibility for health.

The success of all the commission's plans ultimately depends on those few hundreds of Gold Coast children who will reach school-certificate standard in the coming years. Could not an illustrated synopsis of this report be prepared which will fire their imaginations ?

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1. Report of the Commission of Enquiry into the Health Needs of the Gold Coast. Government printing department, Accra. 1952. Pp. 64. 5s.
2. Statement by Gold Coast Government on the Report of the Commission of Enquiry into the Health Needs of the Gold Coast. Government printing department, Accra. 1952. Pp. 5. 2s.

TESTOSTERONE AND POSTOPERATIVE LIVER DAMAGE

THE danger of the liver being damaged by volatile anæsthetics has been appreciated since their early days. Before we knew something about the factors which affect the susceptibility of the liver to exogenous toxins, little could be done to prevent this damage, apart from avoiding gross overdosage. It is now firmly established, however, that depletion of the hepatic stores of protein and glycogen greatly increases this suceptibility, and the postoperative recovery of patients so depleted may be much improved by inducing a positive nitrogen balance before operation. However, great difficulties may arise in ensuring a suitable diet, either because of the distaste for food that often accompanies long-standing disease, or because of disease of the alimentary canal itself. The introduction of parenteral feeding with protein hydrolysates, with or without emulsified fat, has gone a long way towards overcoming these difficulties; but in the presence of malignant disease it may be hard to achieve a positive nitrogen balance even with large parenteral feeds. The anabolic effects of some of the steroid hormones, especially testosterone, have proved valuable in such cases.

Hayes et al.[1] have made a detailed metabolic study of 8 patients with œsophageal or gastric neoplasms which prevented feeding by mouth. The patients were men between the ages of 69 and 78, and they had lost from 13 to 28 lb. in weight. They all had a period of preoperative parenteral feeding (which included hydrolysed casein equivalent to about 51 g. of protein daily) during which the nitrogen balance was estimated. Daily intramuscular injections of 50 mg. of testosterone proprionate were given to 3 of them for seven days before operation and throughout the period of the investigation. The other 5 patients acted as controls. The effect of the hormone on protein anabolism was striking. Whereas a negative nitrogen balance persisted despite the parenteral feeding, the giving of testosterone was followed by nitrogen retention within twenty-four hours. This retention persisted throughout the experiment despite the katabolic effect of the operation itself. The corresponding retention of potassium supported the view that the nitrogen retention was actually due to protein formation. Hayes et al. also demonstrated the value of this preoperative treatment in raising the liver glycogen. For this purpose the rise in blood-sugar levels following a standard subcutaneous injection of adrenaline was taken as a measure of the hepatic glycogen reserve. A definite improvement was produced by parenteral feeding, and a further increase in the response to adrenaline followed doses of testosterone.

Liver-function tests were performed before and after operation, to study the effects of the improved protein and carbohydrate reserves of the liver upon its resistance to the stress of the operation and the anæsthetic. There was a sharp distinction between the testosterone-treated cases and the controls. Thus, the serum-bilirubin level, which remained within normal limits in all 3 treated cases, rose above normal in 4 of the 5 controls; bromsulphalein retention after forty-five minutes was less than 10% in all the treated group, and between 30% and 40% in the controls; and the twenty-four-hour excretion of urobilinogen, which remained normal in the testosterone group, was considerably raised in the 4 controls in which it was estimated.

Hayes et al. conclude from these impressive results that the anabolic effects of testosterone are of great value in the preoperative reinforcement of hepatic resistance. Of little less importance to the patient is the simultaneous increase in blood volume and plasma-protein, for this considerably reduces the subsequent risk of shock. They are careful to point out, however, that testosterone may reduce the sensitivity of the pituitary to stress, and delay the secretion of adrenocorticotropic hormone in response to the particular stress of the operation. In this way it may interfere with steroid homœostasis; but this effect may be controlled by regular eosinophil-counts, and by the intravenous administration of aqueous cortical extract when the count shows this to be necessary.

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[1] Hayes, A. M., Hodgson, P. E., Coller, F. A. *Ann. Surg.* 1952, 136, 643.

FAINTING

FAINTING is a dramatic event, a death in life. For some, perhaps unaware of what they are doing, this is an avenue of escape from fear, pain, or an unwanted situation. On the other hand, fainting has many purely physical causes. Usually it is accompanied by a decrease in blood-pressure which leads to cerebral anæmia and unconsciousness. In the erect position the force of gravity helps to drain blood from the head; whereas in recumbency loss of consciousness is less usual, though weakness, nausea, and other symptoms may be present. In the common vasodepressor type of syncope[1] the fall of blood-pressure is due, not to bradycardia, but to extreme dilatation of the vascular bed in the muscles, with constriction of skin vessels[2] and no compensatory increase in cardiac output, owing to diminished venous return. Barcroft and Edholm[2] clearly showed the central origin of these autonomic effects, since muscle vasodilatation in the arm was abolished in patients by forelimb sympathectomy, and in normal men by nerve-block. They also found evidence of active vasodilatation, as well as inhibition of constriction, in the blood-vessels concerned. Sometimes heart-block develops just before unconsciousness supervenes,[1] but although atropine prevents the heart-block it does not prevent the unconsciousness. If consciousness is lost for more than 15–20 seconds, and especially if the subject is kept erect, mild clonic convulsions may result.[1] During the period of unconsciousness, but not immediately before or immediately after it, electro-encephalography shows characteristic slow waves.[3] The causes of vasodepressor syncope include intense pain, great fear, neuroses, and occasionally hypersensitivity to cold.[1] Hæmorrhage can induce a similar type of faint; but in those accustomed to being bled it occurs, in the recumbent position, only after 15–20% of the normal blood volume has been removed.[4] Orthostatic hypotension may produce fainting which differs from the vasodepressor type in that the loss of consciousness is often unaccompanied by signs of general autonomic disturbance, such as sweating and pallor.[5] In this type there seems to be an imperfection of those vasoconstrictor reflexes normally activated by pooling or shunting of blood. The condition may be temporary with illness or exhaustion; it is seen in diabetes mellitus[6]; and it may be an inborn inadequacy.

Cardiac asystole is a less common and more serious cause of fainting. Asystole, which is often unheralded,[1] may occur in the Stokes-Adam syndrome or from stimulation of nerve-fibres linked with the cardio-inhibitory part of the vagus nerve—for example, by pressure on the carotid sinus from turning the head or wearing a tight stiff collar. In paroxysmal tachycardia the cause of fainting seems to be cardiac standstill at the beginning or end of the paroxysm, and not a reduction in cardiac output.[7] Death may result if asystole persists. Another cause of fainting is an increase in intrathoracic pressure so that venous return to the heart is seriously impeded. This type of faint may follow violent bouts of coughing (the so-called laryngeal epilepsy [8]); it may also take place in cases of emphysema or of tumours obstructing the trachea. As entertainment it is induced with mistaken lightheartedness by school-children and Servicemen [9] by the simple device of taking a deep breath, closing the glottis, and allowing the thorax to be compressed. The loss of consciousness that occurs in major and minor epileptic attacks is of cerebral origin. Finally, hyperventilation is a fruitful source of fainting. It may occur with exertion in the presence of a failing heart, in states of anxiety, and in hysterical subjects. The mechanism seems to be that the changed blood chemistry so alters brain metabolism, as reflected in electroencephalography,[10] that the vasodepressor reflex is facilitated.

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[1] Engel, G. L. Fainting. Springfield, Ill., 1950.
[2] Barcroft, H., Edholm, O. G. *J. Physiol.* 1945, 104, 161.
[3] Engel, G. L., Romano, L., McLin, T. *Arch. intern. Med.* 1944, 74, 100.
[4] Ebert, R. V., Stead, E. A. jun., Gibson, J. G. *Ibid.* 1941, 68, 578.
[5] Stead, E. A. jun. *Amer. J. Med.* 1952, 13, 387.
[6] Hickam, J. B., Pryor, W. W. *J. clin. Invest.* 1951, 30, 401.
[7] Comeau, W. J. *New Engl. J. Med.* 1942, 227, 134.

For treatment of repeated fainting correct diagnosis is essential; and for this careful history-taking is important. The subjects of hysterical faints often show no anxiety at their condition, and during the faint the blood-pressure, skin colour, and electroencephalogram remain normal.[11] In most instances the treatment of a faint, particularly an isolated one, is simple—namely, to keep the patient recumbent and prevent him from standing too soon or too rapidly.

BEHAVIOUR UNDER STRESS

IN an Ernest Jones lecture, under the auspices of the British Psycho-Analytical Society, on Dec. 1, Prof. Roger W. Russell spoke of behaviour under stress. He explained his approach by citing some words of Dr. Ernest Jones [12]:

> "The limits bounding the field of knowledge studied by various scientific societies are often jealously drawn, and it is unfortunately not a very frequent event for such a society to show any desire to coöperate with another one. Yet the advantages of interchange of ideas among workers in neighbouring fields are undeniable, and many examples could be given of suggestions proffered by an investigator in one branch of knowledge proving exceedingly fruitful on being taken up and developed by someone whose main concern is with some other branch."

One basic characteristic of life, said Professor Russell, was its constant adjustment to environmental forces. Some forms of adjustment were age-long, concerned with the survival of species or civilisations; others momentary, affecting the response of a given organism at one particular instant. Such adjustive processes occurred in all the organism's activities, from its metabolic functions to its behavioural responses to environmental stimuli. Through all this range homœostasis [13] was aimed at; and if adjustment was not possible, disorganisation ensued.

The concept of stress, borrowed from the physicists, was useful for the analogies it provided between the strain undergone by physical objects from environmental stress, which within certain limits of elasticity was only temporary but beyond those limits resulted in permanent distortion, and the effects of environmental stimuli on the living organism, which also, beyond certain limits of adjustment, caused disorganisation. In organisms capable of responding to symbols which had come to represent environmental forces, response might take the form of symbolic behaviour, such as thought, so that little or no overt response might be observable. Adjustive processes broke down in two situations: when the organism encountered a stress which it had not the skill or capacity to surmount (frustration); and when two or more incompatible response-tendencies competed with one another, preventing suitable adjustment (conflict). In man conflict was the rule rather than the exception when decisions had to be made. In conflict situations disorganisation resulted in three ways. In the first the subject had impulses both to approach and simultaneously to avoid the same goal—the so-called "approach-avoidance" situation, exemplified by the hen-pecked husband who thirsted for a visit to the "local" but feared his wife's reprisals. The second—the "avoidance-avoidance" situation—was shown by the patriotic soldier who feared to advance because of danger from the enemy and also feared to retreat because of being called a coward by his comrades. The third—the "double approach-avoidance" situation—was the dilemma of Buridan's ass, which starved to death midway between two bales of hay, unable to make up its mind to move further away from either.

The effects of stress on the behaviour of animals had been extensively studied during the past fifty years. Disorganisation of behaviour under stress had been observed in species widely scattered throughout the phylogenetic scale. Research technique in this branch of experimental psychopathology had first been put on a sound basis by Pavlov [14] with his description of the "experimental neurosis" of dogs in conditioned-response studies. Professor Russell cited from the wealth of research the work of Masserman [15] on cats, which in situations of conflict between desire for food and fear of a noxious stimulus showed regressive and "neurotic" behaviour, and that of Maier [16] on rats, which in a situation of insoluble choice showed fixation of behaviour and became incapable of learning to solve a fresh, soluble problem even after hundreds of attempts.

Behaviour under stress had also been studied in children, both normal [17] and neurotic and delinquent [18]; such researches should lead to a better understanding of the part played by stress in human development. Many studies had been made of the effects of stress on adult behaviour, especially as regards skilled performance. One study of pilot error [19] showed that breakdown under stress was preceded either by a progressive decrease in precision, or by precision maintained by increasingly rapid, small, corrective movements. In another experiment [20] adults subjected to the stress of an insoluble choice situation, such as had produced fixated behaviour in Maier's rats, showed their frustration by aggressive, regressive, resigned or stereotyped responses. Some subjects reported that they found themselves compelled to go on making the same choice, although they knew it was wrong.

Professor Russell also referred to work being done in neurophysiology, in psychosomatic medicine, and in experimental genetics. He hoped that psycho-analysts would be impressed, as he was, by the important contributions towards understanding behaviour under stress which were being made by workers in many different fields: physiologists, zoologists, anthropologists, psychologists, and psychiatrists.

This lecture, as Prof. J. C. Flugel remarked, was encouraging to all who hoped for a rapprochement between psycho-analysis and academic psychology and other branches of science. Certainly coöperation between workers in these fields should be especially fruitful amid the stress of our atomic age.

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[8] McCann, W. S. *Arch. intern. Med.* 1949, 84, 845.
[9] Howard, P., Leathart, G. L., Dornhorst, A. C., Sharpey Schafer, E. P. *Brit. med. J.* 1951, ii, 382.
[10] Engel, G. L., Ferris, E. B., Logan, M. *Ann. intern. Med.* 1947, 27, 683.
[11] Romano, J., Engel, G. L. *Psychosom. Med.* 1945, 7, 3.
[12] Jones, E. (Ed.). Social Aspects of Psycho-Analysis. London, 1924.
[13] Cannon, W. B. The Wisdom of the Body. London, 1939.
[14] Pavlov, I. P. Lectures on Conditioned Reflexes. New York. 1941.
[15] Masserman, J. H. Behaviour and Neurosis. Chicago, 1943.
[16] Maier, N. R. F. Frustration: the study of behaviour without a goal. New York, 1949.
[17] Barker, R. G., Dembo, T., Lewin, K. *Univ. Ia Stud. Child Welf.* 1941, 18, no. 1.
[18] Kay, B. R. Ph.D. thesis, University of London, 1952.
[19] Davis, D. R. *J. Neurol. Neurosurg. Psychiat.* 1946, 9, 119.
[20] Marquart, J. I. *J. gen. Psychol.* 1948, 39, 107.

Reconstruction

HOSPITAL STATISTICS

FROM A CORRESPONDENT

ONE of the responsibilities that the Ministry of Health assumed at the appointed day was the publication of hospital statistics on a national basis. In the press of launching the National Health Service the Ministry was, understandably, too occupied in other directions to give much attention to this matter, but now it is doing its best to catch up with events. The review of the *Statistics of the Hospital and Specialist Services for England and Wales* for 1949 was issued last June.[1] The review for 1950 has just appeared[2]; and the review for 1951 is promised before the end of the year. Thereafter it is hoped, says the Ministry, to issue the figures "by the middle of the year following the one to which they relate."

STATISTICAL PURPOSES

These reviews cover staff, beds, and patients. They do not deal with the finance of the hospital services, which is covered by the *Hospital Costing Returns*.[3] The separation of the statistical report from the financial report may be inevitable; but at first sight it seems a pity. The hospitals had become accustomed to the presentation of the two sides in the King's Fund's tables and in the *Hospitals Year Book* in a form in which simple comparisons of cost could be made at a glance. The separation will not, however, be all loss if a separate statistical return gives us a clearer idea of what statistics are really needed as a guide to hospital policy.

Hospital statistics have two main purposes; they may be used as an aid to hospital administration, enabling those managing one hospital to see how another hospital of comparable scale saves either pence or pairs of hands; or they may be used, much as the statistics accompanying the *Hospital Surveys* were used, as data for the consideration of the wider questions of hospital policy. Unfortunately these reviews are not well adapted for either of these purposes. But the Ministry has not had an easy task. It took over their publication at a time when the old approach to hospital statistics was already felt to be obsolete or, more accurately, incomplete, but before any new conception of what is really needed had been formulated to take its place.

Historically hospital statistics in this country sprang from the desire of hospital authorities to compare notes, and the need to satisfy the public that the volume of work done by one hospital did not compare unfavourably with others where the expenditure was roughly comparable. Much was taken for granted; it was assumed that all the beds and other facilities were needed, that there lay ahead, on all hands, a great need that could never be met—as the Book of *Ecclesiasticus* would have put it, that hospital work was as a sandy hill to the feet of the aged. The fundamental idea was to allow one hospital to be compared with another, and hospitals were as far as possible listed in comparable groups according to type, size, and so forth. The tables with which we were familiar thus grew up—bed complement, occupancy, totals of new outpatient attendances, and so on. Sometimes to supplement these data lists of medical, nursing, and other staff were added.

WHAT THE MINISTRY OFFERS

The first and main set of figures in the Ministry series of tables are in this tradition. The hospitals are classified in large categories, rather like those used formerly by the larger local authorities, and arranged in decreasing order of size according to the number of occupied beds.

Thus we find at the top of the list Walton Hospital, Liverpool, with a bed complement of 1351; 1200 beds available, 1032 being the average daily bed occupation during 1950; 15,728 inpatients died or discharged during 1950; 24,098 new outpatients during 1950; 83,549 outpatient attendances; 5 consultants, 2 senior hospital medical officers, 7 senior registrars, 10 registrars, 23 junior medical staff, 2 other medical staff, no dental staff, 2 almoners, 2 caterers, 2 dispensers, 2 engineers, 11 laboratory technicians, 1 occupational therapist, 3 pharmacists, 12 physiotherapists, no psychiatric social workers, 10 radiographers, 1 biochemist, 2 chaplains, 56 maintenance and transport workers and tradesmen and craftsmen, 8 male staff-nurses, 75 female staff-nurses and 23 part-time female staff-nurses, 35 male student nurses, 247 female student nurses, 14 female enrolled assistant nurses and 12 part-time enrolled assistant nurses, 21 staff midwives, 13 pupil midwives, 2 domestic-staff supervisors, 3 food supervisors, 1 kitchen superintendent. 13 cooks and assistant cooks, 13 ward orderlies and attendants, 409 other domestic staff, and 79 laundry staff.

Some helpful changes have been made in the figures for 1950, compared with those for 1949, and it would be useful if future compilers would add a note explaining any changes made. There are rumours of improvements about to be made in the official statistical return known as S.H.3., which will help to correct some of the inaccuracies and anomalies which lurk behind the present returns.

Among so many data students of the hospital service will find much of interest; and since this is presumably the best material available it is better that the Ministry should publish it than that it should be locked away in the archives. Thus it is easy to pick out hospital A, compare it with hospital B, and notice how anomalous such and such items appear to be; but such reflections do not take one far. At their worst data of this kind can be grossly misleading, and official quotations about unstaffed beds and waiting-lists would afford a rich quarry for anyone who wished to show how defective such material is.

REGIONAL FIGURES

In salute to the existence of regions summarised information is given about each regional board and teaching hospital. Beds allocated, waiting-lists, discharges or deaths during the year, new outpatients during the year, total attendances, and weekly number of clinic sessions are shown for general medicine, general surgery, and some twenty-seven other specialties. Information is also given about other departments such as the numbers of auxiliaries in pathological departments, physiotherapy departments, and so forth.

Here is the beginning of what is badly needed and what was lacking in the old hospital statistics—an attempt at subdivision into medical categories. But unfortunately the handling of this part follows the traditions devised for the presentation of morbidity statistics, and shows no appreciation of any new approach adapted to evolving hospital needs. These large figures lumped into totals, a page of figures sufficing for a whole region, and unaccompanied by any comment tell little compared with what we could be told. For comparative statistical purposes the region is too large, and the significant variations for which we are all looking are largely lost. Each hospital management committee (or group of several in a large city) needs to be examined separately. The figures in this section of the reports are no more than a glimpse of material on its way into the calculating machine for the National Health Service statistics.

TRENDS

The reports thus contain two main sets of figures: the more detailed set is based on the already more than half obsolete hospital approach; while the other set—the only figures related to the new conceptions of planned hospital services—is so highly summarised as to lose much of its practical value.

To launch these reports as the best that we can do is to admit failure, so far, to come to grips with the statistical

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1. H.M. Stationery Office, 1952. Pp. 260. 20s.
2. H.M. Stationery Office, 1952. Pp. 253. 20s.
3. See *Lancet*, 1952, ii, 1255.

heart is seriously impeded. This type of faint may follow violent bouts of coughing (the so-called laryngeal epilepsy [8]); it may also take place in cases of emphysema or of tumours obstructing the trachea. As entertainment it is induced with mistaken lightheartedness by school-children and Servicemen [9] by the simple device of taking a deep breath, closing the glottis, and allowing the thorax to be compressed. The loss of consciousness that occurs in major and minor epileptic attacks is of cerebral origin. Finally, hyperventilation is a fruitful source of fainting. It may occur with exertion in the presence of a failing heart, in states of anxiety, and in hysterical subjects. The mechanism seems to be that the changed blood chemistry so alters brain metabolism, as reflected in electroencephalography,[10] that the vaso-depressor reflex is facilitated.

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10. Engel, G. L., Ferris, E. B., Logan, M. *Ann. intern. Med.* 1947, 27, 683.
11. Romano, J., Engel, G. L. *Psychosom. Med.* 1945, 7, 3.
12. Jones, E. (Ed.). Social Aspects of Psycho-Analysis. London, 1924.
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Reconstruction

HOSPITAL STATISTICS

FROM A CORRESPONDENT

ONE of the responsibilities that the Ministry of Health assumed at the appointed day was the publication of hospital statistics on a national basis. In the press of launching the National Health Service the Ministry was, understandably, too occupied in other directions to give much attention to this matter, but now it is doing its best to catch up with events. The review of the *Statistics of the Hospital and Specialist Services for England and Wales* for 1949 was issued last June.[1] The review for 1950 has just appeared[2]; and the review for 1951 is promised before the end of the year. Thereafter it is hoped, says the Ministry, to issue the figures "by the middle of the year following the one to which they relate."

STATISTICAL PURPOSES

These reviews cover staff, beds, and patients. They do not deal with the finance of the hospital services, which is covered by the *Hospital Costing Returns*.[3] The separation of the statistical report from the financial report may be inevitable; but at first sight it seems a pity. The hospitals had become accustomed to the presentation of the two sides in the King's Fund's tables and in the *Hospitals Year Book* in a form in which simple comparisons of cost could be made at a glance. The separation will not, however, be all loss if a separate statistical return gives us a clearer idea of what statistics are really needed as a guide to hospital policy.

Hospital statistics have two main purposes; they may be used as an aid to hospital administration, enabling those managing one hospital to see how another hospital of comparable scale saves either pence or pairs of hands; or they may be used, much as the statistics accompanying the *Hospital Surveys* were used, as data for the consideration of the wider questions of hospital policy. Unfortunately these reviews are not well adapted for either of these purposes. But the Ministry has not had an easy task. It took over their publication at a time when the old approach to hospital statistics was already felt to be obsolete or, more accurately, incomplete, but before any new conception of what is really needed had been formulated to take its place.

Historically hospital statistics in this country sprang from the desire of hospital authorities to compare notes, and the need to satisfy the public that the volume of work done by one hospital did not compare unfavourably with others where the expenditure was roughly comparable. Much was taken for granted; it was assumed that all the beds and other facilities were needed, that there lay ahead, on all hands, a great need that could never be met—as the Book of *Ecclesiasticus* would have put it, that hospital work was as a sandy hill to the feet of the aged. The fundamental idea was to allow one hospital to be compared with another, and hospitals were as far as possible listed in comparable groups according to type, size, and so forth. The tables with which we were familiar thus grew up—bed complement, occupancy, totals of new outpatient attendances, and so on. Sometimes to supplement these data lists of medical, nursing, and other staff were added.

WHAT THE MINISTRY OFFERS

The first and main set of figures in the Ministry series of tables are in this tradition. The hospitals are classified in large categories, rather like those used formerly by the larger local authorities, and arranged in decreasing order of size according to the number of occupied beds. Thus we find at the top of the list Walton Hospital, Liverpool, with a bed complement of 1351; 1200 beds available, 1032 being the average daily bed occupation during 1950; 15,728 inpatients died or discharged during 1950; 24,098 new outpatients during 1950; 83,549 outpatient attendances; 5 consultants, 2 senior hospital medical officers, 7 senior registrars, 10 registrars, 23 junior medical staff, 2 other medical staff, no dental staff, 2 almoners, 2 caterers, 2 dispensers, 2 engineers, 11 laboratory technicians, 1 occupational therapist, 3 pharmacists, 12 physiotherapists, no psychiatric social workers, 10 radiographers, 1 biochemist, 2 chaplains, 56 maintenance and transport workers and tradesmen and craftsmen, 8 male staff-nurses, 75 female staff-nurses and 23 part-time female staff-nurses, 35 male student nurses, 247 female student nurses, 14 female enrolled assistant nurses and 12 part-time enrolled assistant nurses, 21 staff midwives, 13 pupil midwives, 2 domestic-staff supervisors, 3 food supervisors, 1 kitchen superintendent, 13 cooks and assistant cooks, 13 ward orderlies and attendants, 409 other domestic staff, and 79 laundry staff.

Some helpful changes have been made in the figures for 1950, compared with those for 1949, and it would be useful if future compilers would add a note explaining any changes made. There are rumours of improvements about to be made in the official statistical return known as S.H.3., which will help to correct some of the inaccuracies and anomalies which lurk behind the present returns.

Among so many data students of the hospital service will find much of interest; and since this is presumably the best material available it is better that the Ministry should publish it than that it should be locked away in the archives. Thus it is easy to pick out hospital A, compare it with hospital B, and notice how anomalous such and such items appear to be; but such reflections do not take one far. At their worst data of this kind can be grossly misleading, and official quotations about unstaffed beds and waiting-lists would afford a rich quarry for anyone who wished to show how defective such material is.

REGIONAL FIGURES

In salute to the existence of regions summarised information is given about each regional board and teaching hospital. Beds allocated, waiting-lists, discharges or deaths during the year, new outpatients during the year, total attendances, and weekly number of clinic sessions are shown for general medicine, general surgery, and some twenty-seven other specialties. Information is also given about other departments such as the numbers of auxiliaries in pathological departments, physiotherapy departments, and so forth.

Here is the beginning of what is badly needed and what was lacking in the old hospital statistics—an attempt at subdivision into medical categories. But unfortunately the handling of this part follows the traditions devised for the presentation of morbidity statistics, and shows no appreciation of any new approach adapted to evolving hospital needs. These large figures lumped into totals, a page of figures sufficing for a whole region, and unaccompanied by any comment tell little compared with what we could be told. For comparative statistical purposes the region is too large, and the significant variations for which we are all looking are largely lost. Each hospital management committee (or group of several in a large city) needs to be examined separately. The figures in this section of the reports are no more than a glimpse of material on its way into the calculating machine for the National Health Service statistics.

TRENDS

The reports thus contain two main sets of figures: the more detailed set is based on the already more than half obsolete hospital approach; while the other set—the only figures related to the new conceptions of planned hospital services—is so highly summarised as to lose much of its practical value.

To launch these reports as the best that we can do is to admit failure, so far, to come to grips with the statistical

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1. H.M. Stationery Office, 1952. Pp. 260. 20s.
2. H.M. Stationery Office, 1952. Pp. 253. 20s.
3. See *Lancet*, 1952, i, 1255.

side of national hospital planning. When for the old medley of hospital services we substituted the new era of regional boards and hospital management committees on a geographical basis, and a planned spread of medical staff considered carefully category by category, we took an immense stride forward. But have we yet devised at the centre a statistical approach to help forward this new world? It is urgent that a new concept of national hospital statistics to match the new, and often very successful, planning that is going on should be worked out and brought into use before the present approach hardens into a routine. Large changes are now taking place in the use to which hospital beds are being put. Pressure on children's wards is, for example, already much lighter; pressure on medical beds is responding to the new drugs; the problem of the chronic sick is yielding to a more vigorous approach; pressure in the mental hospitals has perhaps passed its peak; and before long the need for tuberculosis beds may slacken. Trends of this kind are all-important in planning hospital services; and national statistics must be designed to show what effect they are having upon allocations of beds, area by area, and where we may expect to have to expand or retract to meet a changing situation.

It is fortunate that the regional boards are there to deal with the impact of this revolution in medicine on the hospital services. Could they not also be asked to submit to the Ministry their own arrangement of statistics and accompanying observations, for publication by the Ministry in a single volume together with reports from the boards of governors of teaching hospitals? Some of them have been trying to show graphically what is really happening. It would be necessary only to insist on a minimum of agreed definitions and formulæ to enable the reader to pass from region to region. It is too soon—and indeed it would be a mistaken policy at this stage—to expect a complete uniformity of approach. Figures derived as we have suggested, and accompanied by brief explanations by the officers of the boards, would show the enormous improvement in our hospital services of which we have every reason to be proud, but about which we have little accurate information. It would, too, help to create a knowledgeable public opinion which will allow the Government to consider realistically whether further expenditure on the hospital services is necessary, or whether the time will soon come to curb the expansionist tendencies which we have inherited from the past.

Special Articles

TWO YEARS' EXPERIENCE

A SCHOOL OF SPEECH THERAPY

DEFECTS of speech arise from many causes, and are often associated with much hampering frustration and anxiety. For these reasons children so afflicted cannot easily be treated in outpatient departments. Dr. C. Worster-Drought and his colleagues in the department of speech disorders, which has been in action at the West End Hospital for Nervous Diseases since 1914, decided a few years ago to found a residential school of speech therapy. This would serve, they thought, as an inpatient department where children with such defects could be admitted for accurate diagnosis and treatment, while at the same time going on with their general education. The project was made possible by the gifts of anonymous donors, and a report[1] on the first two years of work at Moor House School has now appeared.

Dr. Worster-Drought, who has edited it, finds that most of the children referred either to the hospital department or the school fall into seven main groups: mental defectives; those with congenital or infantile deafness; maladjusted, psychoneurotic, or prepsychotic children; those with neurological disorders such as cerebral diplegia, bilateral athetosis, congenital hemiplegia, and bulbar poliomyelitis; various forms of juvenile aphasia; functional disturbances such as dyslalia and stammering; and mechanical defects such as cleft palate and dental abnormalities. Not all these types of case are suitable for treatment in the school, and recently a diagnostic unit has been established there to study each child admitted and refer those who are unsuitable to appropriate centres.

It is found, for instance, that children with an intelligence quotient (I.Q.) below about 80 cannot profit from the training given in the school. Deaf children, whether the defect is partial or of the high-frequency type, though they may be admitted temporarily for diagnosis, are ordinarily sent on to suitable deaf schools. Psychoneurotic and prepsychotic children, too, respond poorly to the treatment offered and can seldom be retained. Dyslalia and stammering can usually be treated successfully from the outpatient department, and are admitted to the school only if they fail to respond; the results have then been satisfactory. Those with mechanical difficulties such as cleft palate do well in the school, even though training may be interrupted by operations.

DEFECTS OF EXECUTION

The children admitted are classified into two groups: those with executive speech defects, referred to as E cases; and those with receptive speech disorders having difficulty in comprehending ordinary spoken speech (R cases). These two groups naturally need different kinds of training.

The E cases, after being allowed to settle down for a few days, are given a thorough physical examination which includes the anatomy and physiology of the speech organs. Speech is assessed, hearing tested, and personality, temperament, and intelligence observed. Every child has an audiometric test to exclude partial deafness. Of 29 E children admitted during the two years, 25 had normal hearing. Slight general deafness was found in 4, 3 being cases of cleft palate and 1 a case of bulbar poliomyelitis.

In all cases of disordered articulation, the speech therapist analyses the speech sounds, transcribes them phonetically, and then encourages the child to produce the missing sound from the nearest existing phonetic sound by imitation or from kinæsthetic memory. Pictures are used to keep his interest up, and as he becomes more expert in producing the correct sounds the staff—who up to now have been at pains to understand him, even at his most unintelligible—begin to look uncomprehending when he gets a word wrong. They do not, however, fall into what Dr. Worster-Drought calls the common fallacy of correcting every mistake the moment he makes it: "such a method defeats its own ends by producing anxiety."

By this time the child is using his newly acquired speech habits confidently among his familiar company, though he will not as yet make conversation with strangers; so he is taken out shopping, makes inquiries at the station, and attends tea-parties. Friendly tradespeople and neighbours willingly help at this time. He joins a "talks club" at school, helps to make puppets and supply them with dialogue, and speaks on a home-made broadcasting system. Progress is assessed not only by phonetic records but by letting the child make gramophone records at intervals, and these have the further advantage that the children like to hear them and criticise their own performance.

Apart from speech training, the children are taught other school subjects including reading, arithmetic (in which they are all backward), music, art and handiwork, gardening, and general knowledge. During the two years under review 7 of the original 28 E cases were discharged with improved speech, 9 were making satisfactory progress, 8 were discharged as unlikely to benefit further, and 4 left for other reasons.

DEFECTS OF RECEPTION

The 36 R-group children admitted during the two years presented quite different problems. They were difficult to test by audiometry, and it was assumed that they were unable to appreciate and retain the auditory image of what they heard—to be, in fact, cases of congenital auditory imperception. Some were found to be trying to get a *visual* image by lip-reading, and could use a few isolated words learnt in this way; otherwise they used pantomime, and noises indicative of anger or pleasure. As it turned out, no fewer than 27 of them had been unable to learn to speak because of deafness, either generalised or of the high-frequency type. Only 1 proved to be a case of congenital auditory imperception.

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[1] Residential Speech Therapy. London: Heinemann Medical Books. 1952. Pp. 150. 15s.

This boy was given special training by means of a "sound alphabet" devised by Dr. W. F. Coningsby: he was taught to copy a sound, as "b-b-b-b," and to end with an explosive shout of a word, such as "bottle." He was helped in this by pictures and by the example of the speech therapist, and he is now able to follow directions and to converse in telegraphic sentences.

The rest of the children in this group, however, have been taught on the lines accepted for the teaching of deaf and partially deaf children. Of the original 36, 4 have been discharged as improved, 9 have been recommended for training in schools for the deaf, 14 were found to be unsuitable for training in the school, either because of mental defect or severe maladjustment, and 4 left for other reasons; 4 of the remaining 5 are making satisfactory progress.

FUTURE PROSPECTS

The school seems as yet to be known to relatively few local education authorities. Up to now the governors have accepted children between the ages of five and eleven, but in the future they hope to take an additional 11 children between the ages of eleven and sixteen. This will enable some of the children already in the school to stay on, but there will be places for several others. One of the most valuable services the school can offer is accurate diagnosis of cases of defective reception, for no effective treatment can be given until the cause is clearly established. Cases of congenital auditory imperception, though rare, are greatly in need of special training; and a scheme is being considered for treating cases of alexia and dyslexia, for which at present no adequate treatment is available. This condition is not at all uncommon, though it is often overlooked or mistaken for mental defect. To pursue this work, and the research which is inseparable from it, and to extend its staff and premises, Moor House School needs more funds than are provided by the fees paid by local authorities. Many benefactors have already contributed to the work, and Dr. Worster-Drought is in hope that their numbers will increase. The school is at Hurst Green, Oxted, Surrey.

KING EDWARD'S HOSPITAL FUND FOR LONDON

PRESIDING over the general council of the Fund on Dec. 9 the Duke of GLOUCESTER said that during the last two years grants to hospitals and convalescent homes had amounted to £342,119. In addition £100,000 had been set aside for homes for the aged sick, bringing the total allocation for that purpose in recent years to £350,000. During these years the management committee had been reviewing policy in the light of reports made to them on visits to hospitals applying for grants. These reports showed how various were the difficulties under which work was carried on in some of the older and outlying institutions.

> "Obsolete plumbing, obsolete standards of staff accommodation, grounds that have for lack of funds been allowed to become half derelict, lack of accommodation for visitors —with some of these things the King's Fund can help, others are beyond its resources; hospitals generally are now alert to the possibility of getting help from the Fund. All our experiences in the last few years show plainly how very necessary periodic visiting is if the Fund is to maintain close touch with hospital affairs."

Referring to the reports on hospital costing lately presented to the Minister of Health by the Nuffield Provincial Hospitals Trust and by the Fund, the Duke said:

> "Most of us are so accustomed to the traditional way of looking at hospital accounts that it is difficult to grasp what a revolution is involved in the recommendations in these reports, and yet how simple they are—nothing more or less than that hospitals should adopt a normal business-like approach towards their accountancy, and abandon once and for all the over-simplified headings which go right back to the accounts of early charitable undertakings."

He added that he hoped the recommendations in the reports would be found to be an acceptable basis for the hospital accountancy of the next generation.

Sir EDWARD PEACOCK, the treasurer, reported that income from investments had reached £320,000, and general legacies during the year amounted to £53,000. There had been in addition, for capital, amounts of £14,000 and £9000 from the estates of Lord and Lady Wakefield. As reported in July last, £50,000 had been received from the Nuffield Trust for the Special Areas, which brought the total to £1,400,000.

Sir ARCHIBALD GRAY, chairman of the distribution committee, said that the amount given for maintenance for hospitals outside the National Health Service was about the same as last year. Subscriptions and donations received by this group of voluntary hospitals had increased slightly and now formed 27% of their income, and they had also received £175,000 in legacies.

Before Our Time

FOOD LORE FROM NURSERY RHYMES

THE rhymes and jingles of our childhood days are often uncertain in origin and difficult to date with any accuracy. It is perhaps for these reasons that the many allusions in them to food customs, habits, likes, and dislikes have not yet found a place in scientific literature. Yet our nursery rhymes are not all so nonsensical as they may appear, and even a quick glance through the Opies' fascinating book* must be stimulating to anyone who is interested in the foods of the past.

The common foods of a few centuries ago were not so different from those we eat today. Stews, sheep's head, haggis, roast beef, veal, giblet pie, leg of lamb, gammon and spinach, peas and beans, bread and cheese, curds and whey, pancakes, all are mentioned, some of them many times over. Ducks were evidently prepared in the well-known way.

> "Mrs. Bond she flew down to the pond in a rage
> With plenty of onions and plenty of sage;
> She cried, Dilly, dilly, dilly, dilly, come to be killed,
> For you must be stuffed and my customers filled!"

The man in the moon wore a hat made of "good cream cheese" and, as all the world knows, he "burnt his mouth with supping cold plum porridge."

So far as drinks are concerned

> "One, two, three,
> I love coffee
> And Billy loves tea,"

appeared about a hundred years ago, but

> "The man in the moon drinks claret,
> But he is a dull jack-a-dandy;
> Would he know a sheep's head from a carrot
> He should learn to drink cider and brandy."

dates from the 17th century. Incidentally there seems to be no reference to milk as a drink in any nursery rhyme.

"Parsley, sage, rosemary, and thyme" was a refrain of an 18th century rhyme, and

> "Nutmeg and ginger, cinnamon and cloves,
> That's what gave me this jolly red nose."

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* Opie, I., Opie, P. Oxford Dictionary of Nursery Rhymes. Oxford, 1951.

comes into a rhyme of two hundred years earlier. The fruits of the country—cherries, apples, pears, and plums—are often mentioned. Oranges and lemons also must have been well enough known in the middle of the 18th century to be coupled with the bells of St. Clements, and, indeed, "Oringes and Lemons" was the name of a dance of the 17th century.

Foods are often promised as treats and punishments for children.

> "When Jacky's a good boy,
> He shall have cakes and custard;
> But when he does nothing but cry,
> He shall have nothing but mustard."

Most of the treats were sweet things, such as treacle, honey, tarts, cakes, plum buns, plum cake, biscuits, comfits and, over and over again, sugar candy.

> "Handy spandy, Jack-a-Dandy,
> Loves plum cake and sugar candy."

Tarts were, of course, the downfall of the Knave of Hearts.

The pie was clearly very popular.

> "A was an apple-pie;
> B bit it,
> C cut it,"

and so on, down to

> "X, Y, Z and ampersand
> All wished for a piece in hand."

Blackbirds entered into the composition of a very famous pie, and

> "Little King Pippin he built a fine hall,
> Pie-crust and pastry-crust that was the wall."

Pie-men and pie-women sold their wares, often mutton pies, in the streets.

> "Simple Simon met a pieman,
> Going to the fair;"

and

> "There was an old woman
> Sold puddings and pies;
> She went to the mill
> And dust blew in her eyes.
> She has hot pies
> And cold pies to sell;
> Wherever she goes
> You may follow her by the smell."

The pudding was something quite different from the pie. It was a boiled concoction made in a bag tied with string. The basis was a cereal of some sort or peas.

> "Flour of England, fruit of Spain,
> Met together in a shower of rain;
> Put in a bag, tied round with a string;
> If you'll tell me this riddle,
> I'll give you a ring."

Puddings evidently formed a substantial part of the meal and the description of the bag-pudding made by King Arthur reads like the dream of a man who knew what it was to be hungry. The basis of the pudding, as described in a previous verse, was barley meal.

> "A bag-pudding the King did make,
> And stuffed it well with plums;
> And put in it great lumps of fat,
> As big as my two thumbs.
> The king and queen did eat thereof,
> And noblemen beside;
> And what they could not eat that night,
> The queen next morning fried."

There were also black puddings, and when the tailor accidentally shot his pig

> "Zooks, quoth the taylor, I care not a louse,
> For we shall have black puddings, chitterlings and souse."

Puddings were eaten either hot or cold

> "Pease-pudding hot,
> Pease-pudding cold,
> Pease-pudding in the pot
> Nine days old."

Fuel was scarce and one good fire probably had to be responsible for several days' food.

The joys of white wheaten bread are brought out in the rhymes again and again. By comparison barley bread was reckoned poor stuff to give to Bonnie Prince Charlie.

> "I'll have none of your nasty beef
> Nor I'll have none of your barley;
> But I'll have some of your very best flour
> To make a white cake for my Charley."

A supper of white bread and butter was something to sing for, and it was worth a journey to Banbury Cross to buy a penny white loaf.

> "Ride a cock-horse
> To Banbury Cross,
> To see what Tommy can buy;
> A penny white loaf,
> A penny white cake,
> And a two-penny apple-pie."

The penny white loaf often crops up in nursery rhymes. By it is meant, no doubt, the penny white loaf which was always listed in the Assize of Bread, an Act which from 1447 fixed the price of bread and ale according to the price of grain.

The drinks people drank, the foods they ate, are in the nursery rhymes for all to read. If only we had the recipes and quantities we might make a dietary survey of the beggars, the children, the old women, and even the man in the moon as they lived in the minds of our great and great-great grand-parents when they were very young.

R. A. McCance.

Public Health

The Fog

First reports indicate that the thick fog which covered London and many other parts of the country from Dec. 6 to 9 produced the customary rise in mortality, notably from respiratory diseases. Last week's fog was particularly fearsome, for it was accompanied by bitter cold; Russell[1] suggested that it is fog and frost combined which especially attack the susceptible chest.

When Logan[2] examined the London mortality figures for the week of the long fog of November, 1948, he found that the number of registered deaths from bronchitis and pneumonia was double the figure for any of the previous four weeks. Deaths from other causes were little affected, though rather more people died from myocardial degeneration and from cancer than in a normal week. Logan's figures showed clearly how the older people suffered most: as far as mortality was concerned, there was no increase at all at ages under 45, and most of those who died from bronchitis and pneumonia were over 65. In the following week, however, an unusually large number of infants died from pneumonia.

Our fogs are undoubtedly cleaner than they were, and less of a "smog" now that electric and gas fires have replaced so many open fires and kitchen ranges. The watch kept on the quality of smokes from factories means that we are unlikely to have such a disaster as happened at Donora, Pennsylvania, in 1948.[3] Nevertheless a further reduction in the output of the country's chimneys would certainly relieve us of much of the distress caused by fogs.

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1. Russell, W. T. *Lancet*, 1924, ii, 335.
2. Logan, W. P. D. *Ibid*, 1949, i, 78.
3. *Ibid*, 1948, ii, 738.

Meanwhile at least one doctor found London's radio-taxi service of use in the fog last week. In urgent need of oxygen apparatus, he got his message through by radio to a taxi in the neighbourhood of the suppliers. The taxi collected the apparatus and delivered it to the doctor at the patient's home with very little delay.

School Health

Since the school health service was started our children have been steadily growing taller, heavier, and healthier; and now, as Sir John Charles points out in his report for 1950–51,[1] the motor-car is a greater menace to them than diphtheria. Indeed of the 3341 deaths among children in 1950, 851 were due to accidents, more than half of which were motor accidents; and only 16 were caused by diphtheria. The incidence of minor and major disabling diseases has also been reduced. For instance, during 1947–51 the number of children with scabies, impetigo, and ringworm of the scalp dropped from 108,000 to 34,000, and the incidence of rheumatism fell by a third. Admittedly there is still room for improvement; over 4000 children are attacked by acute rheumatism each year.

One of the most important tasks of the school health service is to detect any defect as early as possible so that it may, where possible, be corrected. Among the 4½ million children examined during 1951, medical officers found 157,566 with defects in vision and a further 37,499 who needed treatment for squint—a disturbing increase compared with the 31,189 in 1949. 3 children per 1000-odd were found to need treatment for defective hearing, and 5 in just over 1000 were recommended to be kept under observation.

In addition to inspection the school health service nowadays provides a good deal of treatment. In all, local education authorities and regional hospital boards between them run 2350 clinics, about a third of which are specialist clinics. Some consultants hold that the facilities are better in hospital outpatient departments, and clearly the right place for clinics will vary with local conditions; but in any form this collaboration is valuable both to the child and to the medical student. The National Health Service has also strengthened the relations between school doctor and family doctor. There is now, the report points out

> "no question of clinics 'taking the bread out of the mouth of general practitioners.' . . . There should be full and frank interchange of information between the school doctor and family doctor about children in need of advice or treatment or of special educational provision. The more that general practitioners get to know of the work of the school clinics the more they will be prepared to coöperate."

The progress of our own times has a way of tarnishing the advances of previous decades, and the report ends with a critical survey of open-air schools. These schools, the first of which was opened in 1907, have done much for the health of delicate children; but today the modern school-building is often structurally more open-air than the so-called open-air school, which may have degenerated into a rather draughty ramshackle affair. Some of the schools visited by the four medical officers who made this survey were good, but the standards varied. Many of the residential schools were "bare, cheerless and spartan"; sometimes the hygienic arrangements were defective and the physical education of the children was neglected. The surveyors rightly hold that the great merit of these schools is their small size; and they agree that

> "there is still a place for special schools for delicate children, especially for those who live in industrial areas, but we do not consider that there is justification for much expansion of the existing provision. Indeed, a few day schools have vacant places. With a rising standard of living, better housing, the provision of meals and milk in schools, and with a fuller appreciation in the ordinary school of the varying needs of individual children, it may be that the need for special schools for 'delicate' children will diminish with the years."

Examination of Coalminers

The Coal Mines (Medical Examination) General Regulations, 1952,[1] made by the Minister of Fuel and Power, came into operation on Dec. 10. The regulations place upon the owner of every coalmine the responsibility for making arrangements for the medical examination, by a registered medical practitioner approved by the Minister, of persons under the age of 21 first employed, or about to be employed, in or about a coalmine. The doctor will issue certificates of fitness for mining work to the person examined and to the manager of the mine. Any person who fails without reasonable cause to submit himself for examination, or who is found to be unfit for this particular work, will not be allowed to take up employment in or about a coalmine. Of those engaged in mining work before Dec. 10 only those under the age of 18 must be examined; and in certain Welsh counties all those employed at a mine before this date are exempted.

Cancer of the Respiratory System

The Registrar-General's Statistical Review of the year 1950, published this week,[2] indicates that the increase in the number of deaths from malignant disease of the respiratory system shows no sign of stopping. The crude death-rate from this cause was 312 per 1,000,000 population in 1950—exactly double the 1940 figure. The rate rose from 288 in 1949—the highest rise in any single year in the period 1940–50. The increase has been more rapid among men than women: the crude death-rate for men was 266 per 1,000,000 in 1940 and 536 in 1950; and for women the figure rose from 63 to 104 in the same time.

Parliament

Economy in Hospital Staffing

Mr. ARTHUR BLENKINSOP and some forty other Labour members have tabled a motion criticising the proposed reductions in the staffs of hospitals.[3] The motion expresses alarm at the decision of the Government to impose further limitations upon hospital expenditure by reducing hospital staffs, which must lead to a fall in the standard of care or in the number of hospital beds, and calls upon the Government to review this decision without delay.

QUESTION TIME

Outbreaks of Anthrax

In answer to a question Sir THOMAS DUGDALE stated that outbreaks of anthrax from June to November, 1952, were as follows:

June	31
July	90
August	123
September	170
October	185
November	209

Hospital Waiting-lists

In answer to a question Mr. IAIN MACLEOD stated that during 1951 hospital waiting-lists dropped by nearly 27,000 and the average daily number of occupied beds increased by over 4000. A small reduction in the average length of stay of patients or in the proportion of beds unoccupied would make a considerable difference to waiting-lists.

Supplies of Cortisone

In answer to a question Mr. MACLEOD stated that there was some British production of cortisone and A.C.T.H. The F.O.B. value of Government imports of cortisone during the twelve months ended Oct. 31, 1952, was £105,000; and of A.C.T.H., £111,428.

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[1] Health of the School Child. 1950–51. H.M. Stationery Office, 1952. Pp. 144. 5s.

[1] See *Lancet*, Nov. 1, 1952, p. 890.

[2] The Registrar-General's Statistical Review, 1950. Tables. Part I. Medical. H.M. Stationery Office. Pp. 461. 12s. 6d.

[3] See leading article, *Lancet*, Dec. 13, 1952, p. 1168; *Ibid*, p. 1175.

In England Now

A Running Commentary by Peripatetic Correspondents

ONE of the reasons I look forward to 1953 is that it will bring a new calendar. Not that I have anything against the handsome one now on my desk, but I have tired of the verse that surmounts it. This consists of eight lines, of which only the second rhymes with the fourth and the sixth with the eighth. The remaining alternate lines do not rhyme. This savours to my mind of shoddy workmanship. The poem leads off with an admirable sentiment:

"May the Web of your Life be woven
"In strands of the finest gold."

Fair enough. One could wish for nothing better. But it goes on:

"As the Pathway of Life you travel
"May joys that are new unfold."

Now I can't help feeling that there are better rhymes to woven than travel. How about this for an alternative couplet?

"May your soup be shŏved in the ŏven,
"And never served up half cold."

The second quatrain runs:

"May your Christmas be Bright and Happy
"And oncoming Years be Free
"From the clouds of Trouble and Sorrow
"And Blessed with Prosperity."

Nothing to quarrel with there, of course; but happy and sorrow clash a bit surely? Let's see what we can do:

"From calls to parturient wŏmen
"Or other emergency—
"E.g., an acute abdomen—
"May your Christmas Dinner be free."

An improvement, I fancy. But could I sit opposite even that for twelve months?

* * *

What unknown seas of knowledge are spread before us on first looking into the new *World List of Scientific Periodicals*. One wonders what conscientious doctor can afford to be without the *Journal of Successful Medicine*; what surgeon dare ignore the *Surgical Supervisor*; what obscure subjects are brought to light by the *Medical Searchlight*; what secrets are guarded by the *Medical Sentinel*? The *Medical Mentor* will be just the thing for membership candidates and the *Medical Counselor* for those in difficulties of other kinds. *Medical Life* and *Médecine chez-soi* sound as if they deal with the society (not social) aspects of medicine. Alas, we shall probably never know what is published in *Suomen Lääkariliiton Aikakauslehti* because no library in this country takes it, but at least copies of *Oogst* and *Skýrsla um St. Josep-spitala i Reykjavik* are available. Readers of the *Sun Bathing Review* and the *Survey of Thunderstorms* are probably sharply divided in their interests, but surely everyone will enjoy the pastoral serenity of the *Guide to Experiments conducted at the Station Farm, Little Snoring.*

* * *

In our manic phase recently we determined to buy a house. After a preliminary study of the form in the local newspaper and some dickering with agents we finally discovered the only house in England we could afford to buy. Even to our untutored eye it was not in the best of condition, and we timidly approached a local builder to give us an estimate of the necessary repairs before we put in our offer.

The builder, a small active man of a despondent turn of mind, threw himself about the house in a frenzy of estimation. On several occasions he drew sparks from the end of his foot-rule. He peered into the attic and rapped the cistern with his knuckles—"Iniquitous, doctor!"; he stamped on the floorboards—"Neglect, doctor, neglect!" and inspected the fireplaces—"That's a thing I cannot *bear*, doctor!" Outside, the standpipes moved him deeply—"Horrible, doctor!"; and he buzzed gloomily around the drains—"It's illegal, doctor, completely illegal!" He mentally knocked down and rebuilt several walls, lowered the washbasin and raised the sink, and finally squeezed himself through a small bedroom window to inspect the scullery roof. What he saw confirmed his worst suspicions—"Ah, the scoundrels, doctor, the scoundrels!" The garage rendered him speechless, and only after walking away did he find strength to shake his head and mutter "Oh dear, doctor, oh dear!" He brightened at the unmade driveway—"What you want there, doctor, is a load of gravel, not *our* gravel, you understand, doctor, stuff you can roll," but the garden fence shook him again, and he left enveloped in brisk businesslike gloom.

We are once more making a preliminary study of the form in the local newspaper, and have reverted to our depressive phase.

* * *

Like most medical graduates of the University of London, I had several times had occasion to visit the Royal College of Surgeons in Lincoln's Inn Fields, but it was not until last weekend that I went into Sir John Soane's museum, on the opposite side of the square. I struck lucky, for though I only hoped to fill the gap between lunch and tea on a rainy Saturday afternoon I found that half-past two was the precise time for the weekly conducted lecture tour by the museum's curator.

Soane (1753–1837) was a distinguished and successful architect, who spent the last forty years of his life in collecting and arranging furniture, antiquities, and drawings of architectural interest, and some excellent pictures. These are all looked after by trustees under the terms of a private Act of Parliament which he obtained in 1833. The museum is thus a collection chosen by one man, and maintained according to his taste. The house has a striking façade, with the incised ornamentation peculiar to Soane. Its interior also shows his highly individual architectural style, designed to create the feeling of space, vista, and insubstantiality. Among the varied collection I was most taken by a fine pre-Chippendale mahogany chair, probably built for the ample bulk and dignity of a governor of some prosperous City firm, by the famous *Rake's Progress* and *Election* series of William Hogarth, and by the fine sarcophagus of Seti I. This reposes in a domed recess named the Sepulchral Chamber, and there are also catacombs and a "monk's parlour" down in the crypt—evidence of Soane's liking for the Gothic and, perhaps, of his lonely and embittered old age. Despite the numbers of casts and fragments of Roman statuary, the building itself, with its sense of space and airy hollowness, put me in mind of modern sculpture by Henry Moore or Barbara Hepworth, as though I had crept in under the ribs of a mastodon's skeleton out of the raw December weather.

* * *

It is now some weeks since our hamsters were installed. They live in a glass-fronted case in one of the bedrooms, where they may be seen, dim shapes behind the murky glass. Their presence, however, permeates the house, and they are consulted on all domestic affairs and also on matters of more general interest, such as the probability of snow on Christmas Day.

Even more imminent than their own corporeal existence are the countless generations of unborn hamsters due to spring from their loins, and so many of these have been given away already that the market is saturated. Their slightest gesture is interpreted as a sign of incipient maternity, as, for example, when one of them bit a too-familiar visitor to the effusion of blood, and the action was held to show its highly nervous state; or when the other was observed to demolish three cheese biscuits in rapid succession and its perverted appetite was assumed to demonstrate its delicate condition.

Though surrounded by every luxury, they are determined to escape, and spend the watches of the night in scratching holes in odd corners. They have already spent one night at large, and we await with some trepidation their next eruption. A large notice has in fact been erected on the case which reads "Hamsters, John and Mery. Pleese be ceful."

Letters to the Editor

SHORTAGE OF JUNIOR HOSPITAL STAFF

SIR,—The large number of hospitals with vacancies for house-officers that they are unable to fill is a matter of concern, and provides a problem that may endanger the whole hospital system.

The major cause is the great expansion of hospitals that has taken place since 1936. Entirely new hospitals have been built; old public assistance institutions have been upgraded and enlarged; war emergency hospitals have become permanent; many infectious-disease hospitals have been converted to other uses; and provision for chest diseases, maternity care, mental deficiency, &c., has much increased.

It is difficult to obtain exact figures for pre-war hospitals to compare with the recently published statistics of the hospital and specialist services for 1950. The P.E.P. report on the British Health Services gives some figures for 1936. In that year there were 2688 hospitals with a total of 260,829 beds. These include voluntary hospitals of all kinds, public hospitals, and institutions for tuberculosis, maternity, smallpox, and infectious diseases. Apparently they do not include the 107 mental hospitals with 150,000 beds. In 1950 the total beds in hospitals of all kinds numbered 504,321. The figures are not strictly comparable but do reveal the great expansion that has taken place. The number of pre-war house-officers is not ascertainable; but in 1950 there were 5824 (this includes whole-time registrars, senior hospital officers, and junior hospital officers, but not senior registrars); and 1622 of these were in teaching hospitals.

At one time it was thought that there would be a difficulty in providing sufficient posts for the compulsory preregistration year of residence; but in England and Wales 2104 posts in 456 hospitals have been approved. In 1951 there were 1531 new registrations; so assuming that a similar number register next year there will be an excess of 573 approved posts. In Scotland 557 posts have been approved, and in 1951 new registrations were 699 so that the balance of 142 should be available for export. In Ireland posts and registrations are more evenly matched. It appears therefore that in England and Wales about 1670 of the 2104 approved posts may be filled. This would leave 4154 out of the total of 5824 available posts to be filled from other sources. This is a measure of the problem to be faced.

In pre-war days resident posts in non-teaching hospitals were filled either by the newly qualified who had failed to get a post in their own teaching hospitals, or by those who after holding posts in their own hospitals desired further experience before entering general practice. Such posts were desirable, for they gave opportunities of becoming acquainted with local practitioners and a chance of filling any vacancy in general practice which might arise. They were often held for two or three years. Now these posts are less desirable, especially if situated in a "closed" or "restricted" area. The position has been aggravated by the two years of national service. On their return men do not seem willing to return to hospital life. They may be married and anxious to settle down, and married quarters are not usually provided in hospitals.

It is clear that the hospital services have increased beyond the means of staffing them adequately, and the National Health Service has become unbalanced. Owing to the difficulty of entering into general practice, it has been suggested that the number of students entering our medical schools should be reduced to prevent unemployment. But the number who qualify is far short of that necessary for hospital requirements. If the number is increased to meet this need, what is to become of them when hospital days are over?

There cannot be any one solution of the problem. Much could be done by making better use of the hundreds of registrars, most of whom will not reach the grade of senior registrar and be trained for consultant status. Many will enter general practice and could give valuable assistance in taking over duties now performed by resident officers. I foresee a new type of keen practitioner who will spend half his time in hospital and half in general practice. A major contribution could be made by reducing the conscription period to one year. This is a thorny subject but it is hard to be convinced that it is necessary for a fully qualified man, who has spent a year in residence in a hospital, to have two years intensive training to fit him for military requirements. Reduction to one year, with the proviso that the other year should be spent in hospital, would be a great help. Failing this the proportion of those allowed to take a third hospital post before conscription should be increased. Medical women are free to take further posts and should be encouraged to do so, and some contribution may be possible from the Dominions.

Regional boards are naturally jealous of the large proportion of residents in teaching hospitals and on the face of it they have some justification. In teaching hospitals there is one resident to 15 beds and in non-teaching hospitals the proportion is one to 103 beds.

It is important that the high standard of the teaching hospitals should be preserved and that much emphasis should be placed on scientific method. But scientific method should have been inculcated through the whole period of a student's training, and it may be argued that a newly qualified man who is eventually going into general practice may get a better all-round experience in a non-teaching hospital where he will have greater responsibility and see a greater range of cases than with a highly specialised firm in a teaching hospital.

The problem is an urgent one and requires serious discussion and major decisions at high levels if a breakdown of the hospital service is to be avoided.

Birmingham. W. H. WYNN.

SIR,—It is time that someone spoke again of the difficulties of some hospitals that are not attached to a teaching hospital or unit. At these hospitals, which deal with the bulk of all hospital patients, operating-lists are sometimes having to be curtailed or cancelled because there is neither a resident to deal with postoperative care nor a junior anæsthetist for what are termed "registrar lists." Commonly senior specialists have to do, as well as their own work, that of registrar and houseman. This is not fair to the patient, economical, or good medicine.

As we know, after the Appointed Day registrar posts in all three grades were filled wholesale and often unnecessarily, with the result that there have been drastic cuts in both senior and middle grades in an attempt to make the numbers correspond with future consultant appointments. Unfortunately the number of consultants remains below the proposed national establishment; and thus the number of junior posts is correspondingly low. Even though the number of such posts is now more in keeping with consultant vacancies, there is still little incentive for young doctors to take registrar appointments outside a teaching unit; for efforts to specialise by those not in touch with a teaching centre are foredoomed to failure.

The young doctor who proposes to enter general practice no longer feels a need first to do several house-jobs. Thus the outlying hospitals have lost both grades of registrars; and many cannot get enough house-surgeons or house-physicians or junior anæsthetists. These hospitals have been placed at a further disadvantage in that a salary is now offered by all hospitals, whereas before the war junior appointments in non-teaching hospitals were unpaid.

Another difficulty is that increasing specialisation has changed the attitude of residents, so that they are less willing to fill gaps. Gone are the days when a houseman crammed into his days all possible medical experience. Now he hesitates to take responsibility outside his own particular field. In big hospitals this may matter little; but in the not so big hospital the loss is great.

Possibly the introduction next year of the compulsory preregistration twelve months in hospital posts may bring some relief. But can outlying hospitals, even if given an allocation of interns, be sure of obtaining them? Will not the demand continue to exceed the supply?

Sidcup, Kent. URSULA HAMILTON PATERSON.

HOSPITAL COSTS

SIR,—The proposals described in your leading article of Nov. 29 would lead to great improvement in the system of hospital accounting, but might work out to the apparent disadvantage of hospitals with a quick "turnover" of patients. The more quickly investigations and treatment are carried out, the higher will be the cost per patient per day; yet it is obviously in the interests of both patients in hospital and those awaiting admission that the stay should be as brief as is compatible with good treatment. For this reason it would perhaps be better to relate the cost both of inpatient and of outpatient treatment to the total number of patients of each type treated per year.

Paris. K. W. LOVEL.

DIAGNOSIS OF MIXED PAROTID TUMOURS

SIR,—In their very interesting article of Aug. 16, Mr. Patey and Mr. Hand refer to the difficulties which surround the clinical diagnosis of mixed parotid tumours. Certainly these difficulties are especially important now that ideas on the treatment of these tumours are changing. I am, however, only concerned with their statement that "Redon (1952) now incises as a routine all parotid tumours as a first stage of the operation and to excise a small piece for microscopy."

The histological classification of parotid tumours is uncertain; and it would, I believe, be a retrograde step if biopsy came to be accepted as an accurate guide to treatment. Few workers can have had such extensive experience of the histology and prognosis of salivary tumours as McFarland. From an analysis[1] of 421 cases of salivary gland mixed tumours he concluded:

> "From the present study it appears that something more than a simple microscopic examination of a section of tissue will be required before an accurate prognosis of a mixed tumour of the salivary glands becomes possible. At present our methods are no more accurate or scientific than the flipping of a coin."

Ahlbom,[2] too, who also studied a large series, found that the histological approach alone was unsatisfactory and believed that accurate classification must be based on macroscopic, microscopic, and clinical characteristics. On this basis he divided tumours into benign, semi-malignant, and malignant.

Redon's views were expressed in a personal communication; and his reasons for favouring immediate biopsy are not given. Unless his evidence is very weighty, it would surely be unwise to attach too great importance to biopsy findings and to base therapy on histological criteria which are open to such fallacies. In any case there may be other risks associated with biopsy of salivary tumours. There may be, however, as Mr. Patey and Mr. Hand point out, a place for immediate microscopy after preliminary enucleation of a parotid tumour.

London, W.1. REGINALD T. PAYNE.

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1. McFarland, J. *Amer. J. med. Sci.* 1942, 203, 502.
2. Ahlbom, H. E. *Acta radiol., Stockh.* 1935, suppl. 23.

DANGER OF PHENOL WITH PENICILLIN

SIR,—We wish to call attention to a risk attached t the common practice of using 0·5% phenol as a preserv tive in penicillin solutions. This amount of phen injected into muscles, or even into veins, appears to b innocuous; but the intrathecal injection of even ver small quantities of such a solution may be highl dangerous. We have recently had reason to suspec that the accidental employment of a penicillin solutio containing phenol may have been the direct cause c convulsions in an infant with meningitis, and we hav learned of at least one other case in which an eve more minute quantity of phenol injected into the thec was the probable cause of severe damage to the nervou system.

The necessary precautions are simple, but need to b rigidly applied. Firstly, every bottle of penicillin solutio issued by a dispenser, and containing phenol, must b distinctively labelled as such, and as suitable only fo intramuscular injection. Secondly, all hospital medica officers should be reminded that when it is necessary t give penicillin intrathecally the solution should be mad by themselves, at the time of injection, from unopene containers of crystalline penicillin.

R. P. ARONSON
D. G. LEYS
P. N. SWIFT.

Children's Department,
Farnborough Hospital, Kent.

PORPHYRIA TREATED WITH DIMERCAPROL

SIR,—Clinically there are two types of porphyri —acute and congenital. The following case seems t belong to the congenital group, for no suggestion of a toxic cause could be found by careful interrogation and examination of the patient.

History

A married woman, aged 28, had been very fit until the last three months of her first pregnancy two years ago. She then had some albuminuria, followed by two eclamptic attacks immediately before delivery, which was completed by forceps. She was never jaundiced, and the albuminuria stopped two weeks after delivery.

In March, 1952, a month before the delivery of her second child, she noticed that her urine was a peculiar bright-red colour. At this time three bullous eruptions developed on one finger. The bullæ contained a clear liquid, and the surrounding skin was normal. Gradually new eruptions of the same kind appeared on the face and the exposed parts of both arms. There were no symptoms related to the gastro-intestinal tract or nervous system. She had taken no drugs which could account for the condition.

By the end of June the bullæ involved a much wider area, including the neck and the medial aspect of the knees. In some areas the appearances were those of epidermolysis bullosa. New eruptions were constantly breaking out, and the skin on the dorsal surface of both hands finally broke down, leaving large ulcers, 6 to 8 cm. in diameter.

Laboratory Investigations

Urine.—Dark red in colour. Concentrated HCl gave a distinct green colour, changing to yellow after some drops of 3% H_2O_2 were added. Acidified urine gave the characteristic absorption spectrum of porphyrin.

Blood.—Erythrocyte-sedimentation rate (three successive occasions) 67, 60, and 25 mm.; Hb 98%; red cells 4,420,000 per c.mm.; colour-index 1; reticulocytes 0·1%; fragility of red

URINARY ANALYSES BEFORE AND AFTER DIMERCAPROL

—	Before dimercaprol	After dimercaprol	
	June 13, 1952	July 31, 1952	Aug. 4, 1952
Coproporphyrin (µg. per 100 ml.)	65	20	20
Uroporphyrin (µg. per 100 ml.)	2025	930	715
Porphobilinogen	None	None	None

The analysis gives a figure correct to the nearest 5µg.

cells 0·40–0·32% NaCl; icteric index 6; platelets 320,000 per c.mm. Sternal-marrow biopsy was normal.

Liver-function tests.—Normal.

Treatment and Progress

Treatment with dimercaprol (BAL) began on June 25, 1952. 1·8 ml. was given every four hours for forty-eight hours, and then 1·6 ml. four times daily. From June 30 until treatment was stopped on July 5 only 1·5 ml. was given twice daily. New skin lesions appeared on July 22; and a second course, with reduced doses, was given from July 23 to 30.

After two days' treatment, the patient felt definitely better. No fresh bullæ developed after July 22, and the urine became brighter in colour, especially during the afternoon and evening. The skin lesions regressed after a few days, and finally healed completely, though deep scars remained. The amount of coproporphyrin and uroporphyrin in the urine decreased (see accompanying table of analyses kindly performed by Dr. S. L. Sveinsson in the Central Laboratory of the Ullevaal Hospital, Oslo).

At the outset the prognosis seemed poor, and we felt justified in trying the effect of dimercaprol, because a good response has been observed in hæmosiderosis due to multiple blood-transfusion,[1] and hæmosiderosis has been found in several organs, especially the liver, in cases of porphyria at necropsy.[2] The distinct improvement after a few days, the regression of the skin lesions, and the urinary changes suggest that dimercaprol may be of benefit in porphyria. They certainly seem to justify its further trial.

St. Joseph's Hospital,
Porsgrunn, Norway. A. SCHRUMPF.

SUFFERING FROM PERNICIOUS ANÆMIA

SIR,—A patient complained that she had suffered from pernicious anæmia for 20 years.

When asked how she had suffered, it was apparent that she had ascribed all her aches and pains, headache and giddiness, indigestion, weakness, and palpitation to her ailment, which she clearly believed to be most pernicious. When told that a recent examination showed that her blood was in every way perfect and that she could not have been anæmic for 20 years (for she had attended a most efficient hæmatological clinic at a large hospital during the whole period) she refused at first to accept the good news. Evidently, no-one had ever told her that the blood of those with pernicious anæmia can be kept normal indefinitely.

Many patients with pernicious anæmia have similar beliefs. During the late war they would attend hospitals with requests that they be given certificates to excuse them from fire-watching and other public duties, and in other circumstances they may ascribe any symptoms to their disease.

The most enthusiastic devotees of the psychosomatic theory of disease have never suggested that pernicious anæmia has a psychological basis. But these considerations suggest that even in treating those with this disease attention should be paid to their minds. This attention need only be of the simplest kind; the doctor has only to tell the patient at the beginning of treatment that within a few weeks his blood will be normal, and, when this time has passed, that his blood is now normal and will always remain normal provided he attends for his regular injections and an occasional blood examination. From time to time in later years these statements may occasionally be repeated, and it be emphasised that if ever the patient does not feel well some other cause than pernicious anæmia must be sought for his complaints.

It may be argued that patients who suffer from pernicious anæmia must be of hypochondriacal temper, and if they are deprived of the opportunity of ascribing their symptoms to this disease they will still continue to get symptoms and ascribe them to something else. No doubt there is some truth in this, and those of sound personality do not become invalids when they develop pernicious anæmia, even if their medical advisers never tell them the facts about this condition. But this does not excuse the physician who does nothing for his pernicious-anæmia patients except to order them injections and blood-counts. By remembering that they have minds as well as bodies, he can surely do something to discourage them from becoming invalids.

Farnham, Surrey. J. W. TODD.

SPLENOMEGALY IN SCARLET FEVER

SIR,—During a recent appointment at an infectious-diseases hospital in the north of England, I had to deal with a large number of patients with scarlet fever—some 200 cases in three months. Most of these were mild attacks, but I was interested to find that no less than 18 of them showed a moderate splenomegaly.

In most patients the spleen was palpable on admission, but in some it was not palpable until a few days later. The spleen was usually firm, and in no case was it tender.

The duration of the splenomegaly generally varied from 4 to 16 days; but in one or two patients the spleen was still palpable on discharge after 21 days.

None of the patients had enlarged lymph-glands, other than the enlarged and tender tonsillar glands so commonly found in scarlet fever.

Unfortunately, a total and differential white-cell count was carried out in only 6 cases. In 5 of these the differential lymphocyte-count varied from 34 to 50%; the 6th had only 12% of lymphocytes; and the highest total white-cell count was 14,600 per c.mm. In none of the cases did the pathologist note any abnormal lymphocytes or an absolute mononucleosis.

I have not seen enlargement of the spleen mentioned in any textbook as a clinical feature of scarlet fever, and I would be glad of your readers' opinions on the incidence and significance of this finding.

The Radcliffe Infirmary, Oxford. S. O'REILLY.

HEALTH VISITORS

SIR,—Some weeks ago, during a discussion in the correspondence columns of the *Spectator*, a general practitioner deplored the activities of "ubiquitous health visitors, usually in the form of smart young women who visit our patients in shining cars. . . ." It was obvious from the letter that the "health visitors" referred to were officials of the Ministry of National Insurance. A letter from the secretary of the public health section of the Royal College of Nursing later pointed out that the designation "health visitor" was wrong and misleading in this instance. The Ministry of National Insurance itself directs the members of its staff who visit insured persons in their homes to use the title "visiting officer." These visiting officers do work similar to that of the old "sick visitors" of the approved societies who, prior to 1948, were responsible for the administration of sickness benefit under the National Health Insurance Acts which were the forerunners of the present Act.

There seems to be some confusion in the minds of both general practitioners and the public between the very different functions of the visiting officer and the health visitor, and there is little appreciation of the nature of the training of health visitors. The health visitor is employed by the local health authority, and has no connection with the Ministry of National Insurance. Her qualifications are prescribed by regulations of the Ministry of Health. She is a State-registered nurse with an additional qualification in midwifery and with the health visitor's certificate of the Royal Sanitary Institute. Her total training occupies a period of at least four and a half years (and it may extend to over five and a half years). She is a health teacher with an expert knowledge of the care of children and of expectant and nursing mothers. Her work now includes the care of the aged, and advising on the health of the family

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1. Ohlsson, W. T. L. 23rd Congress of Nordic Internal Medicine. Oslo, 1952.
2. Berglund, H., Paul, K. G. *Ibid.*

as a whole and on the measures necessary to prevent the spread of infection. Many health visitors in addition carry out the duties of the school nurse or of the tuberculosis visitor.

While in the past the health visitor has in general had little contact with the family doctor, it is hoped that in future she may work in closer contact with him, so that he can readily call upon her services should a family require them.

London, S.W.1.

N. K. Ross
General Secretary, Women Public Health Officers' Association.

A.C.T.H. IN OIL AND BEESWAX

Sɪʀ,—During the past eight months the department of rheumatism of the Royal Free Hospital has treated 17 patients, suffering from active rheumatoid arthritis, with ᴀ.ᴄ.ᴛ.ʜ. made up in an oil and beeswax base. Bruce and Parkes,[1] as a result of experiments on rats, have suggested that this preparation will act for several days.

In 12 of the 17 cases pain relief and increased freedom of movement resulted from injection of 100 mg. twice a week; the improvement lasted one to three days after each injection; and of 10 outpatients who received this treatment for three to six months, 8 have maintained their improvement during this period. In 4 cases the erythrocyte-sedimentation rate has fallen to normal levels; and in patients who were anæmic the hæmoglobin has risen. The urinary 17-ketosteroid output and the eosinophil-count have not been significantly altered by this dosage.

We have warned patients to attend the hospital if any untoward symptoms arise; but so far no complications have appeared, and we find it a convenient and satisfactory method of using the hormone. Patients attend the follow-up clinic every month. In addition to the convenience of reducing the number of injections, there is also a saving in material.

The only difficulty we have encountered with ᴀ.ᴄ.ᴛ.ʜ. in an oil and beeswax medium is that it has to be used at the right temperature (about 60°C); for otherwise it is difficult to inject. We believe, however, that this preparation effectively prolongs the action of ᴀ.ᴄ.ᴛ.ʜ. and is therefore useful. It may be that in the future some base which is easier to handle will be found more satisfactory, but so far this is the best method we have used.

Mrs. V. David, ʙ.sᴄ., performed the biochemical investigations. Mr. J. W. Hadgraft, ᴘʜ.ᴄ., ᴀ.ʀ.ɪ.ᴄ., prepared the suspensions of ᴀ.ᴄ.ᴛ.ʜ., and is willing to send details to those interested.

Royal Free Hospital,
North Western Branch,
Lawn Road, London, N.W.3.

Eʀɴᴇsᴛ Fʟᴇᴛᴄʜᴇʀ
P. O. Wɪʟʟɪᴀᴍs.

GONORRHŒA IN ANCIENT ROME

Sɪʀ,—Can anyone give me a reference to gonorrhœa in Latin literature of the classical period? It is always taught that this disease was known to the Romans in the palmy days of Rome, but I have come to doubt the truth of this assertion.

It is strange that Ovid in his treatise on love has nothing to say on the dangers of promiscuous amours; stranger still that Catullus is silent on a subject that he could hardly have resisted, and equally strange is it with Petronius; but most strange that the satirists should have ignored so obvious an opportunity to point a moral. An acquaintanceship with Juvenal that extends for forty-six years convinces me that he, had he known of gonorrhœa, would have made good use of his knowledge. Then, there is the medical authority of the period, Celsus; but in his work I can find no mention of venereal disease. Again, the Roman system of morals seems to depend upon immunity from this disaster, for the use of prostitutes was defended on the ground that thereby the chastity of wives was less likely to be assailed. If gonorrhœa had been endemic, surely, since there were no means of protection, we should have heard of the terrible results?

Authors of books on gonorrhœa do not cite the passages nor give the texts or translations from writers who are supposed to support their view that the disease existed in Rome of the classical period.

Orpington, Kent.

H. St. H. Vᴇʀᴛᴜᴇ.

TOXIC DOSES OF ADRENALINE

Sɪʀ,—Scant attention is given in our textbooks to the toxicology of adrenaline.

The latest annual report of the Medical Protection Society describes a case in which 5 ml. of a solution from a bottle marked "adrenaline 1/1000" caused rapid death when injected subcutaneously into the neck of a presumably healthy man. Nine years ago I witnessed the death of a young man after more than twice this dose had been injected into the muscles of the anterior abdominal wall. This man, who had a large kidney abscess, survived several hours—significantly longer than the man who received 5 ml. In neither case was there cerebral hæmorrhage; in both instances the mode of death was abrupt failure of the heart's action.

I do not know of any case in which less than 5 r
of a 1/1000 solution of adrenaline hydrochloride h
caused death. I do know, however, of a man w
survived the injection into a ruptured quadriceps mus
of 10 ml. of 1/1000 adrenaline hydrochloride. It
apparent, therefore, that the distance from the vi
centres, as well as the amount, of the accidental injecti
will determine the outcome. The site of injection w
also determine, to a certain extent, the time befo
death.

Pathological Laboratory,
King Edward Memorial Hospital,
London, W.13.

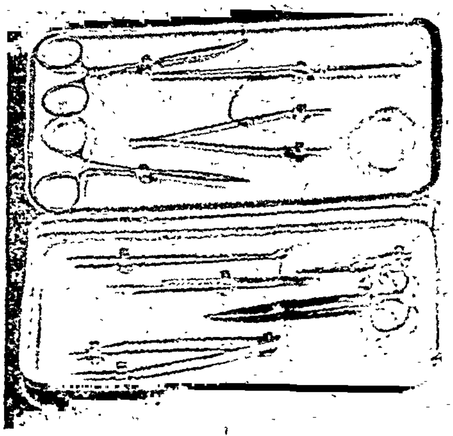
W. S. Kɪʟʟᴘᴀᴄᴋ.

CONTAINERS FOR TRANSFUSION CUT-DOWN SETS

Sɪʀ,—Inside a standard transfusion giving-set box a
two metal plates, each measuring 4 × $9^5/_8$ in. T
lower plate (holding the pair of scissors in the accompan
ing figure) is flat and lies on the bottom of the bo
The upper plate, which is flanged, fits snugly over th
lower plate when the box is closed. These plates a
made into containers, as follows:

Universal-type metal clips, which hold the usual cu
down instruments, are firmly attached to the plates at sui
able levels. Into the flanged plate is let a metal cu
to hold an antiseptic solution. The whole is readil
sterilised.

When the sterile set is required for use the seal is broke
and the colour of the Brown's control tube checked. T
flanged plate is then lifted out and placed in the open
of the box, so that all instruments are readily availab
(see figure). Apart from the usual administration bloo
transfusion set, all that is required is a packet of steri
dressings, catgut, and a bottle of antiseptic solution.



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1. Bruce, H. M., Parkes, A. S. *Lancet*, 1952, i, 71.

These containers have proved their worth both in hospital and in private practice. They are convenient and relatively cheap.

I am indebted to Dr. A. Jordan for his suggestion about the metal cup. The plates are made by Messrs. D. H. Farley, Union Lane, Sheffield, 1; and I am grateful to the directors of this firm for their coöperation.

Department of Hæmatology,
Royal Infirmary, Sheffield.
E. K. BLACKBURN.

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS

SIR,—Recent reports[1] in your columns of investigations into the causes of infusion thrombophlebitis have revealed interesting data which warrant some comment the pH of the solutions administered.

It seems a general practice in hospitals to allow a pH of 4·0 or lower in dextrose or dextrose-saline solutions. The habit of buffering such solutions immediately before use is, so far as I can make out, rare. Other precautions against excess of hydrogen ions can, however, be taken.

In the first place the dextrose used should be the finest available. Unfortunately, *d*-glucose of A.R. quality is very expensive; but apart from this, excellent samples can be chosen. Hudson and Tarlowski[2] obtained infusions of varying pH from different samples of monohydrate. The anhydrate, I find, tends to prove more satisfactory; for suitable samples show only half the original acidity set as a limit in the *B.P.* monograph, and yield a 5% solution of pH 6·5 approximately.

Solutions should be made at room-temperature, and filtered and sterilised without delay. Overheating should be avoided by raising the pressure in the autoclave as rapidly as possible, by maintaining the samples at sterilising temperature (115°C) for the minimum period (45 minutes), and by removing the containers to cool rapidly as soon as the pressure has reached that of the atmosphere. Obviously, the smaller the autoclave and the batch, the more effective are these precautions, and it is a practical consideration how far it is possible to reduce the scale of operation. Much trouble arises from an attempt to deal with too much at once. The figures I have quoted above apply only to half-litre containers.

Using this technique, we produce in this hospital dextrose infusions of pH 4·8–5·2 in batches of 50. The period of storage is a most important factor in maintaining this standard. Batches of infusions are given a three-month expiry date, which is quite adequate; there is very little fall of pH over this period, but after nine months to a year the acidity often reaches pH 4·0 or below.

The figures in the accompanying table show titratable acidity in some random samples.

TITRATABLE ACIDITY IN RANDOM SAMPLES OF INTRAVENOUS INFUSIONS

Sample	pH	Ml. of N acid per litre	Age of sample
Dextrose 5%	5·2	0·056	Fresh
Dextrose 4·3% + NaCl 0·18%	5·1	0·090	Fresh
Dextrose 4% + NaCl 0·45% ..	4·2	0·171	1 year
Dextrose 5%	4·4	0·112	6 months
Dextrose 5% + NaCl 0·9% ..	4·2	0·141	6 months

If we take the buffering capacity of normal blood as 28 ml. of N acid per litre, these figures do not appear alarming, and it seems that titratable acidity, per se, is not a menace in infusion therapy (even when venous blood-flow is small), provided the infusion is given slowly. Yet the evidences of local irritation resulting from the infusion of fluids at pH 4·0 and below surely justify an effort to keep the pH of dextrose solutions as far as possible above this figure.

Pharmaceutical Department,
Southmead Hospital, Bristol.
PETER COOPER.

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1. Handfield-Jones, R. P. C., Lewis, H. B. M. *Lancet*, 1952, i, 585. Bolton Carter, J. F., Milne, E. H., Whittet, T. D. *Ibid*, Oct. 4, 1952, p. 660. Page, B. H., Raine, G., Jones, P. F. *Ibid*, Oct. 18, 1952, p. 778.
2. Hudson, T. A., Tarlowski, L. *Pharm. J.* 1947, 158, 451.

WERNICKE'S ENCEPHALOPATHY

SIR,—In your interesting leading article (Dec. 6) you say that this " disease appears as a sequel to chronic alcoholism, long-continued vomiting of pregnancy, malignant lesions of the gastro-intestinal tract, and primary malnutrition." You certainly refer to papers which are based mainly on cases collected from these categories and, while you do not say so specifically, it is inferred by the authors quoted that the syndrome is met with only rarely, and largely in places like asylums, chronic wards, or prisoner-of-war camps. Indeed, only a few cases of the acute syndrome have been published—e.g., the interesting case described by Jones and Robinson.[1] However, Campbell and Ritchie Russell[2] pointed out that Wernicke's encephalopathy " is a not uncommon condition . . . it occurs as a complication of a wide range of other diseases . . . its incidence in some of these diseases is not generally recognised." The following two case-histories illustrate this statement. (Further details of these and other cases will be published later.)

CASE 1.—A married woman of 43 consulted me during the late war, when she carried on with war work in London. She had a mild hepatitis and symptoms and signs of vitamin-B deficiency (tingling in the limbs and fingers, glossitis, angular stomatitis, scaling of the nasolabial folds, and microcytic anæmia).

I saw her again in August, 1947. For many years she had " turns " at the time of her periods, when she became irritable, quarrelsome, and irrational, and her personality changed completely. Her last period was followed by a sudden " turn " on July 22. On July 24 she had a minor car accident in the grounds of her home and since that time her condition had deteriorated. She complained of splitting headaches, irritability, and a " muddled head." She had previously admitted to taking alcohol, but when I saw her with her husband she insisted that she did not drink even when she had guests.

One day she had laid the table for 8 guests; all the drinks were put out, and she was found semiconscious on the floor. After this she became more and more peculiar and confused, she refused food, and her speech became slurred. As she had fractured her skull at the age of 15, the possibility of a brain tumour was entertained.

She was a well-nourished woman, and lay quietly in bed with eyes closed. She did not recognise her surroundings, and replied incoherently to persistent questioning. She had completely lost her memory, and was severely disorientated in time and place. There was a slight internal strabismus; and abduction of both eyes was incomplete, with horizontal nystagmus. The cranial nerves were otherwise intact. The ankle-jerk was depressed. There was considerable ataxia on standing, and she could hardly walk, even with assistance.

While the husband was collecting some ampoules of aneurine from a chemist about 20 miles away, the servants were questioned. It seemed that the patient had been a secret drinker since April; when guests came along (as they often did) she never touched a drink in their company, but she was often seen in another room drinking a tumblerful of gin or whisky. She would then return to the party and again refuse to touch alcohol. Many empty bottles were found hidden in her wardrobe.

Within two hours of an intravenous injection of 30 mg. of aneurine she recognised the persons present, she could carry on a sensible conversation, and she asked for a meal. The external-rectus palsy became hardly noticeable. The effect did not last long, but another 30 mg. injected next morning was followed by a similar temporary improvement. She was transferred to hospital for further treatment. All the symptoms disappeared within four weeks, the last to go being the ataxia.

CASE 2.—A robust man of 84, with emphysema, bronchitis, and a mild asthmatic state for the past six months, was admitted to hospital with acute retention on Nov. 7, 1948. He had not drunk or smoked for over twenty years. Prostatectomy was performed that night, and the patient's condition was satisfactory for some days after the operation, with the exception of increasing anorexia.

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1. Jones, F. A., Robinson, V. C. *Lancet*, 1947, ii, 297.
2. Campbell, C. P., Ritchie Russell, W. *Quart. J. Med.* 1941, 10, 41.

On Nov. 12 he was quiet and somnolent, but he answered questions promptly. However, his condition became suddenly worse, and when seen at midnight, he was agitated and talked nonsense continuously for two hours. He pulled the drip needle out, and was restless and confused. He was completely unaware of where he was and unable to answer questions sensibly. He confabulated and was completely disorientated in time and place. The pupils reacted to light and convergence, and there was a moderate bilateral weakness of the external recti. He apparently had diplopia, for he constantly closed one eye. The ankle-jerks were absent and the knee-jerks diminished. Nystagmus was not present and ataxia could not be tested. He had 22 litres of glucose-saline solution in five days, and very little food.

The diagnosis of uræmia was considered; but he was given 100 mg. of aneurine intramuscularly. As the blood-urea level the next morning was 22 mg. per 100 ml., an intravenous injection of 100 mg. of aneurine, 30 mg. of riboflavine, and 200 mg. of nicotinamide was then given three times daily.

His condition improved so much by lunch-time the next day that the glucose-saline drip could be continued, and the doses of aneurine, riboflavine, and nicotinamide were given into the drip for three more days.

On the morning of Nov. 14 he became quite reasonable and clear-headed, though he retained some amnesia about the past two days. All neurological signs disappeared by Nov. 15. Vitamins (50 mg. of aneurine, 20 mg. of riboflavine, and 100 mg. of nicotinic acid intramuscularly daily) were continued until his discharge on Nov. 30.

These two cases are representative of certain types of Wernicke's encephalopathy met with as acute emergencies. Dipsomania may sometimes be hidden even from the closest members of the family. The water-soluble B vitamins, especially aneurine, may easily be washed out from the tissues by continuous glucose infusions, particularly in older patients whose stores are usually very low.[3] [4] This was demonstrated exceedingly well in the cases described by Phillips et al.[5] Their patients received, for the first few days only, glucose-saline infusions which were followed by an intensification of all neurological symptoms and signs.

The condition may easily be mistaken for uræmia or arteriosclerosis, especially where Wernicke's syndrome presents itself with apathy, somnolence, and loss of consciousness. If it happens postoperatively, as in case 2, the continuation of infusions will soon deepen the coma and lead to fatal lesions of the hypothalamus.

London, W.1. Z. A. LEITNER.

PLASMA-UREA LEVELS IN WEST AFRICA

SIR,—In the course of a metabolic investigation on West African subjects, unexpectedly low concentrations of plasma-urea were consistently encountered. An investigation of the "normal" level of plasma-urea, undertaken on a larger series of subjects, confirmed our observation.

The subjects, ten in number, were male West Africans who were employed in the laboratory and who gave no history of renal disease. The estimations were made in samples of heparinised plasma by the method of Karr[6]; the final colorimetric determination was made in a 'Coleman Junior' spectrophotometer set at a wave-length of 5000A°. A number of standard solutions of urea were treated simultaneously and the unknown concentrations read from the standard curve so prepared. As controls a smaller number of plasma samples from European subjects resident in the unit were treated alongside the African samples. A number of the estimations were confirmed by means of the manometric hypobromite method of Van Slyke; good agreement was obtained between the two techniques.

The values obtained, each the mean of determinations on two plasma samples, are recorded in the accompanying table.

PLASMA-UREA CONCENTRATION IN AFRICANS AND EUROPEANS

Africans		Europeans	
Subject no.	Plasma-urea (mg. per 100 ml.)	Subject no.	Plasma-urea (mg. per 100 ml.)
1	15·0	1	31·0
2	13·5		
3	12·7	2	31·8
4	10·6		
5	10·2	3	25·6
6	10·7		
7	11·9	4	24·5
8	16·7		
9	18·8	5	20·6
10	19·6		
Mean	13·9	Mean	26·7

These results may be compared with the finding of Beaudisnet[7] that the average blood-urea concentration of natives of the Cameroons was 17 mg. per 100 ml. There is an indication that these low values may be related to the economic status of the subject operating through the diet; the lowest values observed were in four daily paid labourers, and the higher values in members of the permanent staff.

We would be interested to know whether such low concentrations have been observed in other, similar populations.

Hot Climate Physiology
Research Unit,
Oshodi, Lagos, Nigeria.

P. G. PHILLIPS
R. A. KENNEY.

CALCIUM CHLORIDE AEROSOL IN CHRONIC BRONCHITIS

SIR,—In patients suffering from chronic bronchitis, wheezing is often a distressing symptom and one which may be hard to relieve. Hitherto such drugs as stramonium, ephedrine, or aminophylline have been given for this purpose by mouth or by injection. The report of Charlier and Phillipot,[8] however, indicated that inhalation of certain preparations in the form of an aerosol might be an effective method of treatment. In particular, the results of these workers with a solution of calcium chloride seemed worthy of further exploration, and a clinical trial was undertaken.

A group of patients with chronic bronchitis and prominent wheezing was chosen: 6 patients were in the geriatric research unit at St. John's Hospital, Battersea; and 12 patients were treated at Queen's Hospital, Croydon. None had any expectorant mixture while under observation; and ephedrine, aminophylline, and other antispasmodics were not used during the experiment. The routine treatment was an inhalation of 3 ml. of a 10% solution of calcium chloride in water three times a day. The fluid was vaporised by means of an oxygen cylinder.

Only 2 of the patients failed to improve, and the remainder gradually lost their wheezing and dyspnœa. On examining the chest, rhonchi and sibili were no longer heard. Most patients began to get relief after the first inhalation, and only one took as long as three days before his wheezing began to go. A woman (who was treated as an outpatient and is not included in this series) stated that she was very short of breath on her way to the hospital before treatment, but could always walk home quite briskly after her inhalation.

As a result of this experiment, several patients with acute exacerbations of chronic bronchitis have been treated with inhalations of either penicillin or streptomycin dissolved in the calcium chloride solution. All responded promptly; and 3, who were treated in the original experiment, lost their wheezing as quickly as before. One of them has had two separate exacerbations cut short in this way. There is at present no evidence to suggest that this technique cannot be repeated time after time without losing its effect. As the solution of calcium chloride is both cheap and easy to prepare, it seems to offer many advantages over other drugs in the treatment of wheezing.

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[3] Sydenstricker, V. P. *Ann. intern. Med.* 1941, 14, 1499.
[4] Leitner, Z. A. *Brit. med. J.* 1948, i, 917.
[5] Phillips, G. B., Victor, M., Adams, R. D., Davidson, C. S. *J. clin. Invest.* 1952, 31, 859.
[6] Karr, J. *J. Lab. clin. Med.* 1924, 9, 3.
[7] Beaudisnet, R. *Bull. Soc. Pat. exot.* 1937, 30, 147.
[8] Charlier, R., Phillipot, E. *Arch. int. Pharmacodyn.* 1949, 78, 339.

St. John's Hospital,
London, S.W.11.

T. H. HOWELL.

ANOTHER HOT-WATER BOTTLE CASE

SIR,—I should like to add something to the account of this case in your issue of Nov. 29.

The North Liverpool Hospital Management Committee decided to resist this claim after giving the matter careful consideration, although in the present state of the law the prospects of success were not good.

The view of the case which I put before the committee was as follows:

> The patient was admitted to Walton Hospital for her confinement and she was treated with particular care because she had had difficulties over a previous confinement. After delivery there was excessive bleeding which was clearly associated with the retention of a piece of placenta. As soon as this was discovered the midwife in charge sent for the doctors; an anæsthetic was given, and on manual exploration of the uterus a piece of placenta was found and removed. After this there was serious shock, and as a result of hæmorrhage and shock the condition of the patient became very grave. Blood and plasma were administered by intravenous drip; and at one point the doctor in charge, being dissatisfied with the speed of the infusion, asked that additional bottles should be applied with the object of causing dilatation of the superficial veins. The bottles ordinarily used for maternity cases were already in position, and from my investigations it seemed to me that the accepted nursing regulations with regard to hot bottles had been carefully observed throughout. The bottle which caused the burn was one of the additional bottles ordered by the doctor.
>
> In a person with the normal circulation in the skin it is not possible to cause a burn with a bottle used in the way described; but if, for any reason such as deep shock, the circulation is in abeyance the heat is not carried away quickly enough from the part to which the bottle is applied and burning may occur. I regarded the defective circulation as the deciding factor in this case. The patient was suffering from hæmorrhage and shock, and presumably the peripheral circulation was impaired. The burn occurred only at the upper part of the right thigh because this was a relatively resistant part and the weight of the bottle increased the effect of the heat.
>
> The question then arises as to whether the doctor could properly be accused of negligence for ordering hot bottles for a patient in the condition described. Unfortunately he is in Africa and was not available to give evidence; but when I made my inquiries just after the incident he was quite definite in his statement that he had specially ordered the bottles to dilate the veins. Abundant evidence could be called to show that in a patient with a normal circulation this effect will be produced, but it is probable that in a condition of deep shock there will be no such effect and the application of heat will indeed be dangerous. A doctor who is fully alive to this danger may be placed in a difficult position. His patient does not present a static problem: her condition is changing from moment to moment, and whether the change will be for the better or the worse may depend on his treatment. It must be difficult to determine just the point she has reached, and in any case he must give her the benefit of any doubt. If the shock is of a certain degree a burn may easily be caused and the doctor may be faced with an action for damages. It would be deplorable if the fear of possible litigation should interfere with the freedom of his clinical judgment and should deter him from carrying out treatment that he may believe to be the best for his patient.

One of the dangers of a highly organised health service is that methods of treatment may become unduly standardised, and if this should happen any departure from orthodoxy would become grounds for a successful claim for damages.

In the trial of the case expert evidence was called to describe the theory of burning in cases of shock set out above; but it was admitted that this theory was not as yet the view of all the members of the profession; and apparently the judge did not accept it.

In reaching his judgment the judge came to the conclusion that there must have been negligence in the use of the water-bottles by someone, possibly a nurse who had not been called. The defence was unable to prove a negative; and, as you have reported, damages were awarded. In making this assumption the judge was able to make a decision without bringing in the question of medical responsibility for an injury resulting from treatment given in good faith and with every care; so this important issue was left undecided.

HENRY H. MACWILLIAM
Late Medical Superintendent,
Walton Hospital, Liverpool.

SUCCINYLCHOLINE APNŒA

SIR,—Several cases of long-continued apnœa following the use of succinylcholine have now been reported. The following case includes features that have not hitherto been described.

The patient was a man, aged 48, weighing 9 st. 6 lb., who had carcinoma of the rectum. Resection of the growth followed by end-to-end anastomosis of colon to rectum was performed. The premedication was 'Omnopon' gr. $^1/_3$, scopolamine gr. $^1/_{150}$. The preoperative blood-pressure was 120/80 mm. Hg.

The throat was sprayed with 2% amethocaine hydrochloride. A drip was set up comprising a 0·16% solution of succinylcholine chloride in normal saline solution. Thereafter the sequence of events was as follows:

2.23 P.M.—Induction of anæsthesia with 8 ml. of 5% sodium thiopentone solution. The drip was set going at 30 drops per minute. An endotracheal tube was introduced under direct vision and the throat packed off. Gas/oxygen (6 : 2) administered by semi-open circuit without an absorber.

2.26 P.M.—Pethidine 25 mg. intravenously. The patient was put into the Trendelenburg position with a 20° tilt.

2.30 P.M.—Operation begun.

2.34 P.M.—As the muscles were obviously "tight" the drip was speeded to 50 drops per minute for the peritoneal opening. Adequate spontaneous respiration.

2.37 P.M.—Thiopentone 2 ml.

2.39 P.M.—The surgeon complained that the peritoneum was tight. Drip speeded to 70 drops per minute to give adequate relaxation. Small spontaneous respirations present. Respiration assisted.

2.42 P.M.—Self-retaining retractor introduced. Drip slowed to 52 drops per minute. Adequate spontaneous respiration.

2.44 P.M.—As relaxation was adequate the drip was slowed to 44 drops per minute, and this rate was found to give satisfactory relaxation.

2.57 P.M.—Pethidine 25 mg.

3.6 P.M.—Thiopentone 1 ml.

Since the commencement of the resection the blood-pressure and pulse (which were taken at 5-minute intervals) had varied little, the former being 100/70, and the latter 92 per minute. The respiration, except for the period 2.39–2.42 P.M., had been fully adequate to maintain good oxygenation. There had been no undue trauma and the patient had lost relatively little blood.

3.36 P.M.—As the surgeon commenced the anastomosis, it was noted that the respirations had become very small and that the blood-pressure had dropped to 70/50. The drip was slowed from 44 to 22 per minute and the respirations assisted. A few minutes later no spontaneous respirations could be detected. The drip was further slowed to 14 drops per minute.

From 3.38 to 3.58 P.M. the blood-pressure remained at about 65/45, and the patient remained in apnœa from about 3.39 to 3.50 P.M. However, the skin was warm and of good colour, the peripheral veins were full, and the arteriocapillary reflex time remained good.

3.58 P.M.—It was decided to stop the succinylcholine administration, replacing it with dextran, which was run at about 80 drops per minute. (Unfortunately there was no blood available for administration on the lines suggested by Evans et al.[1]) Small spontaneous respirations. Respiration assisted.

4.6 P.M.—Pethidine 25 mg.

4.8 P.M.—Closure of the peritoneum was begun. The peritoneum was a little tight but the closure was managed without undue difficulty; it was considered inadvisable to administer any relaxant.

4.30 P.M.—*Operation ended.*

Between the closure of the peritoneum and the termination of the operation the blood-pressure had gradually risen to 85/40. At 4.25 P.M. the respirations became deeper and no longer required assistance, and at 4.35 P.M. the respirations were of good amplitude, although the rate was only 10 per minute, and the general muscle tone was fairly good. The cough reflex was not present on extubation. The further course of the case was uneventful.

The total amount of succinylcholine chloride given was 384 mg. (240 ml.).

This case has several unusual features:

1. The drip-rate required to produce adequate relaxation for the exploration of the abdomen (70 per minute) is, in my experience, much higher than the average.

2. After maintaining spontaneous respiration for 1 hour 8 minutes the patient suddenly became apnœic without any concomitant acute surgical or anæsthetic reason.

3. After the blood-pressure had remained steady for about 40 minutes it suddenly dropped severely and remained low without any apparent surgical or anæsthetic cause. The pulse, which had remained at about 92 per minute, rose at 3.36 P.M. to 120 per minute, and remained at this rate till the end of the operation.

4. During the period of hypotension the patient's condition strongly resembled that of a patient under hexamethonium.

The events in this case are not easily explained. I have used this technique without any such hazard in a large series of cases, including many where the total dose was much greater and where the duration was considerably longer. It is possible that the production of cholinesterase became exhausted or ceased temporarily, and the consequent rapid build-up of succinylcholine resulted in a high degree of myoneural block and, in addition, gave rise to autonomic-ganglion block.

Bovet et al.[2] and other workers have, however, found no evidence of the occurrence of autonomic-ganglion block with succinylcholine. In any case it is difficult to see why the production of cholinesterase should suddenly become insufficient after being maintained for over an hour in adequate quantity.

Manchester. MARK SWERDLOW.

SIR,—We should now like to report the results of the further work on plasma-cholinesterase levels to which we referred in our earlier note (Sept. 27). The main facts are summarised in the accompanying table, from which it will be seen that the depression of plasma-pseudocholinesterase is much greater in patients showing delayed recovery from succinylcholine ('Scoline') than that estimated on whole blood. This is what we expected, and confirms the work of Bourne et al.[3] and Evans et al.[4] Perhaps we did not emphasise sufficiently in our previous letter that the simple Michel electrometric method is equally applicable to the estimation of plasma-pseudocholinesterase and is not restricted to determinations on whole blood. Our intention was to point out that this simple technique is a sufficiently sensitive measure of cholinesterase activity to confirm the findings of other workers using the more accurate Warburg technique.

Of particular interest is case F. In this case the estimation of cholinesterase activity was carried out nine months after the observation of prolonged apnœa after administration of succinylcholine. We would b glad to hear of any other cases in which the cholinesteras level has been found to be lowered over so long a period Aldridge and Davies[5] cite evidence that after poisonin with organo-phosphorous compounds regeneration o cholinesterase is slow. In this connection it is perhap significant that for three months in the early part of thi year patient F was employed at work which entaile contact with shale-oil distillates.

FINDINGS IN SIX CASES AFTER ADMINISTRATION OF SUCCINYLCHOLINE

Case	Duration of apnœa (min.)	Whole-blood-cholinesterase number *	Plasma-cholinesterase number *
A	<5	139	77
B	<5	126	100
C	<5	112	88
D	10	99	26
E	20	100	40
F	60	108	29

* The "cholinesterase number" is the fall in pH of a buffer syste produced in 1 hour by 0·1 ml. of whole blood or plasma × 10 The normals are given by Aldridge and Davies[5] as whol blood 80–129, plasma 40–100.

Royal Victoria Hospital, Belfast.

J. E. REID
D. W. NEILL.

ŒSOPHAGEAL CONTRACTION AND CARDIAC PAIN

SIR,—Dr. William Evans in his article on this subject (Dec. 6) describes certain changes in the behaviour of the œsophagus during the swallowing of thick barium paste as œsophageal arrhythmia. The phenomenon appears to be identical with a normally functioning phrenic ampulla,[6] from which Dr. Evans gives no differential diagnosis. Furthermore, he states that œsophageal arrhythmia in health is not uncommon, but he makes no reference to the stage of respiration at which the phenomenon was observed.

We believe that this phenomenon, associated with the formation of a phrenic ampulla, can be seen in the majority of normal individuals, if instructed to hold the breath in the inspiratory position as the bolus is passing through the lower œsophagus. The reasons why a phrenic ampulla is produced are not yet full understood.

Radcliffe Infirmary, Oxford.

G. M. ARDRAN
F. H. KEMP.

DANCKWERTS AWARD

SIR,—The distribution of back pay has given a chance to medical practitioners to help the Royal Medical Benevolent Fund. In fact this letter was suggested by a writer enclosing a cheque for £50; and several other contributions of a similar amount have already been received.

With the rising cost of living there are many old people trying to make ends meet on meagre incomes. The urgent need is for increased grants. I appeal to your readers, who are willing to help this deserving charity, to send their cheques to the Secretary, Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15.

FRANK JULER.
Hon. Treasurer.

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2. Bovet, D., et al. *R.C. Ist. sup. Sanit.* 1949, 12, 106.
3. Bourne, J. G., Collier, H. O. J., Somers, G. F. *Lancet*, 1952, i, 1225.
4. Evans, F. T., Gray, P. W. S., Lehmann, H., Silk, E. *Ibid*, p. 1229.
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Obituary

KAREN HORNEY

M.D. Berlin

Dr. Horney, founder of the American Institute for Psychoanalysis, died in New York on Dec. 5.

She was born in Hamburg in 1885, and she obtained her medical qualification in Berlin, where she also received her psychiatric and psycho-analytic training. She was a member of the Berlin Psycho-analytic Institute from 1920 until 1932, when she went to America and settled there.

K. T. writes: "Dr. Horney's early contribution to psycho-analytic literature already showed that spirit of independent thought and argument which has been the outstanding characteristic of her scientific career. She threw doubt on the validity of Freud's exclusively phallic conception of infantile sexuality, and her alternative views on the psychosexual development of women have since been widely accepted.

"Life in the United States seemed to kindle the spirit of independence in her. She began to examine critically the premises and concepts of psycho-analytic teaching which, she said, had 'come into a blind alley, manifesting itself in a rank growth of abstruse theories and the use of shadowy terminology.' Her declaration of independence was set out in a series of books, appearing between 1936 and 1951—*The Neurotic Personality of Our Time*, *New Ways in Psychoanalysis*, *Self-Analysis*, *Our Inner Conflicts*, and *Neurosis and Human Growth*. In 1941 she founded the American Institute for Psychoanalysis for the teaching and propagation of her views.

"She rejected Freud's biological and 'instinctivistic' orientation and replaced it by a cultural and sociological approach. She held that the main motive force of human behaviour did not, as Freud thought, lie in instinctual urges to obtain satisfaction, but in a universal desire for safety in a world that was considered as menacing. The core of neurosis was not a libidinal conflict, but a basic anxiety about being lonely and helpless in a hostile social environment. To overcome this basic anxiety three kinds of attitude could be adopted in human relationships: a movement towards people, causing 'compliant' personality types yearning for the affection of others; a movement against people, producing 'tough' persons striving for power, prestige, and possessions: and a movement away from people, causing 'detached' and emotionally distant personalities.

"Karen Horney has sponsored new ways in psycho-analysis which have run close to the modern trend of thought in social psychology. Her emphasis on the importance of cultural differences and on the significance of interpersonal relations in the moulding of character and personality has appealed to many who were unable to follow more orthodox psycho-analysts into the labyrinthine recesses of intrapsychic conflicts."

Births, Marriages, and Deaths

BIRTHS

ALLEN.—On Dec. 6, at Farley House, Farnborough, Hants, to Edna (née Browne), wife of Dr. P. L. Allen—a son.

HARVEY.—On Dec. 7, to Jean (née Jeffery), wife of Mr. Thomas G. Harvey F.R.C.S., of Upper Basildon, Berks—a daughter.

MATTHEWS.—On Dec. 9, at Lambeth Hospital, to Mary (née Dendy), wife of Dr. Michael Matthews—a daughter.

MARRIAGES

DOW—MILLBANK.—On Nov. 28, at Shoeburyness, James Dow, M.B., to Jean Millbank.

SETH-SMITH—REID.—On Nov. 29, David William Seth-Smith, M.R.C.S., of London, to Jean McClymont Reid, of the Argentine Republic.

DEATHS

BODMAN.—On Dec. 7, at Addlestone, Richard David Bodman, M.A., M.B. Brist., aged 43.

DAY.—On Dec. 9, at Hans Place, London, Bernard Day, M.D. Camb., M.R.C.P., formerly of Kuala Lumpur.

EVE.—On Dec. 7, Frank Cecil Eve, B.A., M.D. Camb., F.R.C.P., of 9, Newbegin, Beverley, Yorkshire, aged 81.

HARTLEY.—On Dec. 6, at Headington, Oxford, Harold Hartley, M.D. Lond., F.R.C.S., aged 79.

ORD.—On Dec. 7, at Dumfries, Gavin Ernest Ord, O.B.E., M.B. Aberd., lieut.-colonel, R.A.M.C. retd.

PIGOTT.—On Dec. 8, at Shrewsbury, John George Glynn Pigott, O.B.E., L.R.C.P.I.

WATSON.—On Dec. 6, George Trustram Watson, O.B.E., M.A., M.B. Camb., F.R.C.S., of Tunbridge Wells.

Notes and News

U.S. HEALTH PLAN

LAST January President Truman set up a commission, under the chairmanship of Dr. Paul Magnuson, to review the health needs of the United States "from an impartial and non-controversial viewpoint." The report of this commission was being published on Dec. 18. Dr. Magnuson has announced (*New York Times*, Dec. 4) that the commission believes that comprehensive health care can be made available to all the people in the United States on an insurable basis without continuing federal subsidies. It believes that any scheme should be started by "the people at the grass roots" by the extension of existing voluntary and industrial health prepayment schemes. "The job can be done by private plans, by the tremendous medical set-ups of industry, by the doctors in the home town," Dr. Magnuson said. "Federal grants in aid can be used to stimulate the growth of private prepayment, but without continuing subsidies." He added that the commission contemplated health centres being set up and run by local communities, all the work being done by local doctors and the nearest group of consultants. Federal grants in aid might be used to stimulate the growth of diagnostic centres, to build up health personnel and facilities, and for large-scale research.

ELIZABETHAN PHYSICIAN

Dr. Walter Baily, physician to Queen Elizabeth I, is known to fame for having tactfully refused to provide the henchmen of Lord Robert Dudley with a bottle of physic for the unhappy Amy Robsart. He thought, not without reason, that poison might be added before it was administered, and he had no wish to be hanged as a cover for someone else's sin. Little else is known about him. Mr. Horton-Smith [1] has traced the descent of the Baily family through seven generations, starting with the physician's father. The text of this book is crowded with detailed bibliographical material. Though it is written in legal language and cannot be read at all easily, it contains a vast amount of detailed research which will be of great value to anyone interested in the family.

ADVERSITY OVERCOME

Dr. Carlson's autobiography [2] which appeared in the United States in 1941, has now been published in this country. It is an inspiring account of how a "spastic" has overcome both poverty and his disability, and has been able to qualify in medicine and devote his life to those similarly afflicted. Perhaps the most striking part of the book is the account of his visit to relatives in Sweden "who found it strange that their contact with members of the family who had gone to America should be resumed through the appearance of the one least fitted for survival." The book would interest any kind of reader, but it can be specially recommended to the parents of children with cerebral palsy, or indeed with physical handicaps of any kind.

University of Oxford

Sir Howard Florey, F.R.S., has been elected to an honorary fellowship at Magdalen College.

University of Cambridge

The Raymond Horton-Smith prize for 1951-52 has been awarded to Dr. D. R. Smith and Dr. J. P. Henry.

Royal College of Physicians of Ireland

On Dec. 5 the following, having passed the final examination of the Conjoint Board of Ireland, were admitted licentiates in medicine and midwifery:

K. A. Beahan, Adrian Blake, M. F. Bonar, Romuald Calo, G. J. Coghlan, A. W. Eldemire, J. E. Fahy, M. B. Griffin, W. W. Kobler, L. G. Meagher, Pawel Michalski, J. A. Moffitt, Dermot MacAlister, Frank McCrystal, Marianne Neumann, William Nolan, Gertrude Shaw, Gustawa Stendig, H. R. Trueman, Audrey Wilkinson.

Welsh National School of Medicine

Dr. H. J. Whiteley has been appointed senior lecturer in the department of pathology and bacteriology. Dr. Whiteley is at present lecturer in pathology in the University of Sheffield.

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[1] Dr. Walter Baily (or Bayley), c. 1529–1592. By L. G. H. HORTON-SMITH, M.A., F.S.A. Scot., Barrister-at-Law. St. Albans: Campfield Press. 1952. Pp. 115. 10s. 6d. Copies can be purchased from the author at 26, Rivercourt Road, London, W.6, price 12s., including postage.

[2] Born That Way. By EARL R. CARLSON, M.D. Evesham: Arthur James. 1952. Pp. 136. 8s. 6d.

Royal College of Surgeons of England

At a meeting of the council on Dec. 11, with Sir Cecil Wakeley, the president, in the chair, Mr. A. Dickson Wright was admitted to the court of examiners. A Moynihan lectureship was awarded to Dr. Richard B. Cattell, of the Lahey Clinic, Boston. Mr. G. T. Hankey was appointed Charles Tomes lecturer for 1953, and Prof. H. F. Humphreys Webb-Johnson lecturer for 1954. The Begley prize was presented to J. H. Breed (Westminster Hospital).

Diplomas of fellowship were granted to the following:

C. H. J. Rey, E. H. L. Cook, J. R. G. Edwards, J. N. Aston, Francis Glassow, E. A. Malkin, Leslie Turgill, P. S. Jaikaran, D. G. Maurice, Rustam Jehangir Moolan-Feroze, Helen M. Mellor, P. R. French, M. F. Hunt, G. L. Bourne, T. H. Morgan, L. A. J. Evans, M. H. Stroud, W. R. Denny, P. G. Bevan, Irene M. S. Cade, A. J. Harrold, Cyril Havard, D. J. Oakland, R. A. Payne, R. L. Grynoch, D. W. T. Roberts, Hari Ratan Ker, Joyce M. Daws, [illegible] nu Pada Chatterjee, Arun Kumar Gupta, [illegible] Brun, P. D. Blaxland, J. C. FitzHerbert, [illegible] e Panduranga Pai, H. M. Shaw, E. L. G. [illegible] W. B. Law, Cicely Pepler, R. R. Spencer, [illegible] Henley, G. G. McCloskey, D. H. McMillan, [illegible] G. Moffoot, R. K. Newing, L. H. Pimm, [illegible] G. E. Schofield, G. K. Thomas, M. A. Birnstingl, J. E. Blundell, D. J. Crockett, Kathleen A. M. Frith, N. T. Hamilton, T. A. H. Hurrell, R. O. Parnis, B. E. Pierard, Timothy Savage, Mirisse Hewage Gunadasa Karunatilaka Siriwardena, J. B. L. Taylor, J. G. Toakley, D. J. Tuffley, S. E. Wijetilaka, G. G. Wyllie, Robert Alhadeff, Yahya Cohen, J. L. Connell, W. T. Irvine, D. G. Lane, H. K. McComb, B. V. McEvedy, P. D. O'Donoghue, Guan Bee Ong, A. D. Roy, Geoffrey Wilson, A. F. Grant, G. M. Linehan, T. P. Nash, Nemish Ambalal Shah, J. H. Shoesmith, S. R. Young, J. S. Brown, W. D. Friend, Vithal Madhav Kini, R. M. Mitchell, J. B. Self, W. R. T. Turner, J. S. Karanwal.

A diploma of membership was granted to J. A. McHardy.

Association of Surgeons of Great Britain and Ireland

The annual meeting of this association is to be held in London from April 30 to May 2. The following subjects have been chosen for discussion: Management of Cancer of the Breast (opening speakers, Mr. H. J. B. Atkins and Dr. Gwen Hilton); Perforated Peptic Ulcer (Mr. T. Stewart Heslop); Postoperative Strictures of the Bile-ducts (Mr. Rodney Maingot); *Crohn's Disease (Mr. Harold Edwards).*

World Health Organisation

Dr. Brock Chisholm, director-general of W.H.O. since 1948, has announced that he has decided not to accept the three-year renewal of his contract offered him by the World Health Assembly last May. His present term of office expires in July.

Dr. Jerome S. Peterson (New York), who has been chief medical officer of the United Nations Relief and Works Agency for Palestine Refugees in the Near East, has taken up his appointment at W.H.O. headquarters in Geneva as director of the division dealing with the organisation of public-health services. He succeeded Dr. V. Sutter, who is now assistant director of W.H.O., on Dec. 8.

Swedish Health Insurance

A government committee has proposed that compulsory health insurance for all citizens should be introduced in 1955. The scheme would be combined with a system of voluntary insurance and coördinated with the present accident insurance scheme. The annual cost is estimated at nearly Kr. 700 million (£48,200,000), of which Kr. 206 million will be covered by state grants, Kr. 311 million by private contributions, and Kr. 180 million by employers' contributions.

Emergency X-ray Service

A memorandum (M.O. 209/77/1) from the Ministry of Health suggests ways in which hospitals may provide an X-ray service at times outside the normal working hours of the X-ray department. Regional boards and management committees are asked to review their present arrangements, and to consider one of two plans should a change seem advisable. Under "stand-by arrangements" a radiographer is available at the hospital at night and at weekends; and under "on-call arrangements" the radiographer leaves the hospital but is prepared to be recalled for an emergency. With either scheme radiographers should receive time off during the day in place of time spent on duty out of normal hours. The stand-by system is suitable for large hospitals where night and weekend calls are frequent; and the memorandum suggests that such a hospital might provide a service for other hospitals in the group by arranging for patients to be referred to that hospital when other X-ray departments are closed.

Scottish R.H.B. Appointment

Mr. Edward Macintosh has been appointed chairman of the Northern Regional Hospital Board in succession to Mr. James South who has resigned from this office, but who is to continue as a member of the board.

The Company of New Elizabethans

This company has been formed to raise the standard of reading for children and to combat the influence of the "unwholesome publications of low intelligence and doubtful morality" now often offered to them. Further particulars may be had from the secretary of the company, 12, St. James's Place, London, S.W.1.

New Chest Hospital in Northern Ireland

The Northern Ireland Tuberculosis Authority has announced that the ministry of finance has approved *in principle* of the project to build a three-storey 500-bed chest hospital at Brookhill, near Lisburn, co. Antrim, at a cost of £2 million. Work will begin next spring and it is expected that the first patients will be admitted to the hospital in three to four years' time.

Diary of the Week

DEC. 21 TO 27

Monday, 22nd

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, S.E.1
5 P.M. Dr. T. H. Whittington: Astigmatism and Treatment. Factors affecting Binocular Vision.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Section of Odontology.* Dr. C. H. Tonge: Early Development of Teeth.

MANCHESTER MEDICAL SOCIETY
9 P.M. (University of Manchester) *Section of General Practice.* Prof. W. F. Gaisford: Acute Infections in Childhood.

Appointments

DUDDINGTON, A. J. E., M.B. Lond., D.P.M.: asst., dept. of psychological medicine, St. Luke's Woodside Hospital, London.

GILLIES, HUNTER, M.D. Glasg., F.R.C.P.E., D.P.M.: part-time consultant, psychiatric wards, Stobhill General Hospital, Glasgow.

GREEN, D. L., M.B. Sydney, F.R.C.S.: surgical registrar, Cheltenham General Hospital, Cheltenham.

HARRISON, IRENE, M.B. Cape Town, D.C.H.: asst. M.O., West Ham.

HOBSON, R. F., B.A., M.D. Camb., D.P.M.: asst., outpatient dept. of psychological medicine, Middlesex Hospital, London.

HUTCHISON, ALEXANDER, M.D., PH.D. Glasg., F.R.F.P.S., D.P.H., D.P.A.: M.O.H., Hull.

MCDONALD, CHRISTINA, M.B. Dubl.: asst. M.O., West Ham.

MINOGUE, FRANCES, M.B. N.U.I.: S.H.M.O., Royal Western Counties Institution, Starcross.

PENMAN, AGNES, M.B. Edin., D.OBST.: asst. M.O.H., Kirkcaldy.

RAINSFORD, C. R. C., M.D. Belf., D.P.H.: asst. county M.O. and M.O.H., Retford borough and rural district, Notts.

East Anglian Regional Hospital Board:

ABSON, E. P., M.B. Manc., D.OBST.: surgical registrar, United Norwich Hospitals.

JENNINGS, H. B. N., M.D. Lpool, D.OBST., D.P.M.: consultant psychiatrist, St. Andrew's Mental Hospital, Northampton.

JENNINGS, J. H., M.B. Edin.: surgical registrar, West Suffolk General Hospital.

MACGILLIVRAY, R. C., M.B. Edin., F.R.F.P.S., D.P.M.: asst. psychiatrist, Little Plumstead Mental Deficiency Colony.

MILLER, W. T., M.B. Aberd.: medical registrar, Nayland Sanatorium.

MORLEY, J. S. J., M.R.C.S.: surgical registrar, Norfolk and Norwich Hospital.

O'SULLIVAN, J. G., M.B., M.A.O. N.U.I., M.R.C.O.G.: registrar in obstetrics and gynæcology, East Suffolk and Ipswich area.

Appointed Factory Doctor:

DAMREL, J. R. G., M.R.C.S.: Rocester district, Stafford.

MCGREGOR, A. MCK., M.B. Aberd.: Westray district, Orkney.

MORRISON, JOHN, M.B. Aberd.: Portree district, Inverness.

YOUNG, ANGUS, M.B. Glasg.: Bonnybridge district, Stirlingshire.

Staffordshire County Council:

CAMERON, A. N., M.B. Lpool, F.R.C.S.E., D.O.M.S.: ophthalmic specialist.

JEVONS, N. A., L.M.S.S.A.: ophthalmic specialist.

KILLEN, B. U., M.B. Belf., D.O.M.S.: ophthalmic specialist.

PATERSON, W. D., M.B. St. And., F.R.C.S.E.: E.N.T. specialist.

WARWICK, NINA, M.B. Manc., D.O.M.S.: ophthalmic specialist.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

PRECISION IN DIAGNOSIS

JOHN W. TODD
M.D. Lond., M.R.C.P.
CONSULTANT PHYSICIAN, FARNHAM HOSPITAL, SURREY

THERE is a widespread assumption that it should be possible to attach to a patient a diagnosis. The perusal of a death-certificate book, for example, makes it clear that people have to die of some definite disease; no provision is made for them dying of "an obscure and baffling illness." Even such comparatively definite conditions as "cardiac failure" are condemned in the introduction, the reader being urged to employ instead some such pathological term as "myocardial degeneration." In the Services, in order to be invalided a man must have a disability; these procedures cannot be justified merely on the grounds that he has been found useless to the Service. In civil life the medical history sheets of hospitals have a small space for the diagnosis. If this is left blank or filled by some vague term an objection may be raised on the ground that the patient's condition cannot be classified properly in the card-index system. And medical students are given the impression that the bewildering diagnostic problems which they study in the wards and outpatient departments are capable of solution.

In an official work, *The Nomenclature of Diseases*, published by H.M. Stationery Office and drawn up by a committee appointed by the Royal College of Physicians of London, is listed a vast number of diagnoses. Although it is not stated that to every patient can be attached one of them, many people seem to act as if this were so, and the fact that a diagnosis appears in the *Nomenclature* gives it official status.

The *British Medical Journal*[1] says:

> "... W.H.O. has published a small booklet that describes the structure of the death certificate; explains the importance of recording the causes of death lucidly, concisely, and in correct order if the certifier's meaning is to be properly understood; and illustrates what is meant by direct antecedent, underlying, and contributory causes of death and how they should be distinguished and recorded. The underlying cause of death, which is the one selected for statistical assignment, is the condition which initiated the train of events leading to death; in a properly completed certificate it would be the last or the only cause to be mentioned in Part I of the form. The booklet also explains why certain terms are considered indefinite or inadequate and lists many of the descriptions that are found unsatisfactory and that lead to requests for clarification or for additional details."

All this seems to imply that if a doctor is shrewd enough and careful enough it is *possible* for him so to complete a death certificate that the statements therein explain just why the patient has died.

Finally, a perusal of medical textbooks gives the impression that patients can be fitted into some more or less definite category. The books are divided into chapters dealing with the diseases of the different systems of the body, with additional chapters devoted to general diseases such as the specific fevers. Even the chapter devoted to psychological disorders may be divided under such headings as "schizophrenia," "anxiety neurosis," and "hysteria," suggesting that in practice patients satisfactorily fit into these categories. With the organic diseases is a section devoted to pathology. Only in a few conditions, idiopathic epilepsy and migraine for example, will it be stated that there is no convincing pathological basis. Similarly, with the psychological disorders may appear a section on "psychopathology," often couched in the most confident terms.

THE NATURE OF DIAGNOSIS

It is apparently taken for granted that everyone knows what diagnosis *is*. At first glance the dictionary definition —"identification of disease by means of patient's symptoms &c." (*Concise Oxford Dictionary*)—may seem satisfactory. But many people with symptoms are clearly not suffering from anything which is usually described as a *disease*—typically those with a condition often given the name "anxiety neurosis." A better definition of diagnosis would therefore be "the provision of an explanation of the patient's symptoms."

The symptoms can never be explained wholly by a single organic cause; the patient's state of mind must also be taken into consideration. The degree of pain felt by an injured man does not depend on the nature of his injury alone. If he is of sensitive temperament he may suffer great pain; if he is phlegmatic and unimaginative his pain may be slight. If the suggested definition is accepted, therefore, a complete diagnosis cannot consist of a single disease entity. Nevertheless, in the case of most acute and recoverable conditions, for all practical purposes the psychological aspect of diagnosis can be left out of consideration. It makes very little difference to the assessment and management of a case of acute appendicitis that the patient is of sensitive temperament and constantly groaning or grimacing, or of phlegmatic temperament and lying impassively in bed without a murmur. In regard to progressively fatal diseases, too, the organic process is so overwhelmingly important that a diagnosis consisting of this alone is adequate.

But when a patient has a chronic and comparatively benign organic process a purely organic diagnosis is sometimes incomplete, and may be positively misleading. If a man with a sebaceous cyst which he is convinced is a cancer is given the diagnosis "sebaceous cyst," he is obviously being diagnosed wrongly. No-one would dispute that this unqualified organic diagnosis is wrong, and few would be so narrow in their outlook as to make it. But when the psychological element is not so conspicuous a purely organic diagnosis can more easily be made and may have disastrous consequences.

Striking examples of this error are those cases in which an improper surgical operation follows upon the mistaken diagnosis. A fruitful field is the chronic orthopædic conditions; and the orthopædic surgeon who ignores his patients' personalities while concentrating his whole attention upon deformities, bones, and ligaments is a menace. He may operate upon complaining hysterics with hallux valgus, pes cavus, or persistent sciatic pain, who subsequently stay in hospital for months and complain far more than they ever did before their operations.

The subjects of valvular heart lesions which do not much impair cardiac function may be diagnosed and managed very wrongly if they are studied from a purely organic angle. Dizziness, aching in the chest, and palpitation, do not justify the unqualified diagnosis "mitral stenosis," since this does not explain these symptoms. This mistaken diagnosis may be followed by the failure of the doctor to explain the true cause of these symptoms, and the patient will probably take it for granted that they are all due to a badly diseased heart. Whereas a correct diagnosis and a full reassurance and explanation may diminish or abolish the symptoms and improve the patient's state of mind.

The diagnosis in a patient with a chronic and fairly innocent organic lesion should, then, consist not merely of the name or description of that lesion. In addition, there should be some reference to the state of mind.

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[1] Leading article, *Brit. med. J.* 1952, i, 641.

THE DIAGNOSIS OF BODILY SYMPTOMS

If these considerations are ignored, and it is assumed that a single label can rightly be given to subjects with bodily symptoms, it is still often impossible to make a satisfactory diagnosis.

Many syndromes, which appear to be more or less definite entities, such as most varieties of non-articular "rheumatism," have no convincing pathology. But patients who complain of pains in the back, neck, or limbs, "pins and needles" and numbness in the hands, and the other symptoms of this group of disorders may be given such labels as "fibrositis" or "neuritis." Fanciful pathological states may be hypothesised, and even described in textbooks, with descriptions of round-celled infiltration, aggregations of fibroblasts, and œdema around nerve-fibres.

In recent years many symptoms of this type have been ascribed to prolapsed intervertebral disc, especially when pain is severe and there is objective evidence of trouble in the shape of diminished deep reflexes, muscular wasting, and stiffness of the back. No doubt there are good reasons for supposing that prolapsed disc is a real condition which explains many symptoms, but it is well to remember that before it was discovered many of the patients who would now be given this diagnosis were confidently stated to be suffering from "sacro-iliac strain" or brachial or sciatic "neuritis."

A proportion of dyspeptic symptoms can truthfully be ascribed to definite pathological causes, such as carcinoma of the stomach, peptic ulcer, colitis, and pancreatitis. But many dyspeptic subjects who appear to be free of relevant pathological changes may be told they have chronic gastritis, colitis, visceroptosis, hyperchlorhydria, and various other conditions bearing little or no relation to their symptoms. Diagnoses of this kind tend to vary from year to year according to current fashions, and the patient who thirty years ago might have been considered to have visceroptosis would, twenty years later when the gastroscope had become a popular instrument, have been thought to be suffering from chronic hypertrophic gastritis.

It is now widely believed that psychological upsets may cause dyspeptic symptoms, and many dyspeptic subjects have been given—no doubt correctly in some cases—psychological diagnoses. But to diagnose "anxiety neurosis," or even nervous dyspepsia, merely because organic lesions have been excluded is just as mistaken as is diagnosing visceroptosis from the radiological demonstration that the hollow viscera are situated unusually low in the abdomen. There are surely many dyspeptics who can no more be given a psychological than an organic diagnosis, though whatever the main cause of dyspepsia—or equally when there is no definite cause—emotional disturbances will often aggravate the symptoms.

Perhaps the commonest of all symptoms is headache. In medical articles elaborate classification of the causes of headache may be given, including a variety of intracranial states from cerebral tumour to migraine, affections of the skull, cranial air sinuses, and the structures overlying the skull, such as "fibrositis" of the fascii or "neuralgia," prolapsed cervical disc, numerous general or distant disturbances such as fevers, chronic constipation, high blood-pressure, and eyestrain, and "psychoneurosis" and other psychological disorders. But in a high proportion of the common cases of chronic or recurrent headache there is no good evidence that any organic condition is present—or if present is related to the headache. Leaving aside those who complain of pressure on top of the skull and such sensations as numbness and deadness, there is also rarely sufficient reason for diagnosing "psychoneurosis," though emotional stress is often related to individual attacks of headache.

As a rule, therefore, the only diagnosis which can truthfully be given to the subjects of headache is "headache," though in some cases a guarded psychological diagnosis can be added, and in others there is justification for using the term migraine. But the desire to attach definite labels is responsible for many wrong diagnoses. If the blood-pressure of those with headache is high, they may be said to have hypertension; if their cranial air sinuses reveal such radiological changes as thickened lining membrane, they may be said to have sinusitis; and if they have errors of refraction they may be supplied with spectacles, implying that their eyes are responsible. (It is not denied that there is never any association between raised blood-pressure and headache, nor that sinusitis and refractive errors are sometimes responsible for headache.)

PSYCHOLOGICAL DIAGNOSIS

Psychological disorders, since by their nature they lack an organic basis, are less satisfactory to those who like to deal with precise entities than are organic diseases. Nevertheless, even in the psychological field many fairly definite labels are now commonly attached to patients—such as manic-depressive psychosis, schizophrenia, involutional melancholia, conversion hysteria, and anxiety neurosis. Many of these labels may sometimes make genuine progress, by implying a fairly definite mode of behaviour and prognosis. But among that vast mass of humanity who forever remain outside the walls of mental hospitals but provide so high a proportion of the patients who frequent doctors' surgeries, it may well be doubted whether exact labels of this kind often reflect accurately what is happening. Do not such homely phrases as "depressed and worried about himself," "nervous and irritable," and "stupid and self-centred" often give a better understanding of the symptoms?

DISCUSSION

In the wards of hospitals patients affected by gross and often obscure organic lesions tend to be collected. Here it is often possible to reach a more or less precise pathological diagnosis. Should the patient's disease remain in doubt when he is alive, it may become apparent when he is on the post-mortem table—at least, if he dies between childhood and advanced middle age.

It is in the surgeries of the general practitioners that those numerous people with vague complaints without definite pathology congregate, and medical students do not penetrate there. In recent years such cases have increasingly overflowed to the outpatient departments of hospitals, often to the dismay of those medical men to whom an "interesting case" is one with gross lesions and striking physical signs. But medical students may still see comparatively little of them because the chief may select the "interesting" cases, while the others are relegated to the small rooms where registrars and clinical assistants work alone.

The great stress which is laid upon pathology is also illustrated by the frequent references to the practice of "excluding organic disease." It is commonly said that, before labelling a patient with bodily symptoms as neurotic, no effort should be spared to exclude organic disease. But this practice is demonstrably false for several reasons:

(1) The only good ground for concluding that a patient is neurotic is from the positive evidence that his behaviour and symptoms are of a neurotic character.

(2) The patient who has organic disease may also be neurotic, and the disease may be irrelevant to his symptoms, which are of psychological origin.

(3) The patient who is apparently free of any definite pathological state may not be neurotic.

(4) It is often impossible to exclude organic disease by any method short of exploratory operation—and even that may be unsuccessful. How can a cerebral glioma, a carcinoma of the body of the pancreas, a prolapsed disc, or atheroma of the coronary arteries be excluded ?

The most important reason for the great stress which is laid upon pathology in hospitals is no doubt the desire for definiteness. And the discovery of a pathological basis is a clear advance in the understanding of a patient's symptoms. By contrast, a syndrome of the muscular "rheumatism" group, recurrent headache, and the vague symptoms bound up with psychological disturbances appear to many of those with "tidy" minds highly unsatisfactory and hardly real.

Medical and surgical treatment, too, is often effective for cases with known pathology. Whereas the other cases are seldom fatal, may seem trivial, and as a rule can be treated only by symptomatic drugs, physiotherapy (the value of which is highly problematical), and reassurance, explanation, and encouragement—remedies in which many medical men take little interest.

There is, indeed, a profound desire in men's hearts to find a cause for developments. The laity often refuse absolutely to accept a doctor's statement that symptoms have no known cause. They tend to be more interested in ætiology than in actual pathology. While willing to accept the diagnosis "rheumatism" for most pains, they may show no desire to know what rheumatism is, though they will insist, in the face of all statements from their doctor to the contrary, that it is due to a damp house or a change in the weather. And they may have no objection to being told that they are merely suffering from "indigestion," which they confidently ascribe to poor food—if in the Army to the "greasy Army food"—or to bad smells. Some medical men, on the other hand, are unwilling to admit the absence of a pathological cause, while having less objection to an agnostic viewpoint in the ætiological field. But even in ætiology unjustifiable conclusions are often reached in medical circles, as is illustrated by the statements in medical textbooks, usually made on very flimsy grounds, that so many diseases are partly due to such factors as strain, fatigue, and lowered resistance. There have been phases in medical history during which a single ætiological factor has been thought to be responsible for numerous diseases. A decade or two ago, the septic focus was such a factor, and in recent years many diseases have been said to be psychosomatic, on evidence little stronger than that supporting the septic focus theory.

Though the doctor in his heart of hearts may appreciate his inability to make a pathological diagnosis, reasons of prestige may sometimes persuade him to do so. This may be not so much to please patients as to impress medical students, nursing sisters, or physiotherapists. The physician who confidently states that a patient has subacute interstitial fasciitis may seem at the moment more impressive than his more modest colleague who can only say that a similar patient is suffering from a "persistent pain in the back."

The practice of making pathological diagnoses on insufficient grounds is inevitably responsible for erroneous statistics, and consequently for all sorts of other erroneous conclusions. During the recent war, many diagnoses recorded on military hospital record cards, such as coryza, influenza, dengue fever, and clinical malaria, were used quite loosely, according to individual taste. The value even of many of the statements made on death certificates is highly problematical, especially the popular diagnoses given to the very old, such as myocardial degeneration, coronary arteriosclerosis, and cerebral arteriosclerosis.

I suggest, therefore, that those concerned with administrative medicine should ask for precision only when precision is possible. When it is not, they should encourage the doctors who fill the forms to leave their answers vague. If Army medical officers were told to diagnose dengue and sandfly fever only from convincing evidence, to diagnose coryza only when the symptoms are those of the common cold, and when the cause of fever is obscure to diagnose "short fever of undetermined origin," the statistics at the medical directorate would be far more valuable. Similar considerations apply to death certification. If it were laid down that indefinite terms like senility, cardiac failure, and "sudden cardiac death without demonstrable basis" *should* be used when no gross cause of death can be found, the value of the statistics relating to the definite causes of death would be enhanced. It might also be sound to include a small space on the death certificate in which the compiler could fill in the number 1, 2, 3, or 4, to represent the degree of likelihood of his statements. Thus, 1 would mean the diagnosis given is virtually certain, 2 that it is highly probable, 3 that it is fairly likely, and 4 that it is a reasonable possibility. And why should not a similar attitude be encouraged in coroners' courts ? At present, medicolegal pathologists make completely confident statements as to the cause of death, which must often be a severe strain on their consciences. Why should not they be allowed to state that a patient has died of, say, "natural causes of undetermined type" ?

CONCLUSION

In a high proportion of patients it is impossible to make a pathological diagnosis. Many of them complain of symptoms of psychological origin, and in their case some sort of psychological diagnosis can be reached, though it will inevitably lack the precision of a pathological one. Moreover, "anxiety neurosis," "conversion hysteria," and other comparatively precise psychological labels are often best avoided, the true state of affairs being better represented by more indefinite terms. But many more patients—typically those with non-articular "rheumatism"—no doubt have a pathological basis to their symptoms, but a basis whose nature is not at present fully understood. Nothing could be further from my intention than to belittle the importance of pathology, or to suggest that it is not often the right course to attempt to find a pathological basis to symptoms. But I believe that there has been a general tendency to assume that nearly all that matters in medicine can be reduced to pathological terms, and I urge that doctors should view their diagnostic problems with humility, should realise how often they are in the dark, and, if only a vague diagnosis can be legitimately reached, should avoid the pretence of a precise one.

When pathology has advanced as far as it can advance, a bald pathological label will still remain an incomplete diagnosis, even for those patients who have a pathological lesion which is related to their symptoms. For patients with some grave or fatal organic disease, and especially for those with an acute and recoverable illness, the pathological diagnosis usually represents sufficient of the truth for all practical purposes. It is the patients with chronic and fairly benign organic lesions whose diagnoses should indicate more than just these lesions. The man with a sebaceous cyst which he fears is a cancer and the woman with varicose veins which she believes are so ugly that everyone stares at her, should be diagnosed, not by a word or two, but by a sentence. The practice of attaching a single diagnostic label to patients is, therefore, not only wrong now; it will always remain wrong when applied to those with chronic benign lesions.

I wish to thank my father for his help in revision, and Dr. C. C. Thomas for his advice and criticism.

INFLUENCE OF A MERCURIAL DIURETIC ON THE MECHANISM OF DIURESIS IN CONGESTIVE CARDIAC FAILURE

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IN a previous paper (Lowe 1951) it was shown, in a series of œdematous patients with congestive cardiac failure, that water is lost from the body during diuresis in a manner which conforms to a uniform pattern. It was concluded from these observations that there exists a mechanism which controls the water content of the body, and some of its characteristics were defined. Subsequently (Lowe and Sayers 1952) this concept was analysed in terms of an "open" storage system, and the mechanism was shown to contain volume-disturbing and volume-restoring forces. It was also shown in the cases discussed, that where diuresis had followed rest in bed and dietary measures these forces were acting in an essentially normal fashion even though the patient was still œdematous. During recovery the major change in the mechanism was an increase in sensitivity.

This paper presents a study of changes in weight and fluid balance in œdematous patients with congestive cardiac failure to whom a mercurial diuretic ('Mersalyl') was given. Several types of behaviour can be recognised, and the six cases described resemble many others seen during our investigations. These observations are discussed in the light of the hypothesis, already enunciated, that there is a mechanism in the body which controls the total water volume and which behaves as an "open" system.

PROCEDURE

After admission to the ward these patients were confined to bed for the greater part of the period of observation. As in the previous series, they were placed on a diet of known and fixed caloric value, the sodium content of which was kept constant throughout the period of observation (see table). The patients were encouraged to drink freely of sodium-free fluids. Digitalis preparations were given only if the patient had been receiving them before admission or for the treatment of an arrhythmia. Intramuscular injections of mersalyl were given in the doses and at the times indicated. The fluid intake and output and, when possible, the weights were recorded daily. From these figures the fluid-balance curve was constructed with the corrections previously discussed (Lowe 1951).

As the weight curve is usually more accurate than the fluid-balance figures, this curve has been differentiated to give a fluid-balance curve. The curve so derived is shown superimposed on the observed fluid-balance curve as a check on the accuracy of measurements.

CASE-RECORDS

Case 1.—A man, aged 88, was admitted to hospital shortness of breath on slight exertion and œdema of his and ankles. Examination revealed tense œdema of lower limbs. Moist sounds were present in the lungs. No gross abnormality was detected in the heart. His blood-pressure was 140/90 mm. Hg. He was treated by rest in bed and with the usual dietary régime, and his weight and fluid balance were observed over 25 days. The weight curve (fig. 1) shows that his weight fluctuated up and down over the first 17 days. This indicated an oscillating fluid balance, at first retention, then loss, and again fluid retention. On the 18th day injections of mersalyl (2 ml.) were begun and they were given on alternate days for 6 days. These led to pronounced diuresis, which was maximal after the first injection and then diminished as indicated in the curve. By the 24th day the patient was free from œdema.

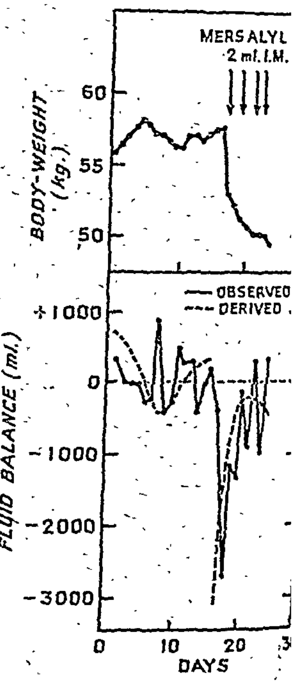

Fig. 1—Weight and fluid balance in case

Case 2.—A woman, aged 42, was admitted to hospital for investigation and treatment of malignant hypertension. She ha had shortness of breath and œdema of the legs for the pas 2 years. Examination revealed an enlarged heart, blood pressure 240/150, no increase in venous pressure, some live enlargement, moist sounds throughout the lungs, and seven œdema of the legs. Her ocular fundi showed gross papillœdem and some hæmorrhages. She was treated at first by rest in be and with dietary régime and digitalis. Over the first 15 day her weight increased although she showed some symptomati improvement. The fluid-balance curve (fig. 2) showed a oscillating fluid retention. From the 15th to the 43rd day sh was given intramuscular mersalyl 1 ml. daily. This produce an increasing loss of weight. Coincident with the first injectio of mersalyl the fluid-balance curve, which had been in a phas of retention, indicated a sudden loss of fluid and then oscillated By the 43rd day she was free from œdema, and her weigh

DATA ON ŒDEMATOUS PATIENTS

Case no.	Sex	Age (yr.)	*Diagnosis*	Excess body-fluid (litres)	Fig.	Sodium intake (g. per day)	Average daily fluid intake (ml.)	Treatment before admission	Treatment during observation
1	M	88	Atherosclerosis, myocardial degeneration	7	1	1	1600	Nil	Routine; mercurial diuretic on days 18, 20, 22, and 24
2	F	42	Malignant hypertension	15	2	1	2000	Rest in bed, digitalis, mercurial diuretics	Routine; *digitalis*; mercurial diuretic daily from days 15 to 43
3	F	53	Hypertension	3·5	3	1·5	1400	Nil	Routine; mercurial diuretic on days 8, 9, and 31
4	M	61	*Chronic rheumatic valvulitis (mitral and aortic) and carditis; auricular fibrillation*	About 11	4	2	1900	Periods of rest in bed, digitalis and mercurial diuretics, intermittently for two years	Routine; digitalis (after 17th *day*); mercurial diuretic as indicated in fig. 4
5	M	58	Hypertension	13	5	1	1900	Digitalis	Routine; *digitalis*; mercurial diuretic on day 7 and every second day from day 22 to day 36
6	M	53	Atherosclerosis, myocardial degeneration	About 11	6	0·5	2500	Rest in bed, digitalis, mercurial diuretics for at least two years	Routine; digitalis; mercurial diuretic every 2nd day; ammon. chloride 1 g. t.d.s.; acupuncture of legs on 35th day

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* Aided partly by a grant from the National Health and Medical Research Council, Australia.

remained constant during the remainder of the period of observation.

Case 3.—A woman, aged 53, was admitted to hospital with a year's history of shortness of breath on exertion. This dyspnœa had progressively increased until at the time of admission she was orthopnœic. She gave no history of any previous illness. Examination revealed distension of her neck veins to 6 cm. above the clavicle when she sat upright. Her heart was grossly enlarged, and a basal systolic murmur was heard. Her blood-pressure was 160/120. Her liver was enlarged. She had moderate œdema of the lower limbs.

She was treated by rest in bed and with the standard diet. On the 8th day, as the œdema was still marked, a small test dose of mersalyl was given, and on the 9th day a dose of 2 ml. was injected intramuscularly. Fig. 3 shows that, although her weight at first increased, the fluid-balance curve indicated a reduced rate of water retention from the start of rest in bed. Then followed an increasing fluid loss which continued until the day after the second injection of mercury. The curve then reversed its direction, showing in order a diminishing fluid loss, an increasing fluid retention, and a cycle of fluid loss and retention.

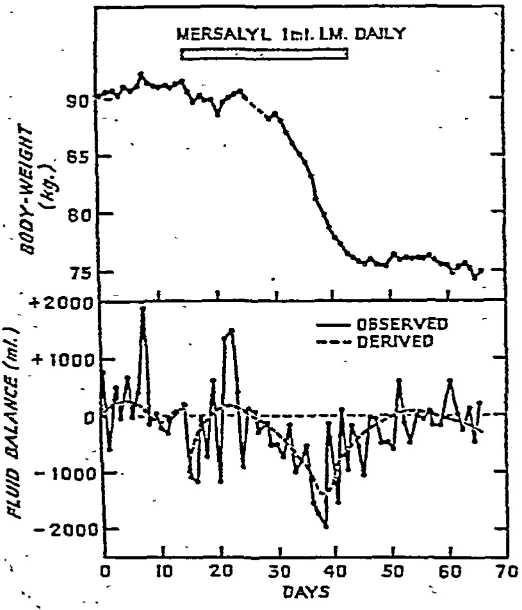

Fig. 2—Weight and fluid balance in case 2.

On the 31st day another injection of mersalyl 2 ml. was given, and this was followed by a rapid diuresis. The balance curve on this occasion revealed a sudden change from fluid retention to fluid loss, which in succeeding days diminished and gave way to fluid retention. By the 40th day she was free from œdema and other signs of congestive cardiac failure.

Case 4.—A man, aged 61, was admitted to hospital with three months' history of steadily increasing congestive cardiac failure. A similar episode a year before had responded to treatment. He had had rheumatic fever in childhood. Examination showed distension of the neck veins to 7·5 cm. above the clavicle when he sat upright, considerable enlargement of the liver, and generalised œdema. Fast auricular fibrillation (ventricular rate 136–150) was present. The heart sounds and murmurs were those of mitral stenosis. (The presence of this lesion was confirmed at necropsy 15 months later.) Moist sounds were present throughout the lungs. He was treated by rest in bed and with the usual dietary régime, and intramuscular mersalyl 2 ml. on alternate days. The fluid-balance curve (fig. 4) shows an increasing fluid loss. The jugular venous pressure fell to 3·5 cm. above the clavicle, but the tachycardia persisted. Rapid digitalisation was then instituted, and the ventricular rate fell to 80 beats a minute.

After the 17th day, as his œdema had almost disappeared, the injections of mersalyl were given at increasing intervals (fig. 4). The balance curve shows that at this stage each injection was followed by considerable diuresis.

Observation of this patient ceased after the 45th day, when he was free from all signs of congestive failure.

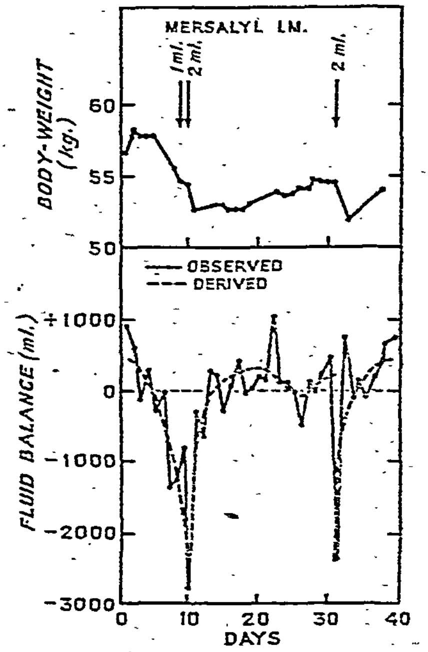

Fig. 3—Weight and fluid balance in case 3.

Case 5.—A man, aged 58, had had hypertension for 12 years. During the 4 months before admission he had become dyspnœic on exertion and his legs had become swollen. Examination revealed an orthopnœic man with neck veins distended to 5 cm. above the clavicle. His heart was enlarged, and moist sounds were heard in both lungs. His liver was considerably enlarged. There was gross œdema of the legs and sacrum. He was treated with the usual dietary régime and digitalis in the same dose as he had had previously. He was given one intramuscular injection of mersalyl 2 ml. on the 7th day. On the 22nd day regular intramuscular injections of mersalyl were started and continued on alternate days to the 36th day. His weight (fig. 5) diminished from the time of admission, and his fluid-balance curve showed an oscillating fluid loss but no sudden disturbances. He was free from œdema and had no signs of congestive failure by the 35th day.

Case 6.—A man, aged 53, was admitted to hospital with a 5 years' history of recurrent episodes of congestive cardiac failure. He had diastolic hypertension (blood-pressure 136/110) and cardiac enlargement. He had been treated by rest in bed and with digitalis and mercurial diuretics. However, over the past 3 months œdema and shortness of breath had become gross.

On admission he was treated by rest in bed and with digitalis in the same dosage as previously, a dietary régime with a sodium intake of 250 mg. a day, ammonium chloride 1 g. three times a day, and intramuscular mersalyl 2 ml. on alternate days. Because his œdema and dyspnœa were so gross it was impossible to weigh him daily, and his fluid balance was computed from his intake and output of water.

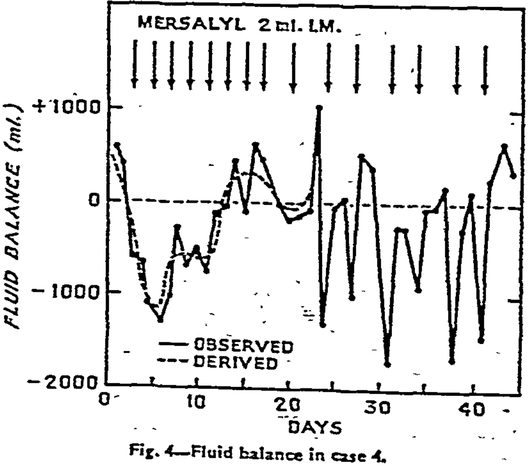

Fig. 4—Fluid balance in case 4.

The curve (fig. 6) indicates that the rate of water retention diminished from the time of admission, and alternating periods of fluid retention and fluid loss occurred. However, by the 34th day there had been no net loss of weight, for the periods of fluid loss were balanced by periods of fluid retention. At this time, in view of his poor general condition and high venous pressure, 500 ml. of blood was removed by rapid venesection. This, however, effected no improvement; so on the 35th day the skin of both legs was incised in many places and a considerable loss of fluid ensued during the next 48 hours. Fig. 6 shows that after this time a diuresis followed most of the injections of mersalyl, and that he was, on the average, losing fluid. By the 55th day he was free from œdema and from signs of congestive cardiac failure although he had little exercise tolerance.

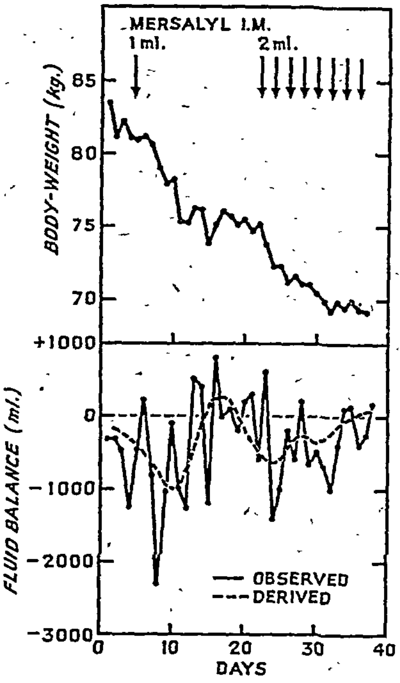

Fig. 5—Weight and fluid balance in case 5.

DISCUSSION

Inspection of the fluid-balance curves of these cases shows that the type of cyclic curve previously described is present in all. Cases 1 and 2 were, at first, treated under the same conditions as in the previous series, and in them the curve executed a typical complete cycle before mersalyl was given. A similar cycle is seen in case 3 between the two groups of injections of mersalyl.

However, two modifications of the curves are seen after the exhibition of mercurial diuretics. In cases 1 and 2, and after the third injection of mersalyl in case 3, there was a sudden change of the curve from fluid retention to fluid loss, and this change coincided with the exhibition of mersalyl. After this sudden upset the curve returned to its cyclic form, even though injections of mersalyl were continued.

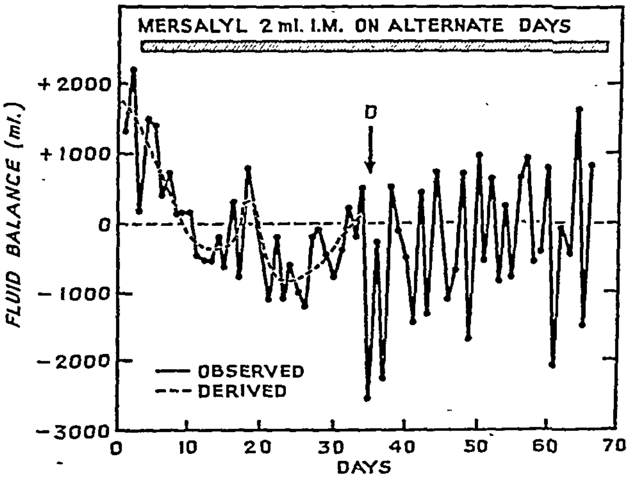

Fig. 6—Fluid balance in case 6, showing response after drainage (D) of œdema fluid from legs.

In cases 4, 5, and 6 the administration of mersalyl produced no sudden change in the cyclic curve, but in cases 4 and 5 the diminishing fluid-loss phase of the cycle was interrupted by a short cycle of increasing fluid loss, giving the appearance of a hump on the rising slope of the curve. In case 6 there is a similar hump near the trough of the curve. Further, in case 4, when the patient was free from œdema and the time between injections of mersalyl was increased, the fluid-balance curve became broken up, with a considerable diuresis following each injection. Between these sudden diureses the curve swung towards or across the zero balance line in much the same manner as is in case 3 after the isolated mersalyl injection. In case 6 the smooth cyclic curve persisted during mersalyl administration until acupuncture was performed, when a sudden dislocation of the curve from fluid retention to fluid loss occurred. Thereafter nearly every injection produced a pronounced diuresis followed by a rapid swing to fluid retention.

It is a matter of clinical observation that the response to mercurial diuretics varies from patient to patient. Sometimes a good diuresis follows each injection; sometimes there is not much fluid loss with each injection but a steady sustained diuresis; and at other times mercurial diuretics produce no diuresis even though their action is augmented with ammonium chloride and correction of blood-electrolyte patterns. These types of response are all illustrated by the cases presented, which, together with other similar studies, afford a possible explanation of the variations in response to this therapy.

In our cases a sudden onset of diuresis was seen only when the cyclic fluid-balance curve was rising and the patient was in a phase of fluid retention. The exhibition of mersalyl then produced a sudden change to fluid loss. If, however, the balance curve was falling, as in the first two injections of case 3 and in cases 4 and 5, there was no such displacement and the only change is a probable exaggeration and prolongation of the fluid-loss phase of the cycle.

The curves presented show also differences in the response of patients to isolated and repeated injections of mersalyl. These differences can be explained by the observations of Burch et al. (1950), who studied the rate of disappearance from the blood of mercurial diuretics in different people. They noticed that in patients with congestive cardiac failure the blood-mercury level often fell more slowly than in normal persons. Further, their results indicated that daily doses of a mercurial diuretic would build up a steady concentration of mercury in the blood-stream, and often in the presence of cardiac failure doses administered at intervals of 48 hours would also do this.

Thus in case 3, where the blood-mercury level was not maintained, it appears that the volume-controlling mechanism soon reverted to its original state and the diuresis diminished rapidly, giving way to fluid retention.

In case 4 administration of mersalyl every second day appears to have produced a continuous mercury effect on the system; but after the 15th day, when the time between doses was increased, probably a blood-mercury level above therapeutic levels was not maintained and the system behaved as though each dose were isolated.

The curves of cases 1, 2, and 5 and portions of the curves of cases 4 and 6 suggest that the repeated injection of mersalyl produced a continuous mercury effect, which once established gave a smooth water-balance curve.

Case 6 is an example of a patient clinically resistant to mersalyl but in whom the smooth cyclic curve can be seen, probably moving very slowly towards an effective diuresis. In this case acupuncture produced a sudden dislocation of the rising curve, and thereafter the system became sensitive to mersalyl in a manner similar to the response of other cases to single doses or widely spaced doses. This suggests that the rate of excretion of mercury had now been increased, and a steady therapeutic concentration was not being maintained in the body.

When considered in the light of an "open" system containing volume-restoring and volume-disturbing forces, these results suggest that mercurial diuretics act on one of the forces, either inhibiting one or enhancing the action of the other. The sudden and obvious change in the system which results when mercurial diuretics are exhibited during a rising phase of fluid retention suggests inhibition of the dominant factor rather than an exaggeration of the recessive one. On the contrary, when the diuretic is given on a falling curve, the relatively minor changes produced suggest enhancement of the dominant factor or blocking of the recessive factor.

If the forces in this system, represented as volume-restoring and volume-disturbing, are biochemical reactions, it is reasonable to assume that a mercurial diuretic inhibits one, for Goth et al. (1950) have shown that mersalyl inhibits an enzyme system in the kidney cells.

Now, if the affected process is dominant at the time of inhibition, the system will be thrown towards the other extreme and the fluid-balance curve suddenly displaced. By contrast, if the process is not dominant, only a small effect will be seen and no change in the direction of movement of the system will occur.

That the affected factor is not kept completely inhibited is shown by the way in which the cyclic curve continues even though the body concentration of the mercurial diuretic is maintained. The system is, however, modified, as is indicated by the "hump" in the cyclic curves. The continuance of a smooth cyclic curve implies the continued action of opposing forces.

The curves of case 6 indicate that a sudden displacement of the system can be produced by agents other than mercurial diuretics. In this instance a cyclic curve, modified by a mercurial diuretic, was suddenly altered by acupuncture which released fluid from the body reservoir. This permitted a readjustment of the volume-restoring and volume-disturbing forces so that an over-all fluid loss continued. Further, it sensitised the system to injections of mercurial diuretics given on alternate days, which then acted as though they were injections isolated by considerable periods of time.

CONCLUSIONS AND SUMMARY

These cases record the various types of response to mercurial diuretics which are seen in patients œdematous from cardiac failure.

These observations support the hypothesis that there exists in man a water-volume-controlling mechanism which has as components volume-restoring and volume-disturbing forces. This mechanism operates at varying sensitivities. These observations also show that it is possible partially to block one of the components with mercurial diuretics. The varying clinical response seen on exhibiting these drugs has a possible explanation in terms of the phase of activity of the system at the time of their exhibition, and of the rate of excretion of mercury by the patient at that time.

It is a pleasure to thank the members of the Baker Institute and Clinical Research Unit for their help in collecting and assessing the data used in this investigation.

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CUTANEOUS ARTERIAL SPIDERS FOLLOWING USE OF ADRENOCORTICOTROPIC HORMONE

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VARIOUS cutaneous reactions and vascular phenomena have been noted after the use of adrenocorticotropic hormone (A.C.T.H.) and cortisone, and these are commonly associated with signs and symptoms resembling Cushing's syndrome (pituitary basophilism). Similar changes, such as brown pigmentation and an increased tendency to bruise, are sometimes seen in normal pregnancy. In the case described here cutaneous arterial spiders (*Lancet* 1946) appeared during treatment with A.C.T.H. I have been unable to trace any previous record of this happening.

CASE-RECORD

A married woman, aged 25, was admitted to Drammen Hospital last May with a diagnosis of rheumatism. There was no family history of hæmorrhagic tendencies or telangiectases, and during a normal pregnancy 8 years earlier the patient had not developed telangiectases. Her health had been good and her periods regular. She had had no liver disease. She now complained of a week's pyrexia, painful swelling of the ankles, and red tender nodes on both legs.

Condition on Admission

Her temperature was 101·6°F (38·7°C) and her pulse regular. She had typical erythema nodosum on the front of both legs. Her skin was moist with some moles on her back and limbs, but otherwise normal except for the erythema nodosum. Both ankle-joints were swollen and tender, with some limitation of motion. Her lungs, heart, and abdomen were normal. Her blood-pressure was 115/70 mm. Hg. A blood-count showed Hb 75%, red cells 3,800,000 per c.mm., white cells 11,200 per c.mm., and eosinophils 203 per c.mm. The erythrocyte-sedimentation rate (E.S.R.) was 86 mm. in one hour (Westergren). Her urine, sp. gr. 1·023, was normal. Meinicke's test was negative. The urinary excretion of 17-ketosteroids during a 72-hour period was 8·9 mg. in 24 hours. An electrocardiogram was normal. Radiography of the chest showed clear lungs. A tuberculin test was negative.

Treatment and Progress

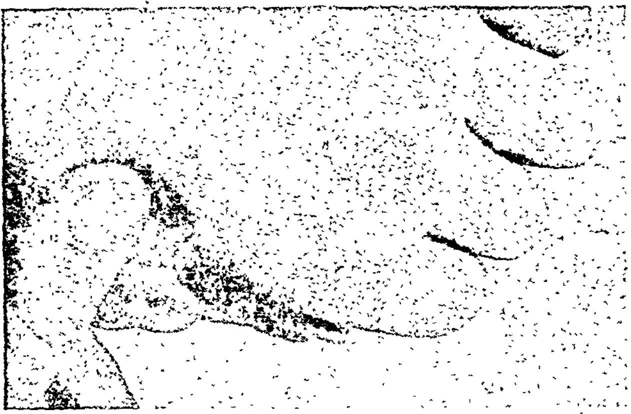
Our diagnosis being acute rheumatoid arthritis with erythema nodosum, A.C.T.H. therapy was started with 'Corticotropin' (Nyco), a preparation of A.C.T.H. made from the frontal lobes of pituitary glands of whales. I am informed that the extraction procedure used yields a product substantially free from gonadotropins and thyrotropin, but regular tests for the presence of posterior-lobe contaminants are made by the manufacturers, who keep the oxytocin content below 0·2 I.U. per 100 ml. The presence of some growth-hormone activity cannot be excluded.

The treatment was started with intravenous infusions of corticotropin 10 I.U. in 1000 ml. of 5% glucose given over a period of 8 hours daily on 5 successive days. The eosinophils immediately disappeared. At the end of this course of treatment the patient felt perfectly well, with normal temperature and no joint pains; and the erythema nodosum had gone leaving only some discoloration of the skin. The E.S.R. was now 30 mm. in one hour. In the next 4 weeks, with the exception of a few days, small doses of intramuscular A.C.T.H. were given daily to a total of 300 mg.

Side-effects of Treatment

After 2 weeks' intramuscular A.C.T.H. therapy the patient's face became rounded, she had sweating and furunculosis of her face and upper thorax, and her limbs tended to bruise easily. She said she felt as though she had a hump on the back of her neck, where a moderate amount of fat appeared. In the 3rd week she had an increased growth of hair over the lower parts of her legs, and her pubic hair extended upwards toward the navel. She developed many pigmented nævi on her limbs, brown pigment appeared at the sites of needle punctures, and her moles became darker.

At the beginning of the 4th week ten telangiectases were found. At the end of the week four more had appeared and those already present had become bigger One was at the root



Arterial spider on patient's hand.

of the nose, one on the left shoulder, two on each upper arm, one on each lower arm, and the rest on the backs of the hands. Two of them were larger than the others and macroscopically resembled cutaneous arterial spiders. They had a raised central pulsating point, from which branching vessels radiated like the legs of a spider (see figure), and they were surrounded by an area of erythema. They did not show any tendency to bleed. The mucosa of the mouth, tongue, pharynx, and nose was not affected.

At this juncture pregnancy was excluded by gynæcological examination and by the fact that the patient's periods were normal. Liver disease was excluded by functional tests, including the thymol-turbidity test, the Takata-Ara reaction, and the prothrombin value.

A.C.T.H. Discontinued and Resumed

A.C.T.H. therapy was then stopped for 10 days, at the end of which the number of telangiectases remained unchanged but some were much smaller. The pulsation of the two arterial spiders was no longer visible to the naked eye.

During the following 10 days A.C.T.H. was again given daily intramuscularly. By the end of this time four new telangiectases had appeared—two on the back of the left hand and two on the volar side of the right fifth finger. The two vascular spiders were distinctly enlarged, and pulsation could once more easily be demonstrated. It should perhaps be emphasised that these changes neither coincided with nor preceded a menstrual period. The urinary excretion of 17-ketosteroids was now increased to 24 mg. in 24 hours. The urinary excretion of corticoids was 4·72 mg. in 24 hours. The excretion of œstrogens was within normal limits—17 M.U. per 1000 ml.

The patient had no complaints and was discharged after being in hospital 33 days. Her E.S.R. was then 15 mm. in one hour.

Follow-up

Since discharge the patient has attended hospital as an outpatient for 5 months. Her periods have been regular and liver-function tests normal. There have been no symptoms or signs of relapse of her rheumatism. 6 weeks after the last injection of A.C.T.H. the urinary excretion of 17-ketosteroids, corticoids, and œstrogens was normal (7·8 mg. in 24 hours, 0·82 mg. in 24 hours, and 56 M.U. per 1000 ml. respectively). The fullness of her face and her excessive sweating have disappeared, but mild acne persists. The hirsutism and pigmentation are unchanged. Seven of the telangiectases have vanished in the week after discharge from hospital, and all the rest are smaller, most being scarcely visible. Pulsation in the arterial spiders could not be detected at the end of the first week.

DISCUSSION

Arterial spiders have previously been observed in patients with rheumatic disease, but apparently only in association with clinical signs of heart-failure and cardiac cirrhosis. Such signs were absent in the present case. The vascular lesions in the present case seemed to be caused by A.C.T.H.; and their number and the size were indisputably influenced by the interruption and the resumption of A.C.T.H. therapy.

The development of the telangiectases and arterial spiders in the present case coincided with that of several features of Cushing's syndrome. It is therefore of interest to recall that two out of twelve of Cushing's patients with this syndrome had telangiectases (Cushing 1932), one of the cases being that published by Friedman (1921). Bean (1945) observed typical vascular spider in a case of Cushing's syndrome where (as in our case) liver disease could be excluded. Bean (1945) held that these vascular alterations may be related to abnormality in the metabolism of certain 17-ketosteroids.

The development of arterial spiders in liver disease and during pregnancy is well known. Alterations in 17-ketosteroid metabolism have been reported in liver cirrhosis (Edmondson et al. 1939), and the period of increased excretion of œstrogens in pregnancy coincides with that during which the vascular spiders tend to appear. This led Bean to administer œstrogens in liver disease. Vascular spiders developed in two of three chronic addicts to alcohol after therapy with œstrogenic 17-ketosteroids (Bean 1942).

In our patient the development of cutaneous arterial spiders after A.C.T.H. therapy, and the considerable increase in urinary excretion of 17-ketosteroids, further supports the hypothesis that these alterations of the small arteries of the skin are caused by a disturbance of the balance and level of the 17-ketosteroids.

Since this article was drafted I have seen a single pulsating arterial spider in a woman treated with A.C.T.H. for colitis; it lasted three days and then disappeared. Liver disease and pregnancy were excluded.

SUMMARY

Telangiectases and cutaneous arterial spiders developed simultaneously with Cushing's syndrome in a woman, aged 25, treated with A.C.T.H. for acute rheumatoid arthritis. These vascular lesions regressed in number and size with the interruption of A.C.T.H. therapy and progressed with its resumption.

None of the usual predisposing causes (pregnancy, liver disease, deficiency disease) were present. The development of arterial spiders seems to be related to alterations in the metabolism of 17-ketosteroids.

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"PROTEINURIA" IN THE NEWBORN

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The occurrence of protein in the urine of an infant during the first two weeks of life is regarded by many authorities as one of the physiological peculiarities of the neonatal period (Brennemann 1948, Bamberger et al. 1942, Debré et al. 1943–45, Feer 1938, Finkelstein 1938, Grulee and Eley 1948, Nelson 1950, Parmelee 1952, von Pfaundler and Schlossmann 1931; von Reuss 1914, Smith 1951, Tow 1937). Czerny and Keller (1925) give the best and most extensive review of the work on proteinuria of the newborn, most of which is to be found in the German literature before 1916.

Proteinuria was found within the first two weeks of life, on at least one occasion, in nearly all the infants included in the extensive surveys of the more recent German workers (Ewald 1916, Franz and von Reuss 1914, Heller 1913). In older articles the incidence of proteinuria was reported to vary from 41 to 93% (Flensburg 1894, Martin and Ruge 1875, Cruse 1877, Hofmeier 1862), whereas no protein was found by French workers at the end of the last century (Audebert and Arnozan 1896, Parrot and Robin 1876). The work of the latter authors was not well documented and gave neither the number of infants studied nor the method of protein estimation. Greer et al. (1928) observed protein in the urine of only 7 of 66 healthy infants.

Before trying to relate the reported proteinuria to other features of the newborn infant, we thought it desirable to reinvestigate its prevalence by methods more reliable than those used by earlier workers.

Some of the urines obtained from newborn infants were scanty, had a deep colour, contained a large deposit, and gave positive tests for protein. As urinary salts can interfere with the tests for protein when the urine is concentrated (Todd and Sanford 1944), the present work was designed to test the hypothesis that the so-called proteinuria of the newborn is due to excessive amounts of urates interfering with the tests for protein.

METHOD

The approximate specific gravity of the urine was determined in many cases after the specimens had been clarified (Dogramaci 1947). For the purposes of protein determination any deposit or cloud remaining after the specimen had been warmed in a water-bath at 37°C was centrifuged off, and the supernatant fluid was used for the test. Protein was estimated by adding 0·1 ml. of 25% (w/v) trichloracetic acid to 1 ml. of urine and comparing the turbidity with that of standard tubes after two minutes (Grey 1930).

If the urine appeared to contain more than 15 mg. of protein per 100 ml., urates were quantitatively removed by a method developed by Hopkins (1891, 1893a and b). The urine was saturated with ammonium chloride (A.R.), and one or two drops of concentrated ammonia were added to give a white gelatinous precipitate of ammonium urate. After standing for two hours the supernatant fluid was tested for protein by the addition of trichloracetic acid. As the urine had been treated with concentrated ammonia, it was necessary to add up to 0·2 ml. instead of 0·1 ml. of trichloracetic acid (25% w/v) to attain the same pH as before.

Treatment of urine with ammonium chloride and ammonia does not remove any organic physiological constituent from the urine except urates and soaps (Cole 1933), but it was considered necessary to ensure that protein was not affected by this procedure.

For this purpose a solution free from urates—i.e., serum—was diluted to give concentrations of protein varying from 10 to 100 mg. per 100 ml. Part of each solution was saturated with ammonium chloride, and ammonia was added. There was no trace of a precipitate, but there was an increase in the volume of solution from 100 to 125% as a result of the saturation with ammonium chloride. When this dilution is taken into consideration, it is clear from the accompanying table that, within the limits of experimental error, there was no loss of protein when the solutions were put through the process for removing urates. Similarly, when pathological urine from nephritic patients was treated with ammonium chloride and ammonia, the observed decrease in protein concentration was compatible with the dilution from saturation with ammonium chloride.

The murexide test, which is specific for urates (Cole 1933), was applied to the deposit from neonatal urine and proved strongly positive. The precipitate (presumably ammonium urate) which appeared when a urine containing "protein" was treated with ammonium chloride and ammonia gave a positive murexide test. Further, the "protein"—i.e., the precipitate obtained when urine was treated with trichloracetic acid—also gave a positive murexide test.

CONCENTRATION OF PROTEIN IN VARIOUS DILUTIONS OF SERUM BEFORE AND AFTER ADDITION OF REAGENTS FOR REMOVAL OF URATES

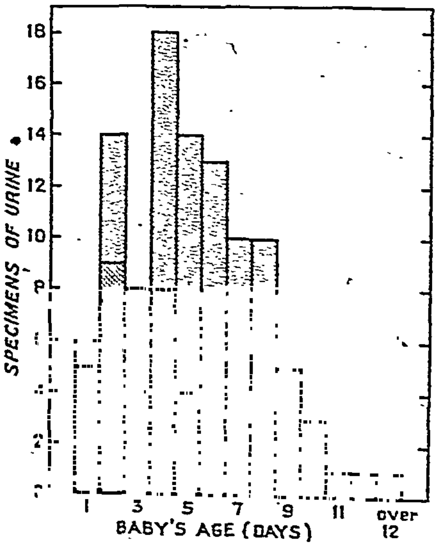
Sample of urine	Protein (mg. per 100 ml.) in diluted serum	
	Before treatment with NH_4Cl and NH_4OH	After treatment with NH_4Cl and NH_4OH
1	95	70
2	80	60
3	70	55
4	65	50
5	60	45
6	50	40
7	40	30
8	30	20
9	20	15

The small decrease in protein concentration is explained by the increase in volume after the addition of the reagents.

If uric acid is dissolved in dilute alkali—e.g., 2% (w/v) sodium carbonate—the insoluble acid can be precipitated again by the addition of one or two drops of concentrated hydrochloric acid. Uric acid can also be precipitated by the addition of 25% (w/v) trichloracetic acid. It is therefore clear that turbidity can be obtained when concentrated urine, obtained from a newborn infant and containing an excess of urates, is treated with the reagents commonly used for estimating protein. The treatment of any protein solution or urine containing protein with reagents which will remove urates does not remove protein but does precipitate the salts of uric acid, which can interfere with the tests for protein in a concentrated urine.

MATERIAL

103 specimens of urine were obtained from 97 clinical healthy newborn male infants, aged 1–21 days, by strapping a 'Pyrex' test-tube to the penis. The mothers of 88 of these children were in good health, whereas the remaining 9 mothers had mild toxæmia. Girls' urine was not studied, because of the difficulty of collecting specimens.



Number of specimens of urine obtained from newborn boys, showing those (hatched) which contained excessive amounts of urates, which gave false positive tests for protein.

RESULTS

Of the 103 specimens of urine 30 had a deep colour and a rather high specific gravity (1·014–1·024), and contained a large deposit which gave a very strongly positive murexide test. It was only the more concentrated specimens of urine passed within the first five days of life which showed these peculiarities and gave a positive test for protein up to amounts of 100 mg. per 100 ml. When urates were removed from these specimens, no protein was detected in the urine from 96 of the 97 newborn infants studied. The urine of 1 infant appeared to contain 70 mg. protein per 100 ml. on the first day and 50 mg. per 100 ml. on the ninth day, but on neither occasion was it possible to exclude the possibility of contamination after collection and before testing it.

DISCUSSION

In this series of observations tests for protein made on clarified urine were positive only in deeply pigmented specimens which had contained a large deposit and had a specific gravity greater than 1·014. No urine with a specific gravity of less than 1·012 gave a precipitate with trichloracetic acid, and it was only during the first five days of life that the more concentrated specimens of urine were passed (Thomson 1944).

When the urates were removed from these concentrated specimens of urine, the test for protein was positive in only 1 case. If urates were not removed before testing for protein, the incidence of "proteinuria" in the present series would have been about 30%, which is not significantly different from that of some of the German workers. As the methods described by previous observers would not distinguish between protein and urates in a concentrated specimen, we can only conclude that their results were fallacious.

It has long been known that there is an increased excretion of urates in the newborn. Schloss and Crawford (1911) found that 7–8% of the total nitrogen of the urine was uric acid within the first few days of life, compared with 1–2% in the adult. Franz and von Reuss (1914) noticed that their tests for "albumin" were more positive when the urine was intensely yellow and contained a large deposit of urates.

Other workers noticed the correlation between "albuminuria" and excessive excretion of urates. Kjellberg (1870) held that the mechanical irritation caused by the excessive amount of urates produced the "albuminuria," whereas Cruse (1877) suspected that the test for "albumin" was fallacious because mucin interfered with the test. Ultzmann (1881) found a close correlation between "uric acid infarct" and "albuminuria." He accepted Virchow's (1856) hypothesis that both manifestations were the result of a local mechanical cause, the presence of a urate deposit in the kidney causing hyperæmia and exudation of protein. Flensburg (1894) studied this phenomenon but concluded that there was not a close correlation between "uric acid infarct" and "albuminuria."

Many authors record a much higher incidence of proteinuria in infants born of eclamptic mothers than in those born of healthy mothers.

Salmi (1935) recorded proteinuria in 6 of 17 infants born of eclamptic mothers and in only 2 of 8 infants born of healthy mothers. Greer et al. (1928) observed proteinuria in 7 of 66 infants born of healthy mothers, in 12 of 13 infants born of pre-eclamptic mothers, in 4 infants where both mother and child had acute infections, and in 3 of 6 infants born after difficult labours. Brash (1949) found albumin in the urine on the third day of life in 1 of 10 infants of toxæmic mothers and in 10 of 25 infants of healthy mothers.

Of the 97 mothers whose infants were included in the present survey 9 had toxæmia. The infant which seemed to have protein in its urine was born to a mother without toxæmia.

It therefore seems that the earlier French workers who did not find proteinuria in the newborn were correct, but it is noteworthy that one of the best-known French pædiatric textbooks (Debré et al. 1943–45) ignores their work. Similarly the most authoritative American textbook (Smith 1951) ignores the work of Greer et al. (1928) and, on the evidence from the earlier German papers, says:

> "Tests for albumin have been so consistently positi especially during the second to fifth days after birth, t albumin is to be considered a more or less 'physiologic constituent of the newborn infants' urine."

The work reported here has shown that neona proteinuria as a physiological phenomenon does exist. We suggest that any occurrence of "tru protein is very rare and may indicate disease.

SUMMARY

The incidence of proteinuria in the newborn infa has been reinvestigated.

A third of the specimens of urine obtained from ne born infants was highly pigmented and contained a lar deposit which gave a strongly positive murexide te and appeared to contain protein.

When urates were removed from the more conce trated specimens, which were produced only within t first five days of life, the "protein" disappeared.

Proteinuria as a physiological phenomenon in t newborn infant does not exist. The fallacy has aris from the excessive excretion of urates in the first few da of life, interfering with the test for protein.

Our thanks are due to Prof. R. S. Illingworth for his advi in the preparation of this paper and to Dr. Thomas Colver f permission to obtain specimens from some of his patients.

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PERFORATION OF APPARENTLY NORMAL COLON AFTER A BARIUM MEAL

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Several cases of perforation of a diseased colon after a barium meal or barium enema have been published; but we know of no report of perforation of an apparently normal colon after a barium meal.

CASE-RECORD

Mrs. A, aged 67, was first seen on March 26, 1952, complaining of intermittent abdominal pain and vomiting of five or six years' duration. The trouble seemed to consist of retching more often than actual vomiting. She complained of anorexia and loss of weight. She admitted to being a nervous woman but had no domestic worries. There was no relevant previous history.

Apart from a blood-pressure of 220/120 mm. Hg (benign hypertension) no abnormality was found either in the alimentary system or elsewhere. A provisional diagnosis of nervous dyspepsia was made.

Radiography.—A barium meal was given on the morning of April 1, and radiography showed a normal stomach and duodenum. But when the patient returned at 10 A.M. next day for the follow-through examination she said she had had generalised abdominal pain since 7 A.M. The follow-through films were normal, with discrete masses of barium throughout the colon (fig. 1). As, however, she had generalised abdominal tenderness, with resistance of the abdominal muscles, and did not appear well enough to go home, she was admitted to a medical ward for observation.

Condition on Admission.—She was pale and slightly greyish, with a dry tongue. Her pulse-rate was 72, with some extra systoles, and her blood-pressure was 180/100. Her abdomen was tender and resistant in all areas. Rectal examination showed a gross impaction of hard inspissated barium.

The possibility of perforation was not entertained at this time, especially in view of the normal appearance of the follow-through radiographs. It was thought that the pain might well be due to numerous hard masses of barium in the rectum or the colon. Accordingly the rectal mass was removed digitally, this being followed by two rectal washouts, which were rapidly returned with a moderate amount of barium.

Progress.—At 9 P.M. the patient's condition was worse. Her pulse-rate had risen to 100, her tongue was dry, and the abdominal pain and tenderness were more severe. She had evidently developed peritonitis. Further radiography showed, in addition to the previously noted barium masses, a dense collection of barium in the pouch of Douglas, with thinner streaks in the left paracolic gutter and between loops of bowel (fig. 2). A Ryle's tube was passed and the patient was prepared for operation.

Laparotomy (J. C. B. S.).—At 11.30 P.M. on April 2 a left upper paramedian incision was made. There was generalised peritonitis with purulent free fluid mixed with barium. The stomach, duodenum, and small and large intestines were examined in turn, and a perforation was finally found in the pelvic colon about 2 in. above the peritoneal reflexion. Its diameter was about that of an index finger, and the colon showed no abnormality of any sort, either at that point or elsewhere. The perforation was closed and patched with omentum. As much as possible of the paste-like barium in the pouch of Douglas was removed together with the free fluid. The lesion being too low for exteriorisation, a proximal double-barrelled colostomy was performed in the left inguinal region. Two hard balls of barium about 1 in. in diameter at the site of the colostomy were removed through it, and a Paul's tube was placed in position. During the operation an intravenous infusion was begun, and, the patient's condition being poor immediately after the operation, a pint of blood was given by this route.

The barium masses proved to be solid barium, difficult to cut with a scalpel, but able to disintegrate spontaneously in water.

Postoperative Progress.—Penicillin 500,000 units b.d., streptomycin 0·5 g. six-hourly, and intravenous glucose and saline solution were given, and the stomach contents were aspirated. There was complete ileus for five days, after which the colostomy began to act, aided by softening of the remaining barium masses with olive oil run in through the Paul's tube. Oliguria caused the blood-urea level to rise to 102 mg. per 100 ml. by the third day, but this passed off. There was a troublesome infection of the superficial part of the wound, which eventually healed well. On April 19 the patient was sitting out of bed, and had pain in her left hypochondrium. On April 21 radiography showed free fluid present at the base of the left lung, and next day straw-coloured exudate was aspirated from it. Radiography on April 21 also showed residual barium between the loops of bowel, on the under surface of the liver, and round the spleen (fig. 3). An enterotome was applied to the spur of the colostomy on April 24 and removed on May 1. On May 7 the colostomy was closed (J. C. B. S.). Local cellulitis followed this but was soon

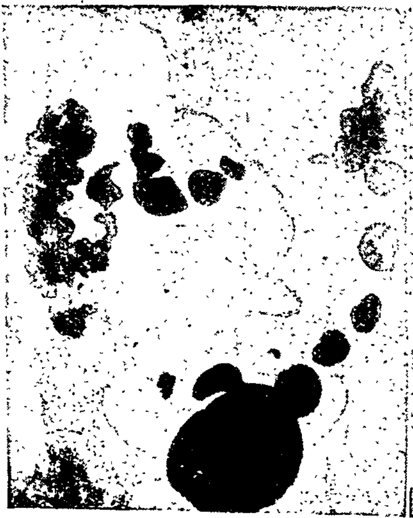

Fig. 1—Follow-through radiograph after barium meal on April 2, showing discrete masses of barium throughout large intestine.

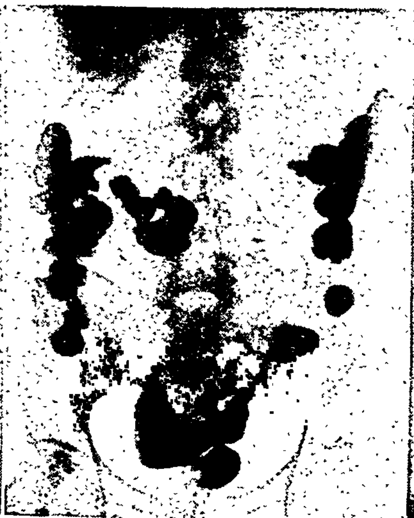

Fig. 2—Radiograph in the evening of April 2, showing collection of barium in pouch of Douglas, and streaks of barium in left paracolic gutter and in between loops of bowel.

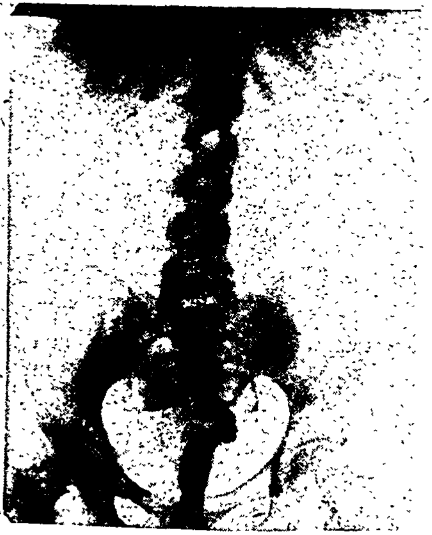

Fig. 3—Radiograph on April 21, showing residual barium between loops of bowel, surrounding spleen, on under-surface of liver, and in rectum.

controlled with chloromycetin. The patient was discharged to a convalescent home on May 19.

Follow-up.—When seen on June 26, her condition was very satisfactory, her only complaints being of general weakness and of œdema of her ankles. The abdominal wounds had healed well, and sigmoidoscopy showed normal rectum and colon. There were no abnormal chest signs. Radiography of the chest on May 20 had shown considerable reduction in the extent of the left basal effusion; but on July 1 the chest was clear.

COMMENT

The original diagnosis of nervous dyspepsia in this case was supported by the absence of any abdominal lesion other than the accidentally perforated colon. There seems to be no clinical doubt that the perforation took place within twenty-four hours of the administration of the barium, which by then had reached the pelvic colon and rectum, where it had formed solid hard masses. Perhaps the patient had previously been a little dehydrated, causing more absorption of water than usual from the barium during its passage through the colon.

The reason for the perforation is unknown. It is difficult to imagine that a necrosing pressure ulcer could develop in so short a time. The subsequent rectal washouts must have contributed to the severity of the peritonitis, but in retrospect it seems clear that the perforation had taken place some hours earlier. Possibly a barium mass was blocking the breach but was forced through it by the enemata. This would account for the normal radiological appearances in the morning.

No comparable case seems to have been published in the last thirty years or so.

Kaulich (1930) reported a case in which, after a barium meal, a barium mass became impacted in the middle of the sigmoid colon and caused obstruction. Twenty-seven days later a barium enema was given, followed by perforation at the site of impaction. In this case there was presumably an ulcer at the site of impaction. The outcome is not recorded.

Scheidt (1950) reported a case in which perforation of the colon above a carcinoma following two barium enemata given at an interval of ten days. The patient was operated on four days later but died of peritonitis.

A case of perforation of the sigmoid colon during the giving of a barium enema is reported by Kleinsasser and Warshaw (1952) in a case of chronic ulcerative colitis. The patient recovered after repeated attacks of obstruction of the small intestine.

Golub (1934) cites three cases of retention of barium masses after barium enemata forming a hard mass of barium, but perforation did not follow in any of them.

Himmelmann (1932) cites colonic perforation due to barium meal in cases of carcinoma of the rectum and stenosis of the colon.

In all these cases there was a lesion of the colon which determined the onset of perforation, but in the present case there was apparently no such lesion.

Isaacs (1952) reports two cases of escape of barium into the peritoneal cavity during the administration of a barium enema. One patient had a carcinoma of the sigmoid colon, and the other a perforation due to sigmoidoscopy the previous day.

SUMMARY

A case is recorded in which, after a barium meal, masses of inspissated barium caused perforation of an apparently normal colon. The patient recovered after closure of the perforation and proximal colostomy.

We are indebted to Dr. E. G. B. Calvert for permission to publish this case, and to Dr. L. S. Carstairs for his coöperation in the radiological examinations.

References at foot of next column

ACUTE PERFORATION OF A DUODENAL ULCER IMMEDIATELY AFTER BARIUM MEAL

COMPLICATED BY INTESTINAL OBSTRUCTION

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Rosenthal, cited by Gross (1941), was the first to record in 1916 a perforation of a peptic ulcer on the X-ray table, when the barium was seen in the lesser sac. Lang (1926) reported the perforation of a gastric ulcer during X-ray examination of a man aged 65. The patient was operated on and made an uneventful recovery. Barium was found only in the vicinity of the ulcer. Singer (1934a), discussing barium meals in the presence of unrecognised perforations, refers to cases where local abscesses were detected during examination. These were no doubt cases of "subacute perforations" with a slow leak. In one case the abscess ruptured during examination. An operation was done, but the patient died. Gross (1941) reported a case of his own where at operation the ulcer was oversewn and parts of the lesser omentum were excised to remove the adherent barium. The patient recovered.

The following case is presented, however, not only on account of its rarity but also because of the most unexpected complication which ensued.

CASE-RECORD

A Greek, aged 34, officer on a tanker, was brought into the casualty department of this hospital at 10.50 P.M. on Nov. 15, 1951, in an extremely shocked state, complaining of agonising abdominal pain. His own doctor, who accompanied him, said that the patient, who forty minutes earlier had had a barium meal, got off the X-ray table and was immediately doubled up with this pain. One of the radiographs already taken showed an ulcer crater in the duodenum. The patient had left Greece three months earlier. About then he started getting attacks of upper abdominal indigestion related to meals. The attacks had become gradually worse and during the past week had been almost continuous. He had lost weight. As soon as the ship docked he sought medical advice.

On examination he was writhing in agony, retching violently, and bringing up small quantities of barium. His extremities were cold and cyanosed, and his pulse was barely perceptible. His abdomen was board-like all over and extremely tender.

Treatment.—Morphine gr. $^{1}/_{4}$ was given intravenously and a dextrose-saline drip was started. An attempt to aspirate the stomach was unproductive, but the Ryle's tube was left in. The patient was left undisturbed. By 2 A.M. he was warm and his blood-pressure was normal.

Operation.—At 2.30 A.M. on Nov. 16, under thiopentone, curare, and endotracheal gas and oxygen, a right upper paramedian incision was made. The parietal peritoneum was found œdematous, and free gas escaped. The entire peritoneal cavity was smeared with barium of creamy consistence intimately mixed with exudate. The surfaces of all the viscera were covered with a fine layer of adherent barium. The whole of the visceral peritoneum showed intense œdema, as much as would be seen in a 24-hour ordinary perforation. The inferior surface of the liver was lightly adherent to the duodenum. On the anterior surface of the first part of the duodenum was a perforation about 3 mm.

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across, through which barium and gas were escaping. The perforation was closed with an omental graft. As much as possible of the creamy fluid was swabbed and sucked away, but the adherent barium could not be removed. The neighbourhood of the ulcer was lightly dusted with penicillin and sulphonamide powder. The abdomen was closed without drainage. On return to the ward at 3.15 A.M. the patient's condition was satisfactory, but in view of the extensive œdema a pint of plasma was given and a slow dextrose-saline drip was continued.

Subsequent Progress.—On Nov. 16 there were considerable abdominal pain and restlessness requiring repeated doses of morphine, pethidine, and sodium phenobarbitone. Intermittent gastric aspiration was done. The patient's pulse-rate was 90–100 per min. On Nov. 18 he was still distressed. No flatus was passed. The abdomen was uniformly distended, tender, and silent. Gastric aspiration for the day totalled 36 oz. In the evening the tube was removed, but the patient complained of nausea, and reinsertion was followed by aspiration of 10 oz. of green fluid. The intravenous drip was continued. On Nov. 19 distension was more severe, and the patient was very restless and complaining of pains. A good deal was aspirated from the stomach. No flatus was passed. The pulse was good. Enemata morning and evening were without result. On Nov. 20 the abdomen was still very distended, and distressing pains continued. A radiograph was taken of the abdomen (fig. 1). The insertion of a flatus tube was followed by the passage of a very small quantity of gas, but enemata were without effect. On Nov. 21 4 oz. of olive oil was run into the rectum, and a 3-pint washout had no appreciable effect on the distension. Peristaltic sounds were now audible. Another radiograph was taken of the abdomen (fig. 2). On Nov. 22 a colonic washout was repeated with an excellent result, large quantities of barium and flatus being passed, and the abdomen becoming deflated. The patient was very comfortable, and gastric suction and intravenous drip were discontinued. The patient was allowed up next day, and the sutures were removed on the 10th postoperative day. He was discharged on Nov. 30. A radiograph taken on Nov. 28 showed residual barium. The patient was last seen just before Christmas and was then having no symptoms. He left for Greece by air a few days later and was advised to see his doctor there.

DISCUSSION

The frequency with which peptic ulcers perforate during or after a barium-meal examination has been variously estimated. Hummelman (1932) put it as high as 29·4%, whereas Singer (1934a and b) estimated it as 0·08% of 5000 examinations at the Cook County Hospital. These variations seem to be due to different intervals between the examination and the perforation. This interval in the published cases is between two hours and six days. It therefore appears futile to attempt a statistical estimation of frequency; but one can say that it must be very rare for a peptic ulcer to perforate during or immediately after a barium meal.

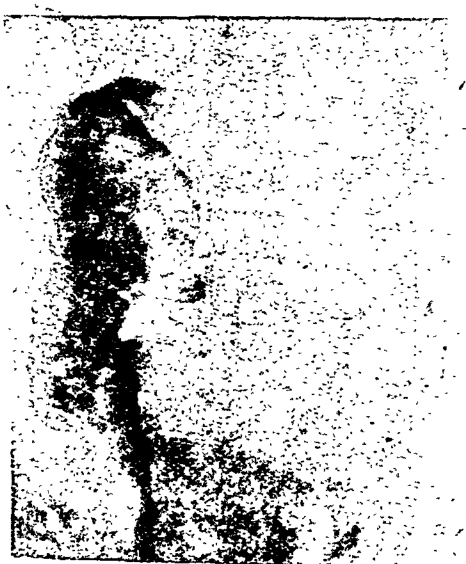
Fig. 1—Full-blown ileus. Head of barium has reached hepatic flexure.

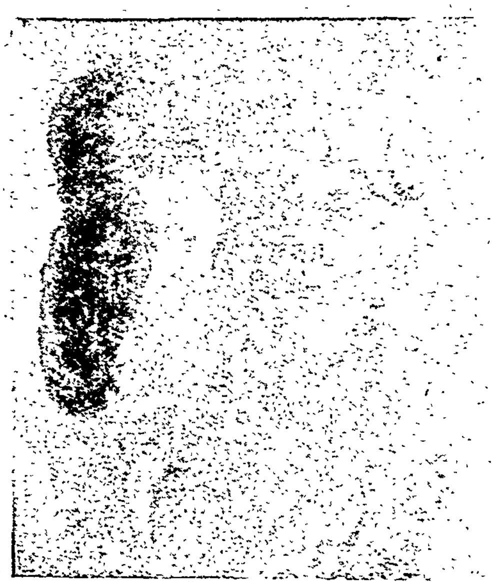
Fig. 2—Day after fig. 1. Ileus not so severe. Appearance suggests that barium is caking in ascending colon. Clinically there was evidence of mechanical obstruction.

The ætiological relation between the barium-meal examination and the perforation is not easy to assess. Very likely the barium meal has very little to do with it; the perforations would have taken place anyhow. This is borne out by the fact that in all the cases published there had been a recent exacerbation of symptoms, as in the present case. The most that can be said is that the barium meal accelerates the perforation. Eckman (1928), reporting 5 ulcers which perforated from a few to thirty-six hours after radiography, stated that patients with a recently active ulcer should be warned, after barium-meal examination, to remain within convenient distance of medical attention till the danger of perforation had passed. Singer (1934b), on the other hand, emphasises that in such cases barium-meal examination should be postponed until medical treatment has caused a retrogression of symptoms. The radiographic demonstration of an ulcer in the acute phase does not in any way alter the treatment, and only exposes the patient to additional hazards.

SUMMARY

A case is recorded where a duodenal ulcer perforated immediately after a barium-meal examination.

After an operation to close the perforation the convalescence was stormy and complicated by intestinal obstruction caused by the ingested barium.

The importance of postponing barium-meal examinations during the exacerbation of ulcer symptoms is emphasised.

I wish to thank Mr. Eric Greenwood, under whose care this case was admitted, for permission to operate and advice on the management; Dr. Angus Campbell, the house-surgeon, for his keen coöperation; and Dr. J. M. Corall for help in interpreting the radiographs.

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THE VASOMOTOR DISTURBANCE IN PINK DISEASE*

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COLDNESS of the hands and feet is characteristic of pink disease and was mentioned by Selter (1903) in what is possibly the earliest account of this condition. It is, in part, a peripheral vascular disorder, but investigations of the kind used in the study of Raynaud's disease and acrocyanosis have not been published.

The skin-temperature of normal hands and feet varies over a wide range, depending on the need for retention or dissipation of heat in the regulation of body-temperature. Even under the same environmental conditions there may be fairly wide individual differences. By a long series of careful observations on normal children, Talbot (1931) has established that, except in premature babies, the behaviour of the surface temperature in children does not differ widely from that in adults. With variation in room-temperature the temperature of the extremities alters most, while the temperature of the trunk remains relatively constant.

The skin-temperature of the hands and feet is a useful indicator of changes in blood-flow, especially in the lower range, although it is not a precise measure of the flow. In the upper range big variations in flow cause small variations in temperature (Cooper et al. 1949).

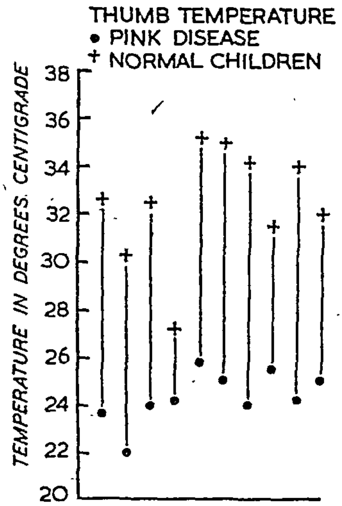

Fig. 1—Comparison between the skin-temperature of the thumb in 10 children with pink disease and in 10 convalescent children of similar age chosen at random from the ward.

Ordinary clinical observation of children with pink disease, and assessment of their hand and foot temperature by touch at short intervals, show that their extremities are generally colder than those of other patients of the same age in the same ward. According to Lewis (1936) such coldness signifies a decreased flow of blood through the skin arterioles or the small arteriolo-venous anastomoses. However, contact of the child's hand with a warm object, such as its own body, raises the temperature of the hand more rapidly than would be expected from simple thermal conduction, and this is presumably due to dilatation of the same vessels in response to direct heat.

In pink disease the colour of the hands and feet is always more intense than normal, but the tint varies from red to bluish-red according to their temperature. Even when they are quite warm the increased intensity remains. Clearly, the capillaries or the subpapillary venous plexuses are dilated, as in other conditions with habitually cold extremities—e.g., acrocyanosis (Lewis and Landis 1930).

The hands and feet are also moist from increased sweating, which is part of a generalised hyperhidrosis and is increased by warming the body.

INVESTIGATIONS

A direct-reading copper-constantan thermocouple of the type designed by Lewis and modified by Grant (1935) was used; this proved accurate within 0·3°C. The leads were fixed to the skin with small strips of zinc-oxide strapping and the infant was restrained as little as possible. For each experiment the infant was dressed in two short-sleeved upper garments (one of wool and the other of cotton) and a napkin. The recordings were made in cubicles kept at a temperature that was constant within about 1°C during the experiment; all the infants remained under these conditions for at least half an hour before the temperatures were taken.

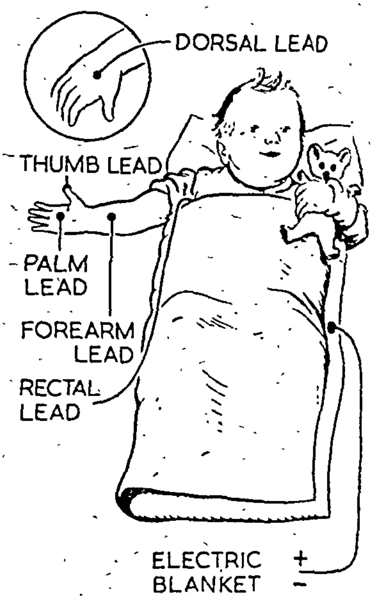

Fig. 2—Points from which skin-temperatures were taken, and method used for warming trunk and legs with electric blanket.

Under these conditions the clinical observation mentioned above was confirmed—the infants with pink disease had colder extremities than normal, especially the hands. Fig. 1 shows the skin-temperature of the thumb in 10 patients with pink disease as compared with 10 other convalescent patients of the same age chosen at random from the ward. For each pair the room-temperature did not differ by more than 1·5°C. The temperature of the trunk, forehead, and proximal parts of the limbs did not differ significantly from normal. The rectal temperatures were usually in the upper range of normal or slightly higher.

Reflex Dilatation

The next step was to determine, by attempting to obtain reflex vasodilatation, whether the coldness was due simply to excessive vasoconstriction of the skin arterioles.

Reflex vasodilatation in response to warming the body occurs readily in normal children. Fig. 2 shows the

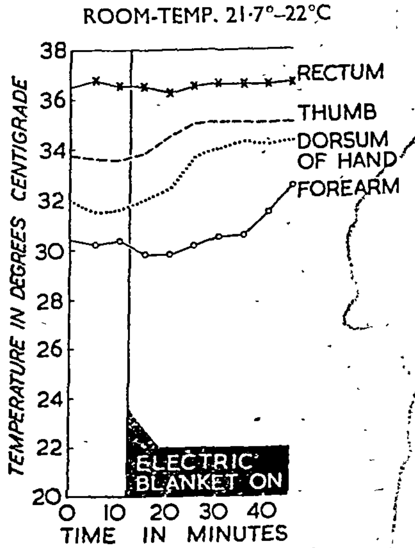

Fig. 3—Reflex vasodilatation in hand on warming trunk and legs, in normal child, aged 11 months, after stabilisation at fairly constant room-temperature.

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* Based on a thesis accepted for a degree of M.D. in the University of Cambridge.

EXPERIMENTAL FINDINGS

Case no.	Age (mos.)	Reflex vasodilatation		Ulnar-nerve block	T.E.A.B.	Priscol
		At peak of disease	On recovery			
1	11	Absent (2 tests)	Present	Vasodilatation in 5th finger	..	Vasodilatation
2	14	Absent (3 tests)	Present	Vasodilatation in 5th finger	..	Vasodilatation
3	16	Absent (2 tests)	Present without warming trunk	..	Vasodilatation; fall in blood-pressure	Vasodilatation
4	10	Absent (2 tests)	Present	..	..	Vasodilatation
5	13	Absent (2 tests)	Present	..	..	..
6	9	Absent	Present	..	..	..
7	12	Present but delayed	..	..	..	..
8	13	Absent	Present	..	..	..
9	11	Absent	..	..	..	..
10	12	Absent	..	..	..	..
11	11	Absent	..	..	..	..

method of heating with an electric blanket (45°–50°C), and the points from which the readings were taken (to avoid confusion on the charts not all of these are recorded). The temperature of the palm approximately followed that of the dorsum of the hand but was usually a degree or so higher. The electric blanket was covered with an ordinary blanket to insulate it as much as possible and thus to prevent warming of the hand by radiation.

Fig. 3 is an example of the temperature of the hand and arm in a normal baby after remaining for 1/2–3/4 hour under the conditions stated, and shows the immediate warming due to reflex vasodilatation when the trunk and legs were heated. The initial temperatures recorded on this and all the following charts were the first readings after reasonable stability had been reached. In every case the electric blanket remained on until the last skin-temperature measurement had been made.

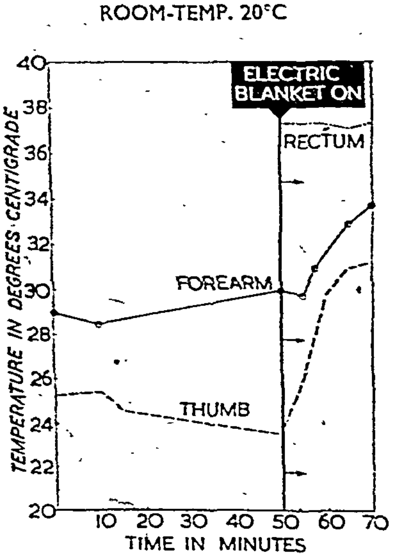


Fig. 4—Immediate reflex vasodilatation in hand on warming trunk and legs in unusual child, aged 2 years, with habitually cold extremities.

Fig. 4 (also from a control) represents the response in a constitutionally cold-handed child. The initial temperatures were much lower, but reflex vasodilatation occurred readily.

In pink disease, however, the response was strikingly different (figs. 5*a* and 6*a*). After keeping on the electric blanket for 40–70 minutes, and in most cases raising the rectal temperature by 1°–3°C, the hand did not become warmer. Eleven infants with pink disease were tested in this way, ten of whom yielded similar results, most of them on more than one occasion (see table). The exceptional infant showed a slow and delayed reflex dilatation after 35 minutes' heating, but in this case clinical recovery was already beginning.

On repeating the investigation when clinical recovery had taken place (six cases), heating was followed by the normal response of reflex vasodilatation (figs. 5*b* and 6*b*).

Warming these infants with pink disease induced excessive sweating, and it was at first considered possible that the evaporation of this sweat from the hand might have prevented the reflex rise in temperature. The same test was therefore made on a child with hyperhidrosis of the hands (fig. 7): in spite of a degree of sweating greater than that seen in pink disease the normal reflex vasodilatation took place.

Calibre of Vessels

The next thing to determine was whether there was structural narrowing of the small arteries or arterioles.

In two infants with pink disease ulnar-nerve block at the elbow with 2% 'Xylocaine' produced a full rise in temperature of the fifth finger, and the thumb remained cold (fig. 8), this being the result of functional interruption of the vasoconstrictor fibres which follow the distribution of the sensory nerves.

Blocking the transmission through the sympathetic ganglia by intramuscular injection of 100 mg. of tetraethylammonium bromide (T.E.A.B.) was followed in another case of pink disease by a similar release of vasomotor tone (fig. 9): the blood-pressure fell from 120/90 to 85/60 mm. Hg.

Intramuscular 'Priscol' (2-benzyl-2-imidazoline) produced rapid vasodilatation (fig. 10) in the four cases where it was used, but no constant change in blood-pressure. The mode of action of priscol is complex:

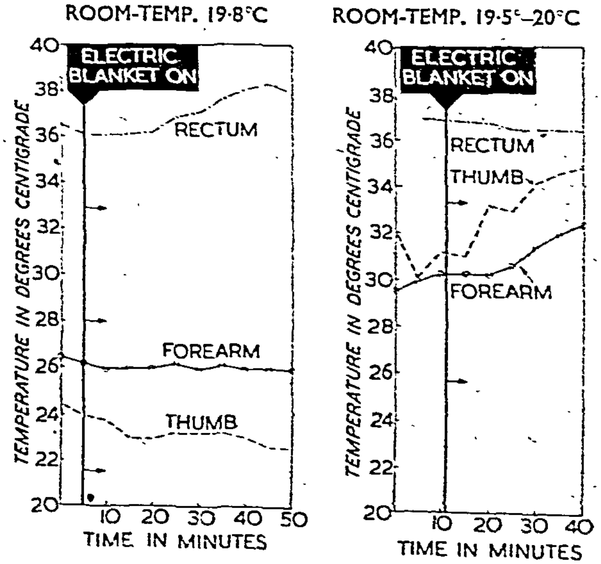
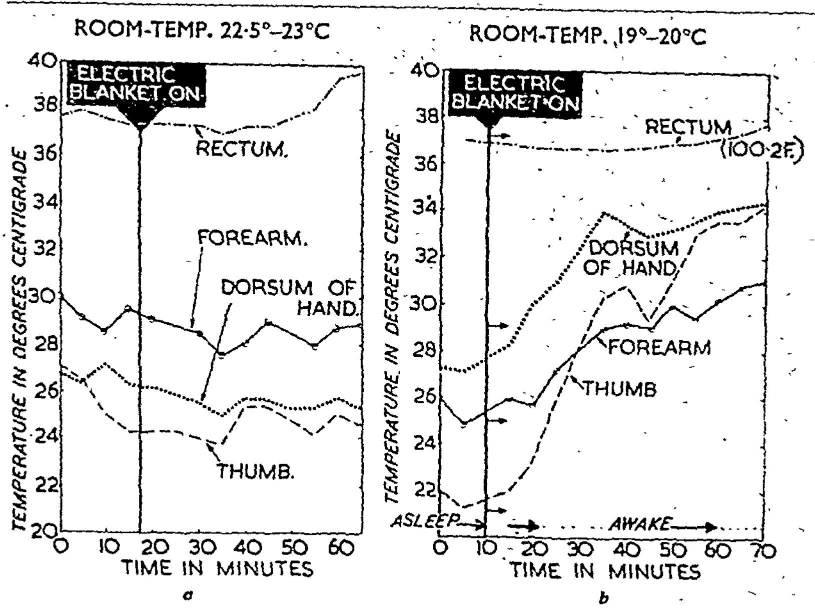


Fig. 5—Results of warming trunk and legs: *a*, in infant, aged 11 months, with pink disease, showing coldness of hand and absence of reflex vasodilatation in spite of significant rise in rectal temperature; *b*, in same infant after clinical recovery, showing further reflex vasodilatation in already warm hand.



a *b*

Fig. 6—Results of warming trunk and legs : *a*, **in infant, aged 10 months, with pink disease, showing absence of reflex vasodilatation in spite of 2°C rise in rectal temperature ;** *b*, **in same infant when clinical recovery was almost complete, tested at lower room-temperature but now showing immediate reflex vasodilatation.**

predominantly, it annuls the excitatory effects of circulating adrenaline (or noradrenaline) and prevents the transmission of excitatory sympathetic nerve impulses from the postganglionic neurones to the effector cells in the blood-vessel wall, but it also increases the cardiac output, which probably explains why the blood-pressure did not fall. Priscol is now being tried in the treatment of pink disease.

In three cases of pink disease the temperature of the hand did not rise during sleep, although clinically it had been noted that at night, during long and deep sleep, the hand did become warmer. The accompanying table summarises the findings.

DISCUSSION

The presence of hypertension, tachycardia, and excessive sweating as prominent clinical features of pink disease led to the conception of it as a disease of the autonomic nervous system, with predominance of sympathetic activity. Feer (1925), who was the first to study it extensively, attributed the whole clinical picture, including the muscular hypotonia, to a "vegetative nervous disorder." His idea gained much support, and other workers elaborated it. Blackfan and McKhann (1933), for instance, after studying 40 cases, concluded that sympathetic overactivity was responsible for most of the symptoms and signs, but that the parasympathetic side was also involved—in the production of the increased salivation and lacrimation.

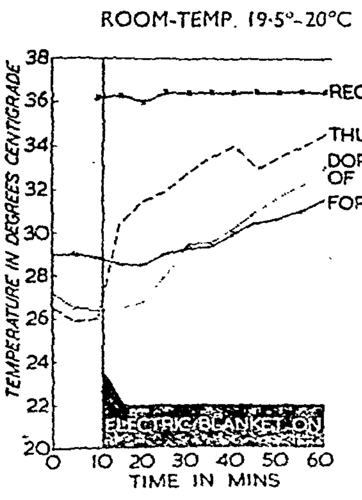


Fig. 7—Reflex vasodilatation in child with severe hyperhidrosis, showing that warming was not prevented by evaporation of sweat.

The notion of sympathicotonia as an explanation for the production of symptoms and signs is, however, insufficiently specific (Darrow 1943). *Pink disease* is likely to be better understood by investigating each separate neurophysiological mechanism concerned. Few attempts have been made to test the function of the autonomic system in pink disease. Day et al. (1939) set out to do so and showed that in three cases the tachycardia could not be significantly increased by emotion, from which they concluded that sympathetic tone was already at a maximum. They also demonstrated a further increase in the pulse-rate after giving atropine and inferred that the vagi were functioning. Hypersecretion of the adrenal medulla has been suggested as a possible explanation of the clinical features (Kühl 1928), and the resemblance of pink disease to the hypertensive paroxysm caused by a phæochromocytoma, with its tachycardia, sweating, and cold extremities, has been noticed (Hubble 1951). I have seen one patient who was confidently diagnosed as pink disease by a reputable pædiatrician until a phæochromocytoma was discovered. Check (1951), however, using a method which he admits is liable to an error of ± 10%, has found no increase in the adrenaline content of the blood in pink disease.

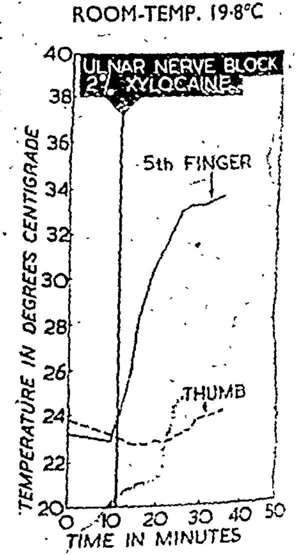


Fig. 8—Vasodilatation in little finger of infant, aged 11 months, with pink disease, after ulnar nerve has been blocked with 2% xylocaine.

Evidence from morbid histology is insufficiently conclusive to be of much help in supporting the hypothesis that pink disease is a disease of the autonomic system. Many of the reported necropsy changes in the nervous system have probably been due to the intercurrent disease which caused death. Péhu et al. (1936), in a critical review of the published findings, concluded that there were probably true widespread non-destructive lesions (chromatolysis, &c.) particularly in the sympathetic nervous system, including the hypothalamus. Lubin and Faber (1938), however, believed *that* such lesions were too inconstant to explain the physical signs, and found in their own case no changes in the hypothalamic region. Woringer (1926) reported hypertrophy of the suprarenal medulla in one case, and there have been other accounts of slight modifications of the histology which are too vague to be convincing.

The present investigation of the skin-temperature shows that in pink disease the blood-flow through the skin of the hands is decreased owing *not to structural* changes in the blood-vessels but to excessive vasoconstriction. This effect is abolished when the nerve-supply of the arterioles is interrupted, whether at the sympathetic ganglia (T.E.A.B.), in the peripheral nerve carrying the sympathetic fibres to *the blood-vessels* (ulnar-nerve block), or at the nerve-ending in the vessel

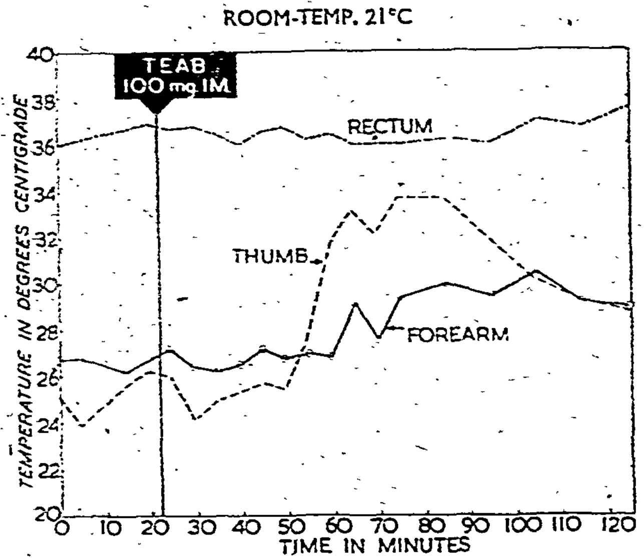


Fig. 9—Vasodilatation in thumb and forearm of infant, aged 16 months, with pink disease, after intramuscular injection of tetraethylammonium bromide 100 mg.

wall (priscol). The absence of reflex vasodilatation when warmed blood reaches the hypothalamus is probably due to the strength of the vasoconstriction, but a possible alternative explanation is that there is a specific disorder of function in the hypothalamus.

Tone in the small blood-vessels of the skin normally depends partly on impulses reaching them through their sympathetic nerve-supply and partly on humoral control. A dominant part is played by adrenergic vasoconstrictor nerves; and though cholinergic vasodilator nerves probably exist (Lewis and Pickering 1931) they are almost certainly much less important. The sympathetic system is influenced by cells in the hypothalamus, and these in turn receive from the cerebral cortex impulses which are probably inhibitory (Kuntz 1946).

The excessive vascular tone in pink disease may thus be due to stimulation of nerve-cells somewhere at or above the sympathetic ganglia, leading to an increased flow of impulses to the periphery. Lesions causing release of the sympathetic centres in the hypothalamus from the inhibitory influence of the cerebral cortex could theoretically produce the same effect. Although the experimental findings are therefore compatible with overactivity of the sympathetic nerves supplying at least the blood-vessels of the skin, the alternative possibility of a circulating vasoconstrictor substance acting directly on the blood-vessel walls is not disproved. It is reasonable to suppose that, if the excessive vasoconstriction were due to such a circulating substance, removal of the normal nervous impulses to the blood-vessels would allow vasodilatation to take place. An alternative possibility is that this substance might exert its action by potentiating the transmission of impulses through synapses or nerve-endings in the sympathetic pathways. Small doses of adrenaline, for example, augment the transmission of impulses through the sympathetic ganglia (Burn 1945). By analogy with a phæochromocytoma of the suprarenal gland, which has already been discussed, the supposed circulating substance might well be a mixture of adrenaline and noradrenaline (Engel and von Euler 1950). Since noradrenaline predominates in the suprarenal gland of early childhood (West et al. 1951), investigations to show whether it is present in excess in pink disease are being undertaken. So far it can only be said that a study of the peripheral vascular responses lends some support to the conception of this disease as a disturbance of the sympathetic-adrenal system.

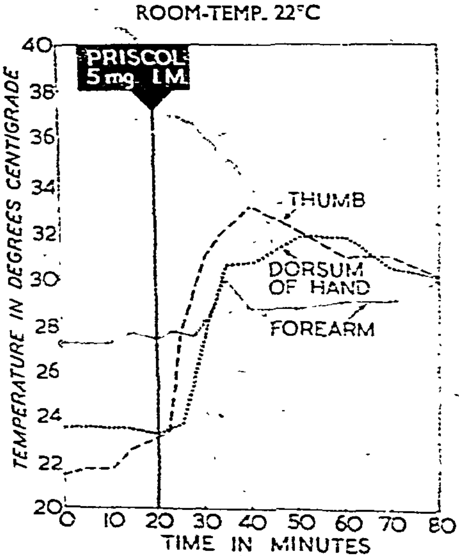


Fig. 10—Immediate vasodilatation in hand after intramuscular injection of priscol 5 mg. in infant, aged 10 months, with pink disease.

SUMMARY

The well-recognised clinical observation of coldness of the hands and feet in pink disease is confirmed by accurate temperature measurements under standard conditions.

Reflex vasodilatation in the hands, which normally follows heating of the trunk and legs, is absent in ten out of eleven cases of pink disease.

The capacity to produce reflex vasodilatation is, however, regained when clinical recovery takes place.

Ulnar-nerve block by local anæsthetic, intramuscular injection of tetraethylammonium bromide, and intramuscular injection of priscol, however, all lead to vasodilatation in the hands.

It is concluded that the coldness is caused not by structural occlusion of the vessels but by excessive vasoconstriction in the arterioles, with capillary dilatation. Certain hypothetical explanations of these findings are discussed.

I wish to thank Dr. P. R. Evans for his great help and encouragement; Dr. H. E. Holling and Dr. E. M. Glaser for advice and helpful criticism; Prof. A. A. Moncrieff and Dr. Wilfrid Sheldon for permission to carry out some of the investigation at the Hospital for Sick Children, Great Ormond Street; and Dr. Eleanor Coll and the sisters, nurses, and medical students who assisted at different times. The figures reproduced in this paper were prepared by Miss M. J. Waldron in the department of medical illustration, Guy's Hospital.

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ACUTE ETHYLENE GLYCOL POISONING TREATED WITH CALCIUM SALTS

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ETHYLENE glycol ('Antifreeze') has an effect like that of alcohol; it has a sweet pleasant taste, and gives a warm sensation when ingested. In the body it is oxidised to oxalic acid, and calcium oxalate is deposited in crystalline form in the kidney and brain.

The toxicity of the glycols first came to public notice by deaths which followed the administration of a solution of sulphanilamide dissolved in diethylene glycol. In 1930 two cases were reported in which the patients died of respiratory failure and convulsions after drinking ethylene glycol (*Journal of the American Medical Association* 1930). The pharmacology of the glycols is now better understood. Ethylene glycol is about twice as toxic as propylene glycol, which is oxidised in the body to lactic or pyruvic acid and combined with glycuronic acid. Ethylene glycol is only half as toxic as diethylene glycol. With these other two glycols, crystals of calcium oxalate are not found; and most of the main symptoms of acute ethylene glycol poisoning seem to be connected with oxalic acid. Smith (1951) described two subacute cases of such poisoning in which the patients died after 11 and 12 days from renal failure. Necropsy showed focal hæmorrhagic necrosis of the renal cortex and hydropic changes in the liver and renal tubules—changes which also occur in poisoning with diethylene glycol.

CASE-HISTORY

The patient, a slightly built male, aged 54, was admitted in deep coma with a vague history of having been exposed to fumes at work on the afternoon shift. He worked in an aircraft factory, and had that day been cleaning out the petrol tanks of an aeroplane; he had apparently entered the tank against regulations. He had left work early, staggering on his way out and falling on his back. Arriving home at 10.30 P.M. apparently drunk, he vomited his meal and staggered up to bed. His wife was not unduly perturbed, but she noticed that he was becoming very confused; and at 2 A.M. he was deeply comatose.

He was admitted to hospital at 7.30 A.M., deeply cyanosed. The respirations were stertorous—30 per minute—the temperature 98·4°F, and the pulse regular at 96 beats per minute. He was deeply comatose; there was no response to any stimulation, all deep and superficial reflexes were absent, and he was incontinent of urine and fæces. Frothy saliva was dribbling from his mouth, and his blood-pressure was 120/80 mm. Hg. The fundi showed no abnormality. His urine showed a trace of albumin, but no other abnormality. The stomach was aspirated as a routine measure, but the contents—20 oz. of foul-smelling fluid—were unfortunately discarded. Lumbar puncture yielded clear cerebrospinal fluid under normal pressure, containing 13 cells per c.mm., protein 120 mg. per 100 ml., and chlorides 840 mg. per 100 ml. He was given oxygen by inhalation, penicillin intramuscularly, and calcium gluconate intravenously. Milk was given by stomach-tube, because acute lead poisoning was suspected. Glucose-saline was given by intravenous drip to remedy dehydration.

The patient remained in deep coma for the next two days, during which administration of calcium gluconate was continued. Inquiry as to the cause was instituted at the works without success. Lead encephalopathy due to tetraethyl lead, which might have been present in the tank of the aircraft, was eliminated by urinary-lead estimation. Methyl bromide poisoning was considered, as on the day of onset he had also been shifting fire-extinguishers. It was not until the fourth day, when he was recovering consciousness, that we learnt that the patient had drunk about three-quarters of a tumbler of antifreeze. (This was confirmed by the patient on recovery.) On that day his urine contained a fair amount of albumin, he had pronounced tremor of the limbs, and he was incoördinated and rowdy. Distinct convergent strabismus was present. On the fifth day he was mentally much clearer, but tremor and squint did not disappear until the eighth day. During this period he felt extremely ill; he vomited bile-stained material, and the urine contained albumin but no bile. Fluids with glucose were given copiously and calcium lactate was administered by mouth. Recovery was gradual; and the patient was discharged, apparently cured although still shaky, after three weeks. A blood-count a this time showed no notable abnormality: red cells 4,400,0 per c.mm., hæmoglobin 82%, film normal. A van den Berg test was negative.

The patient was seen again two and a half years late complaining of general weakness, loss of weight and appetit and peculiar sensations in his abdomen. Complete clinic examination showed no abnormality other than a peculi yellow pigmentation of the face and arms, pronounce tremor, some loss of postural sense in the legs, and accentu tion of the deep reflexes. He was still shaky, lacked co centration, could not stand noises, and was very sensiti to cold. Sensibility to posture and deep pain was impaire in the lower limbs; and he was generally weak; the dee reflexes were increased. Previously a cheerful person all h life, he was now severely depressed. Investigations at th admission were as follows: alkaline phosphatase, 5·2 units thymol turbidity, 1 unit; van den Bergh, no increase albumin, 4·8 g. per 100 ml., globulin, 2·2 g. per 100 ml. barium meal, normal; glucose-tolerance test (fasting and half-hourly intervals after 50 g. glucose), 69, 83, 90, 66, 3 and 66 mg. per 100 ml.

COMMENT

The nervous manifestations presented appeared t fall into three stages:

1. Depression of the higher centres with ataxia and apparen stimulation similar to acute alcoholism, lasting three to fiv hours.
2. Deep coma due to gross depression of the nervous system with pronounced cyanosis and loss of deep and superficia reflexes, lasted four days.
3. Recovery with distinct tremor, incoördination of cortica type, and strabismus, lasting four days—although some evidenc of cortical deterioration was still present after three weeks.

The coma was probably due to a combination o cerebral depression and pulmonary œdema. The patient seems to have suffered permanent cerebral damage there was no evidence of permanent renal damage. The yellowish pigmentation after two and a half years is unexplained.

DISCUSSION

Few cases have been reported in which patients survived such severe ethylene glycol poisoning. The minimal lethal dose has been estimated as 100 ml., although Kahn and Brotchner (1950) report a case o a young man who survived after ingesting 240 ml. It was estimated that the patient described here drank 120-150 ml. He was a chronic drinker and *not* robust. Calcium, given under the initial impression that he was suffering from lead encephalopathy, combined with oxygen, may have enabled him to recover.

In cases coming to necropsy generalised congestion with degenerative fatty changes in the liver cells has been found; but the most pronounced changes seem to be as follows:

1. Well-marked pulmonary œdema, sometimes with early bronchopneumonia.
2. Tubular nephritis with deposition of calcium oxalate crystals, swelling of the lining endothelium, and granularity of the cytoplasm. Despite this there does not seem to be gross epithelial desquamation.
3. Congestion of the brain and meninges with œdema; in severe cases exudative meningo-encephalitis is the most important feature. In the brain and leptomeninges calcium oxalate crystals are found, lying mainly around the blood-vessels. Those present in the brain-substance proper evoke no reaction around them. Damaged cells are found in the motor cortex, brain-stem, and cerebellum. Pons and Custer (1946) suggest that ethylene glycol, like alcohol, becomes slowly concentrated in the cerebrospinal fluid, and that the concentration there is maintained for some time.

The pathology suggests that calcium oxalate crystals themselves are inert. The inflammatory changes are around the blood-vessels in contact with the cerebrospinal fluid, and may perhaps be due to oxalic acid. In the case described here the calcium given in large doses intravenously may have changed this oxalic acid to the relatively inert calcium salt. Milles (1946) suggested calcium or a parathyroid preparation as a possible therapy, although he did not try these substances.

SUMMARY

A case of ethylene glycol poisoning with recovery is described. In this case large doses of calcium given intravenously may have changed oxalic acid to calcium oxalate, thus preventing the destructive action of oxalic acid on the brain.

Re-examination after two years suggested permanent cerebral damage. There was no real evidence of renal or hepatic failure; but a peculiar yellowish pigmentation was observed on the neck and arms.

I am indebted to Dr. James A. Smiley, medical officer of Messrs. Short Bros. & Harland Ltd., for his coöperation.

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PELLAGRA ASSOCIATED WITH CROHN'S DISEASE

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Pellagra secondary to disease of the small intestine and nutritional disturbances depending on malabsorption has often been recorded; but as a complication of Crohn's disease it does not seem to have been described in the last twenty years.

CASE-RECORD

A trained nurse, aged 24, was a patient in a mental hospital where she had symptoms suggestive of catatonic schizophrenia, together with diarrhœa and loss of weight. No cause being found for the diarrhœa, she was transferred to a medical ward at Stracathro Hospital on June 10, 1949.

Condition on Admission

The patient was emaciated, apathetic, and mentally confused, and had a striking pink and white complexion with a malar flush. She was afebrile, her appetite was poor, and she passed fluid stools several times a day. The diarrhœa had started two years previously, after an attack of erythema nodosum. No evidence of any infection was discovered in the mouth, nasal sinuses, skull, or respiratory and cardiovascular systems. Radiography of the chest was negative and a barium meal and barium enema did not reveal any abnormality in the gastro-intestinal tract. The urine and cerebrospinal fluid were normal. There was no evidence of any gastro-intestinal infection, and the Wassermann reaction was negative.

Progress

During the first three weeks in hospital the patient developed spastic paraplegia and ataxia, and her mental condition deteriorated. Her stools became more frequent, and she began to show signs of dehydration. Steatorrhœa was present, but fat-splitting was normal. Her serum-calcium level was only 7·8 g. per 100 ml.; her plasma-proteins were 5·25 g. per 100 ml. (albumin 3·4 g., globulin 1·8 g.). Her blood-sugar was 90 mg. per 100 ml.

On July 9, 1949, a rash appeared on her face, neck, and backs of the hands, and she became completely disoriented and incontinent. Pellagra was diagnosed and treated. Immediate response was noted, and the patient improved so rapidly and gained so much weight that she returned home on Aug. 20, 1949. Her mental condition was then normal, and there was little ataxia or difficulty in walking, but her plantar reflexes, which had throughout been extensor, did not show any change. During the next nine months she was seen at intervals and steadily gained weight and improved in health.

In May, 1950, she complained of abdominal pain, attacks of vomiting, and slight diarrhœa, and developed a left-sided ischiorectal abscess, for which she was readmitted to hospital. The abscess was drained, and coliform organisms were cultured from the pus.

In July, 1950, the patient developed acute appendicitis, and at operation for appendicectomy the lower 18 in. of the ileum were found to be the seat of second-stage Crohn's disease. No further treatment was thought justifiable, and the abdomen was closed.

The patient again came under medical care on Aug. 30, 1950, with vomiting, flatulence, and hot flushes. There was no diarrhœa and no weakness of the limbs; the fingers and toes showed clubbing; and the blood-pressure was 90/50 mm. Hg. The abdomen was rather full; there was slight œdema of the ankles; the plantar responses were extensor on both sides, but there was little ataxia. Considerable anæmia was present, a blood-count showing red cells 3,900,000 per c.mm., white cells 6000 per c.mm. (polymorphs 86%, lymphocytes 8%, monocytes 5%, eosinophils 1%), and Hb 9·2 g. per 100 ml. The reds cells were normocytic and underfilled; and the plasma-proteins were 5 g. per 100 ml. An ischiorectal fistula was present, and this was excised on Nov. 9, 1950. The patient left hospital on Dec. 16, and was asked to return in January, 1951. It was thought that she was still suffering from a deficiency of vitamins as a result of malabsorption due to Crohn's disease.

Resection of Ileum.—On March 12, 1951, about 3 ft. of diseased ileum was removed together with its mesentery, and a primary anastomosis of the small bowel was made. Uninterrupted recovery followed the operation, and on March 28 the patient returned home. On histological examination the two wedges of intestine and omentum showed chronic granulomatous changes with much fibrosis and a few small follicles suggesting tuberculosis.

Follow-up.—The patient was last seen on April 1, 1952, when she weighed 9 st. 8½ lb., and examination of her blood showed red cells 3,700,000 per c.mm., white cells 7000 per c.mm., Hb 88%, colour-index 1·2, mean corpuscular Hb concentration 33%, mean corpuscular volume 105 c.μ., packed-cell volume 39 c.cm., and erythrocyte-sedimentation rate 32 mm. in 1 hr. (Wintrobe). Her plasma-protein level was 6 g. per 100 ml. (albumin-globulin ratio 2 : 1). A blood film showed red cells a little larger than normal and well filled with hæmoglobin; platelets present in adequate numbers. The patient was well nourished, her tongue was clean, her abdomen was well covered, there was no tenderness anywhere, and her liver and spleen were not enlarged. There was slight œdema of her shins, her deep reflexes were all brisk, her blood-pressure was 130/80, and both plantar reflexes were extensor. A fractional test-meal disclosed achylia gastrica, and no starch was noticed in any of the specimens. The only complaint which the patient had was that her bowels tended to be somewhat irritable and she usually passed two or sometimes three stools a day, but they were well formed and there was no diarrhœa. There was obviously no serious interference with nutrition, since she was well nourished and of normal weight.

DISCUSSION

Pellagra has been reported in association with extensive jejuno-ileitis (Killian and Ingelfinger 1944), gastro-enterostomy (Ferguson 1943), chronic amœbic dysentery (Blanc and Siguier), and annular carcinoma of the ileum (Nuzum 1925). Simpson (1934) stated that pellagra may follow a lesion almost anywhere in the gastro-intestinal tract, from the stomach to the rectum. Bean et al. (1944) stated that diseases such as pulmonary tuberculosis and malaria, as well as conditions such as pregnancy and lactation, may be responsible for its appearance in places where malnutrition is endemic.

Nutritional disturbances caused by diminished food intake, lack of absorption due to alteration of the intestinal mucosa, restricted areas for absorption of vital materials after short-circuiting operations, severe and prolonged diarrhœa, loss of protein through a chronic suppurating focus, and loss of body-fluids as after burns or from protracted diarrhœa, have all been cited as causing pellagra.

Mackie et al. (1940) found that in the early stages of vitamin deficiencies there is a disturbance of function, which precedes the structural changes which are found when the deficiency becomes more intense or has lasted a long time. Thus patients with signs of hypovitaminosis may have either reversible or irreversible lesions in the gut. In the present case it was tempting to think that the initial symptoms of hypovitaminosis were due to reversible changes, because the improvement after intense vitamin therapy was so pronounced, and that the relapse was in part due to the ischiorectal fistula. It is impossible, however, to reconcile this idea with the subsequent discovery of Crohn's disease—a condition which can only be regarded as irreversible.

The fact that the patient still has looseness of the bowels and macrocytic anæmia suggests that, though there is no reason to believe that a progressive lesion is still present, she cannot be regarded as cured.

SUMMARY

A case of pellagra in a patient with Crohn's disease is described. Resection of the diseased part of the small bowel was followed by improvement.

I am indebted to Mr. R. V. Liddell for the surgical treatment of this patient, to Dr. A. V. Hendry for his advice, and to Prof. A. C. Lendrum, of the University of St. Andrews, for a histological report on the tissue removed.

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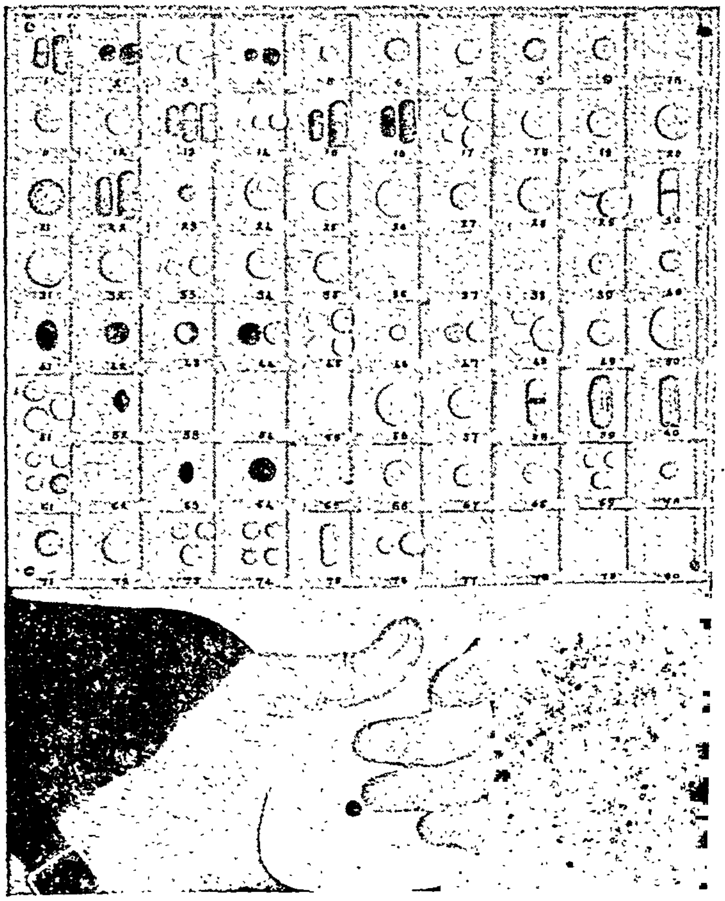
New Inventions

A TABLET-IDENTIFICATION BOX

In the last few years there has been a steady increase in the number of new drugs in common use. To name only the chief groups, there are hypnotics, antihistaminics, analgesics, antibiotics, aperients, and vitamins: their colours are spectral and their shapes and covering diverse; tablets may be smooth or grooved, coloured or white, coated or plain; and pills and capsules come in many sizes and shapes. Some of these are used in the treatment of skin diseases; and others at times cause drug eruptions.



When questioning patients attending a skin department, it is often difficult to discover what drugs they have been taking, and their doctors do not always give this information in the accompanying letters. If a patient is suspected to be suffering from a drug eruption, the elucidation of this point is most important, and only a few outpatients bring their medicaments with them. The need was therefore felt for a compact tablet-identification box which could be kept in the consulting-room, and from which patients could identify the drugs they have taken.

Dr. F. F. Hellier showed one of us such a box used in the skin department at Leeds Royal Infirmary. The box illustrated here is more elaborate and designed for long-continued use. Its chief features are strength and portability, and good visibility and easy recognition of the drugs inside. It can be taken to pieces if necessary for alterations or additions to the contents. A box of this sort is also useful for teaching purposes.

The box (see accompanying figure) is made of $^1/_8$ in. sheet 'Perspex,' and weighs 2 lb. The over-all measurements of the box are $10^1/_4 \times 8^1/_4 \times {}^7/_8$ in., with a handle projecting for $4^1/_2$ in. from one of the longer sides, the grip being $2^1/_4$ in. wide. The box is built around a central sheet of white opaque perspex which is extended to form the handle. The edges of the box itself are $^1/_2$ in. deep, and it is subdivided into 80 compartments, each $^7/_8$ in. square. Both the edges and the internal divisions are fixed to the opaque sheet by perspex cement. The handle is strengthened by cementing to it a piece of $^3/_{16}$ in. perspex of similar shape. When not in use the box may be hung on the wall by a hole through the handle. The front and back are formed by two further sheets of perspex which are held in place at the corners by four brass nuts and bolts.

Both tablets and capsules can be attached to the opaque sheet with 'Dyrofix' or a similar glue. They can easily be removed to change the contents if need be. The squares are numbered in rows of ten, while the key, giving particulars of the dosage and nature of the drugs, is typed on quarto-size paper and inserted between the opaque and the back perspex sheets.

We wish to thank Mr. J. T. Edwards, of the London Hospital Medical College, who kindly constructed the box to our design.

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Reviews of Books

Antibiotics

A Survey of Their Properties and Uses. 2nd ed. Contributors: S. J. EDWARDS, D.SC., A. KEKWICK, F.R.C.P., F. A. ROBINSON, M.SC., G. SYKES, M.SC., B. J. THOMAS, M.P.S. Published by direction of the Council of the Pharmaceutical Society of Great Britain. London: Pharmaceutical Press. 1952. Pp. 274. 25*s.*

THE number and uses of antibiotics have been increasing so rapidly that it has been virtually impossible for anyone to keep himself fully conversant with the latest developments. This book is therefore welcome, since it provides a relatively short and concise, yet remarkably complete, account of the uses and abuses of these drugs. The book is intended primarily for general practitioners, veterinary surgeons, and pharmacists, whose requirements are admirably met. It is perhaps rather overloaded with laboratory details; some of those relating to chemical analysis and biological assay methods might well have been omitted.

Genes and Mutations

Cold Spring Harbor Symposia on Quantitative Biology. Vol. 16. Cold Spring Harbor, New York: Long Island Biological Association. 1952. Pp. 521. $9.

THE science of genetics seems forbiddingly formalistic to many who are not in any way enemies of Mendelism, like the followers of Lysenko. The subject is sometimes thought to be less a branch of experimental biology than a playground for mathematical statisticians. There could hardly be a better corrective to this belief than the contributions to a recent symposium on genes and mutations, organised, like its predecessors, by Professor Demerec and held at Cold Spring Harbor.

In his introductory paper Goldschmidt points out that the idea of correlating one enzyme with each gene, though logical, may require revision. Mutations in neurospora and *Bacterium coli* have repeatedly been shown to produce metabolic alterations or defects which are attributable, according to the work of Horowitz and Leupold, to changes in single enzymes. On the other hand, the "position effect" phenomenon, investigated profoundly by McClintock, especially in maize, points to genes having actions which vary according to the nature of their genic neighbours.

The causes of gene mutation are multiple; and, as Auerbach shows, radiation produces immediate effects whereas those of nitrogen mustards and formalin are often delayed. There is still no known common factor among mutagens. Westergaard and others point out that it is difficult to prove that any substance is not mutagenic, because changes produced may be very slight. A criterion of the difference between true gene mutation and chromosome damage might be the ability to produce back-mutation—a return to the original state. Stadler takes the matter even further, and, on the basis of his experiments, doubts whether there is any way of distinguishing absolutely between gene mutations and other processes, such as crossing-over at very closely adjacent loci.

Thus the ground is prepared for the reception of the idea of "pseudoallelism" as propounded by Lewis. Pseudoalleles are complex genes, of which the rhesus types in man are probably examples, and they are thought to arise in the first place by duplication of one gene, followed by divergent functioning of one of the pair as a result of a "position" effect. Justification for Goldschmidt's assertion that there is no fundamental distinction between chromosome breakages, rearrangements, and point mutations thus becomes evident.

The facts about the genetics of bacteria, as set out by the Lederbergs, may seem incredible enough; but the reader may be pardoned if he gasps with astonishment when Luria describes experiments on mutant genes in the phage infecting *Bact. coli*, and when Hershey and Chase demonstrate recombination, proving that the genes in phage T2H are arranged in linear order. Then again, there is the follow-up, by Hotchkiss, of the work of Avery and McCarty in which he transformed pneumococci into a penicillin-resistant type by adding a desoxyribonucleate prepared from resistant strains.

Of more direct interest to human genetics by analogy is the exact measurement of mutation-rate at specified loci in the mouse. This was found by Russell to average 25×10^{-8} per röntgen—a higher rate than that formerly established for drosophila. Aspects of the influence of cytoplasm on heredity are discussed by Ephrussi and by L'Heritier, and the interaction of cytoplasm and nuclear components in chlamydomonas and paramœcium is explained by Sonneborn.

Altogether there are over thirty papers, every one of which is of first-rate interest. An attractive feature throughout is absence of complacency; ideas are changing, and a vast field of investigation into fundamental biological processes is being rapidly developed. It is becoming clear that, as a small sacrifice to facilitate these advances, many current concepts of the gene and its functions will have to be modified considerably.

Injury of the Xiphoid

MICHAEL BURMAN, M.D., SAMUEL E. SINBERG, M.D. New York: Columbia University Press. London: Oxford University Press. 1952. Pp. 92. 22*s.* 6*d.*

IT seems hard to believe that the xiphoid should be sufficiently important to justify a monograph, but the authors' experience of nearly 100 cases of serious injury shows that it deserves attention. Direct injury, leading to dislocation of the cartilage from its normal site, results from sudden blows in the solar plexus, or when the driver of a car is thrown forward against the lower edge of the steering-wheel in an accident. The surgeon cannot be exonerated from being the cause of a xiphoid fracture when an enthusiastic assistant during a laparotomy exerts unduly vigorous retraction at the upper end of the abdomen. Like the coccyx, the xiphoid may become hypersensitive as a result of injury, and in many such cases the authors recommend its excision. Though the main concentration is on the xiphoid itself, this monograph touches on a slightly wider field than its title would suggest.

Primer on Alcoholism

MARTY MANN, chairman and executive director, National Committee on Alcoholism in America. London: Gollancz. 1952. Pp. 160. 8*s.* 6*d.*

ALL doctors should be adequately informed about alcoholism; and this book, though written by an American expert primarily for her fellow-countrymen, contains much that the British doctor should know. Mrs. Mann was herself an alcoholic, and has been cured. She has become a recognised expert on alcoholism, and has held her present post for seven years, so she is well qualified to speak on the subject. Throughout her book she emphasises that alcoholism is a disease, and therefore should be treated as objectively as pneumonia or diabetes. If this were more generally recognised a great deal of the guilt and shame from which the alcoholic invariably suffers, and in which his family and friends share, might be alleviated and treatment might be more readily accepted.

Mrs. Mann gives a good general description of the course of alcoholism and its effects both on the patient and his family; and she discusses in practical detail what can be done about it. Medical and psychiatric treatment, both at home and in institutions, is outlined and the work of Alcoholics Anonymous is particularly well described. This valuable organisation is already well established in Great Britain, with twenty groups in London, Liverpool, and other cities (headquarters address BM/AAL, London, W.C.1). The work of the Society for the Study of Addiction and the recently formed Advisory Council on Alcoholism is also sympathetically mentioned. There are two brief appendices by British doctors describing the treatment of alcoholism by apomorphine and 'Antabuse.'

Adrenal Cortex

Transactions of the Third Conference, Nov. 15–16, 1951. Editor: ELAINE P. RALLI, department of medicine, College of Medicine, New York. New York: Josiah Macy, Jr., Foundation. 1952. Pp. 204. $3.25.

WHEN such workers as Astwood, Ingle, Kendall, and Pincus (to mention only 4 out of 25) are brought together a verbatim report of their discussion, quickly published, is really up to date. Much of the material in this volume has not yet appeared elsewhere: some of it indeed is still in the stage of pure speculation. This conference dealt with the effects of adrenal cortical hormones on renal function, the rôle of the hypothalamus in regulating A.C.T.H. secretion, the estimation of blood steroids, the biogenesis of the adrenal cortical steroids, and the clinical use of adrenal cortical hormones and A.C.T.H. The discussion has been illustrated with graphs, tables, and photographs.

Anæsthesia for Thoracic Surgery

HENRY K. BEECHER, M.D., professor of research in anesthesia, Harvard University. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 65. 18*s*.

THE methods advocated here are those of the author, and the book is therefore neither a review of present-day techniques nor in any way a critical analysis of them. A valuable account is nevertheless presented of thoracic anæsthesia as practised at the Massachusetts General Hospital.

Professor Beecher is a strong exponent of ether for thoracic anæsthesia. His advocacy of assisted respiration rather than controlled respiration may well be associated with his use of ether, the difficulty of controlling respiration with this anæsthetic being well known. Many of the ideas and practices described are clearly more in accord with surgical conditions in the United States than in this country. One example indicative of the gulf between Beecher's methods and those used here is the brief mention and somewhat offhand dismissal of the use of curare or other relaxants in thoracic anæsthesia.

Anæsthetists will read the book with interest.

Monographs on Surgery 1952

Editor: B. NOLAND CARTER, M.D., PH.D., professor of surgery, University of Cincinnati. 1952. Pp. 430. 95*s*.

THE policy of publishing annual volumes of monographs on surgery seems to be amply justified by this volume, the third in the series. Among the subjects reviewed are the radical surgery of pancreatico-duodenal cancer, stress incontinence in the female, arthroplasty, and current views about the internal fixation of fractures. All the articles are detailed and written by authorities on their subjects. The reader is thus spared the labour of wading through irrelevant and useless papers: the selection has already been made for him by reliable people. Monographs of this kind are of real help to busy surgeons.

Normal Blood-Pressure and Hypertension

New definitions. ARTHUR M. MASTER, M.D., cardiologist, Mount Sinai Hospital, New York, and associate clinical professor of medicine, Columbia University, New York; CHARLES I. GARFIELD, M.D., research assistant in cardiology, Mount Sinai Hospital, New York; MAX B. WALTERS, M.D., F.R.C.P. Can., member, heart station, Vancouver General Hospital, Canada, formerly research assistant in cardiology, Mount Sinai Hospital, New York. London: Henry Kimpton. 1952. Pp. 144. 30*s*.

THE correct interpretation of blood-pressure readings is earnestly to be desired; but opinions vary widely about the range of normal.

During the last thirty years there has been a tendency to accept 140–150 mm. systolic and 90–95 mm. diastolic as the upper limit of the normal, irrespective of age and sex. These authors contend that such limits are too rigid, and set too low; moreover, they are largely based on life-insurance statistics, which are in any case unsound because the material is highly selected, and relates to more men than women; moreover, most of the subjects are young, and the analysis is based on group-mortality. Dr. Master and his colleagues discuss the influence of age, sex, emotion, and other factors, and criticise the value of "basal" readings, concluding that it is more important to find the range of "casual" readings, since these reflect the subject's ordinary life.

They also consider local factors. Thus the relationship between the size of the arm and the width of the cuff greatly influences the accuracy of the pressure reading. It is noteworthy that arterial disease does not affect the reading; but spasm does, producing a false elevation of pressure which can be eliminated by repeated inflation of the cuff. Recommendations for cuff-size, design, and technique are given in detail.

Race, country, altitude, pregnancy, exercise, meals, and starvation do not exert an appreciable effect on the blood-pressure. Height has no influence; but weight is important, and reduction in weight is followed by a lowering of blood-pressure. The blood-pressure normally increases significantly with age, and this rise is more rapid and greater in females than in males after the age of 40.

The authors studied 74,000 unselected subjects representing the average working population between the ages of 16 and 65, and have tabulated their results in detail; and they have summarised their conclusions about normal and hypertensive limits in a final table. They discuss the interpretation and clinical application of the new blood-pressure limits, pointing out that the precise level of the blood-pressure is not so important as the presence or absence of underlying cardiovascular disease. There is no correlation between the height of the blood-pressure and symptoms, rate of progress, or development of complications; and the most important factors in prognosis are cardiac enlargement, albuminuria, changes in the retina, and the electrocardiographic findings.

There is a wide field of application of this new range of pressures in the practice of medicine and in clinical research; and the final table, a spare copy of which can be removed for mounting, should be on every doctor's desk.

Anglo-Saxon Magic and Medicine

J. H. G. GRATTAN and CHARLES SINGER. London: Oxford University Press. 1952. Pp. 234. 28*s*.

THE essential part of this important work is an edition of the definitive text of *Lacnunga*, an Anglo-Saxon book of prescriptions, incantations, and methods of treatment in various diseases. The text was last published in 1866 by Cockayne and is now very rare.

The present edition, which has been issued by the Wellcome Historical Medical Museum, is preceded by a detailed introduction by Professor Singer dealing with the whole subject of Anglo-Saxon medicine and enlivened by a choice and unusual collection of reproductions of contemporary illustrations. The second part of the book consists of the text, some of it in facsimile, of *Lacnunga*, and Professor Grattan's translation, notes, and commentaries.

Barbarian man had no mechanism for recording experience. His views on the nature of disease remained disjointed; but—since he knew well that he could sustain injury at his own hands or those of others—he commonly conceived that his symptoms were due to injuries inflicted by beings like himself, and that his sufferings were produced by weapons or agents identical with those that he himself employed. Elves were often regarded as the cause of disease, but as Christianity penetrated into the country God became pictured as the avenger in their place. The Anglo-Saxon leechdoms are a mass of folly and credulity. This is hardly surprising when it is remembered that there was no proper theory of disease and in consequence no rational remedies could be applied. The writer of *Lacnunga* dwells in the barbarian world of magic and hardly ever emerges. Here is an example of his text:

> "If there be a pock in the eye take marrow soap and hind's milk; mix and beat together; let stand until it be clear. Then take the clear fluid; put into the eyes. With God's help the pock shall away. . . . If a man be swollen within so that he cannot swallow the liquid, sing into his mouth."

This book will be welcomed as a treasure by students of Anglo-Saxon and medical historians interested in that period. The authors have garnished their scholarship with charm and humour.

Progress in Neurology and Psychiatry (Vol. 7. New York: Grune & Stratton. 1952. Pp. 604. $10).—Swelling year by year, this review, edited by Prof. E. A. Spiegel, seems to be approaching the awkward stage at which it must choose between blowziness and austere self-discipline. The book cannot cover everything written within its wide range, and a severely selective policy will save those who use it from the exasperation of looking up articles which turn out worthless. On the whole the neurological section remains the more satisfactory, as well as the more detailed: with the sections on neurosurgery and on the anatomy, physiology, and pharmacology of the nervous system, it takes up nearly two-thirds of the book. In the section on psychiatry the contributors seem unduly numerous, an extreme instance being the chapter of six and a half pages on the neuroses, prepared by no less than twelve doctors and a librarian. The value of the review would be increased by the inclusion of an index of names.

THE LANCET

LONDON: SATURDAY, DEC. 27, 1952

Deficiency of Potassium

Our understanding of the manifestations of sodium deficiency is derived from the classical studies of experimental depletion of sodium in man.[1] There have been no similar accounts of experimental depletion of potassium, because diets lacking this element are difficult to devise; and so our knowledge of potassium depletion is based mainly on clinical studies.

Deficiency of potassium may result from inadequate intake, excessive loss, or increased need. The intake may be inadequate in patients maintained with parenteral fluids. Excessive loss may take place from the alimentary tract[2] by vomiting, diarrhœa, aspiration of gastro-intestinal contents, or drainage from fistulæ; and from the kidney,[3] where acidosis, "osmotic diuresis," and adrenocortical hormone may in different ways lead to increased excretion. The need for potassium is enhanced by the deposition of protein tissue[4] or glycogen,[5] which are laid down with the normal constituents of intracellular fluid. These mechanisms are exemplified in the deficiency of potassium that may be found during the treatment of diabetic coma.[6] While the coma develops the patient loses potassium by vomiting; and he loses it from the kidney because, firstly with the acidosis there is an increased demand for the excretion of base, secondly with the glycosuria there is osmotic diuresis, and lastly there is increase in adrenocortical activity as part of the non-specific reaction to injury. The patient is treated with parenteral fluids which are unlikely to contain potassium; and there is an increased demand for potassium and other constituents of intracellular fluid as glycogen is laid down after administration of insulin. It is understandable, then, that these patients may show a potassium deficit; and this may amount to some 30 g., which is more than one-quarter of the normal content of the body. Yet it is only in recent years that such deficits have been recognised in patients with diabetes and other diseases.[7] This is partly because deficiency of potassium may not be easily demonstrated. Nearly all the body's store of potassium is in intracellular fluid, and serum levels may fail to reflect a deficiency. Though the serum-potassium can fall quite quickly with moderate deficits, it may not fall if there is renal failure or oliguria; and in untreated diabetic coma the serum-potassium level may be raised. Furthermore, the acid-base balance appears to affect the level of serum-potassium.[8] Potassium deficiency itself leads to alkalosis, and conversely alkalosis leads to loss of potassium; but with acidosis the serum-potassium level may be maintained despite a deficit of this ion.

The clinical picture is vague. It is usually described as one of apathy leading to mental confusion and disorientation, with anorexia, vomiting, and intestinal atony or sometimes paralytic ileus.[9] There may be muscular weakness and even flaccid paralysis; but this, though characteristic enough if present, is rare. By an unexplained paradox tetany occurs in other patients.[10] When present, the electrocardiographic changes of potassium deficiency, with depression of the ST segment, prolongation of the QT interval, and appearance of U waves,[11] are very helpful in diagnosis. Since potassium deficiency gives rise to such an indefinite clinical picture its importance may be doubted, except in those few patients who become paralysed or in whom myocardial necrosis is found post mortem.[12]

Two groups of workers in this country have sought to produce potassium deficiency experimentally in man, by giving either a diet from which potassium was removed by an exchange resin or else a normal diet with the resin. By the first method Black and Milne[13] in Manchester produced a deficiency of some 280 m.eq. of potassium. Symptoms were slight. Nevertheless the deficiency was accompanied by a fall in the level of serum-potassium; retention of sodium, mainly in extracellular fluid; and mild alkalosis. As the alkalosis developed, the urine became more alkaline; the alkalosis was not therefore the result of compensation originating in the kidney. Cooke et al.[14] have suggested that the alkalosis is extracellular and a result of the transfer of H ions from extracellular fluid to intracellular fluid to replace potassium there. Fourman and Ainley-Walker,[15] working at Oxford, produced a more severe depletion of potassium, amounting to 600–800 m.eq., by giving resin by mouth; but in their experiments the depletion of potassium was at first complicated by acidosis—presumably a side-effect of giving resin. In their two volunteers symptoms became pronounced, though the level of potassium in the serum fell only moderately in one and not at all in the other. The symptoms—apathy and mental confusion, anorexia and nausea—were in keeping with clinical reports, but may have been aggravated by the complicating acidosis. These experiments showed indirectly that potassium may be lost from the body without corresponding amounts of intracellular water; and, though there may be some intracellular dehydration,[13] loss of potassium leads mainly to a change in the composition of intracellular fluid through loss of the main cation without

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1. McCance, R. A. *Lancet*, 1936, i, 643, 704, 765, 823.
2. Cooke, R. E., Crowley, L. G. *New Engl. J. Med.* 1952, 246, 637; see *Lancet*, Sept. 20, 1952, p. 574.
3. Smith, H. W. The Kidney. New York, 1951.
4. Cannon, P. R., Frazier, L. E., Hughes, R. H. *Metabolism*, 1952, 1, 49.
5. Fenn, W. O. *Physiol. Rev.* 1940, 20, 377.
6. Nabarro, J. D. N., Spencer, A. G., Stowers, J. M. *Quart. J. Med.* 1952, 21, 225.
7. *Lancet*, 1951, i, 393.
8. Darrow, D. C., Schwartz, R., Iannucci, J. F., Coville, F. *J. clin. Invest.* 1948, 27, 198.
9. Lans, H. S., Stein, I. F., Meyer, K. A. *Surg. Gynec. Obstet.* 1952, 95, 321.
10. Eliel, L. P., Pearson, O. H., Rawson, R. W. *New Engl. J. Med.* 1950, 243, 471, 518.
11. Bellet, S., Steiger, W. A., Nadler, C. S., Gazes, P. C. *Amer. J. med. Sci.* 1950, 219, 542.
12. Keye, J. D. jun. *Circulation*, 1952, 6, 766.
13. Black, D. A. K., Milne, M. D. *Lancet*, 1952, i, 244; *Clin. Sci.* 1952, 11, 397.
14. Cooke, R. E., Segar, W. E., Cheek, D. B., Coville, F. E., Darrow, D. C. *J. clin. Invest.* 1952, 31, 798.
15. Fourman, P., Ainley-Walker, K. M. S. *Lancet*, Aug. 23, 1952, p. 368.

an equivalent loss of the corresponding anion, phosphate.[15] This has long been suspected[16] and has been proved in work on animals.[17] The experiments on man also revealed an excessive increase in extracellular fluid, and one subject became œdematous.[15]

All these results suggest that moderate potassium deficiency does not in itself cause serious symptoms but may predispose to œdema; more severe depletion may have important effects, particularly in the presence of acidosis when potassium apparently continues to provide base for the excretion of acid even if the stores of potassium have been depleted. Clinical data suggest, too, that severe depletion—even without acidosis and with sodium available to replace potassium—is best avoided. In babies at least, the mortality from diarrhœa can be greatly reduced by administration of potassium.[18] Because moderate depletion does not produce striking symptoms, the diagnosis of potassium deficiency will often be a matter of conjecture based on the knowledge of the patient's probable intake and losses. When deficiency is suspected—for instance, in ulcerative colitis[19]—one is usually justified in administering potassium. So long as the urinary output is satisfactory this can be done simply and safely with potassium citrate mixture (*N.F.*), which contains about 50 m.eq. of potassium per ounce, or with other salts[7] by mouth. Without clear evidence of deficiency it is not justifiable to risk giving potassium parenterally so long as the patient can take it by mouth; but for many surgical patients, and particularly those with paralytic ileus where deficiency of potassium may be a contributory cause,[20] parenteral administration is necessary. Such patients may conveniently be given the solutions devised by COOKE and CROWLEY[2] to match fluid aspirated from the stomach or intestine; they are given in amounts equivalent to the aspirates, so that severe depletion is avoided from the start. Weaker solutions, such as Ringer's fluid, contain too little potassium to do any good. On the other hand stronger solutions are needed for the treatment of an established deficiency; but their dangers and limitations must be borne in mind.[7]

Searching for Better Anticoagulants

HEPARIN and dicoumarol have great value in the treatment of thrombo-embolic diseases; but both these substances have troublesome disadvantages. Heparin must be given intravenously—intramuscular preparations are still not entirely satisfactory—and the effect of each dose lasts only a few hours. Dicoumarol takes up to 72 hours to exert its maximum effect, and its action continues for at least as long after the last dose. This means that if rapid anticoagulant action is needed—and it often is—heparin must be given for the first 3 days; and if the dicoumarol reduces the prothrombin concentration too far, any hæmorrhage is difficult to control. The success of the anticoagulant treatment of coronary thrombosis has given an immense fillip to the search for better anticoagulant drugs, for coronary thrombosis is one of the most dramatic of modern scourges. As GILCHRIST[1] has put it: "Thirty years ago it was a rarity even in pathological experience. Today we count our cases in hundreds and pass on to the next." And, after much experience, he claims that by efficient use of anticoagulants the death-rate over the first 6 weeks can be halved and the danger of thrombo-embolic complications reduced to negligible proportions.

In 1948 VON REINIS and KUBIK[2] introduced a dicoumarol ester which was given the name 'Tromexan.' Tromexan has the advantage that in therapeutic doses it will effectively reduce the prothrombin level in 24 hours, and that its action ceases a few hours after administration is discontinued. BURT *et al.*[3] reported favourably on it in 1949; and since then there have been several accounts of its value, especially in coronary thrombosis. BRONSTEIN and WITKIND[4] studied a group of 50 patients, 22 of whom had myocardial infarction. To reduce the prothrombin concentration appropriately within 24 hours a "loading dose" of 1500–1800 mg. (five to six times that of dicoumarol) proved necessary. Then, in the first 7 days especially, they noticed that wide fluctuations of prothrombin level were liable to occur, and consequently daily control by prothrombin estimations was essential; even so, in some patients smooth control was possible only by giving the drug in divided instead of single daily doses. If the daily dose was entirely omitted because of low prothrombin the level was liable to rise sharply next day and be difficult to re-establish at a suitable level. Despite these difficulties, they concluded that tromexan was safer than dicoumarol, and no serious hæmorrhage occurred in their patients. ILLINGWORTH[5] aimed at keeping the prothrombin level of his patients at between 30% and 10% of normal. He found that the initial 24 hours, before the action of tromexan reached its maximum, could be covered by a single intravenous dose of 100 mg. of heparin. He also noted the difficulty of forecasting the daily dose; age and weight were no help, and the only method of control was to have the prothrombin estimated every day and not to give the day's dose until the result was known. He gave a table of doses for various levels—at 80% prothrombin concentration about 900 mg. is needed, and at 10% 150 mg. since even at this level the drug should not be entirely stopped. ILLINGWORTH observed that, even with these precautions, patients on tromexan treatment were liable to sudden "escapes" from anticoagulant control. Of 60 patients with cardiac infarction who were treated in this way, only 2 had bleeding episodes, although the prothrombin level was sometimes less than 10%; this compared well with 7 cases of hæmorrhage among 36 patients treated with dicoumarol. Similar results have been described by STIRLING and HUNTER,[6] who had rather a higher rate of hæmorrhage—13 (8·6%) in 151 patients treated.

The most ambitious comparison of dicoumarol and tromexan is that organised by the American Heart Association and embodied in a report by SCARRONE et al.[7] Seven hospitals in various parts of the U.S.A.

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[16] Elkington, J. R., Winkler, A. W., Danowski, T. S. *Yale J. Biol. Med.* 1944, 17, 383.

[17] Cotlove, E., Holliday, M. A., Schwartz, R., Wallace, W. M. *Amer. J. Physiol.* 1951, 167, 665.

[18] Govan, C. D., Darrow, D. C. *J. Pediat.* 1946, 28, 541.

[19] Lubran, M., McAllen, P. M. *Quart. J. Med.* 1951, 20, 221.

[20] Streeten, D. H. P., Ward-McQuaid, J. N. *Brit. med. J.* Sept. 13, 1952, p. 587.

[1] Gilchrist, A. R. *Brit. med. J.* Aug. 16, 1952, p. 351.

[2] von Reinis, Z., Kubik, M. *Schweiz. med. Wschr.* 1948, 78, 956.

[3] Burt, C. D., Wright, H. P., Kubik, M. *Brit. med. J.* 1949, ii, 1250.

[4] Bronstein, M. R., Witkind, E. *Amer. J. med. Sci.* 1951, 222, 677.

[5] Illingworth, D. G. *Brit. med. J.* 1951, ii, 646.

[6] Stirling, M., Hunter, R. B. *Lancet*, 1951, ii, 611.

[7] Scarrone, L. A., Beck, D. F., Wright, I. S. *Circulation*, 1952, 6, 489.

took part; and records were collected of experience with 514 patients, comprising 262 with myocardial infarction, 87 with thrombophlebitis or venous thrombosis, 41 with pulmonary infarction, 20 with other arterial thrombosis or embolism, and 104 to whom the drugs were given for coronary insufficiency or "for prophylactic purposes." The dosage of tromexan and the method of control were similar to those already described. These workers confirm fully the relatively rapid initial action of tromexan and the relatively rapid return of prothrombin levels to normal when the drug is stopped. They suggest that tromexan gives no more protection from thrombo-embolic complications than does dicoumarol; in fact they found that rather more complications were liable to occur when the prothrombin level was within the desirable range. In their series the total rate of gross hæmorrhage was slightly higher during tromexan therapy than during dicoumarol therapy; but they found that this difference was largely due to the difficulty of controlling prothrombin levels with single daily doses of tromexan; and they agree that control is easier with the daily dose divided into two or three portions. No difference in toxicity between the two drugs was found, nor did there seem to be any significant difference between their protective action in myocardial infarction. Clearly tromexan is far from the ideal anticoagulant. Its two advantages—rapid initial action and rapid control of possible hæmorrhage—are counterbalanced by the additional difficulty of determining the daily dose. This justifies MURRAY SCOTT's [8] contention that without a laboratory that can give rapid daily estimations of prothrombin concentration dicoumarol is the safer drug. Recent work with vitamin K_1 has suggested that control of hæmorrhage due to tromexan or dicoumarol may not be so difficult. DOUGLAS and BROWN [9] tested various vitamin-K preparations to see how they corrected the hypoprothrombinæmia induced by these two drugs; they found that only vitamin K_1 (2-methyl-3-phytyl-1:4-naphthaquinone) was effective; and it was consistently effective in doses of 200–340 mg. intravenously. TOOHEY [10] found that a single oral dose of 500 mg. of vitamin K_1 could restore to safe levels a prothrombin concentration depressed by these drugs; the action was perceptible in 4 hours and complete in 8 hours; a single dose was enough to counteract tromexan, but repeated doses were needed when dicoumarol had been administered.

The search for a better anticoagulant continues; and the latest substance to be introduced is phenylindanedione, which differs in its chemical structure from dicoumarol and tromexan. This substance, first used clinically by SOULIER and GUEGUEN [11] in France and by BLAUSTEIN et al.[12] in the U.S.A., has a hypoprothrombinæmic action roughly intermediate in rapidity between dicoumarol and tromexan. Its use in 74 cases (44 of coronary thrombosis) has recently been described by PRESTON and his co-workers [13] in Chicago. They found that as a rule blood-prothrombin levels between 10% and 30% of normal were reached in 18–36 hours with an initial dose of 150–200 mg., and these low levels were maintained by doses of 50 mg. twice daily; all their cases were controlled by daily prothrombin estimations. They had no trouble with "escapes" from control such as occur with tromexan, but 3 patients were somewhat refractory and probably needed larger doses. Minor hæmorrhages occurred in 5 cases. Among the 200 cases hitherto reported, there has been no instance of severe hæmorrhage due to phenylindanedione; but PRESTON and his colleagues reasonably attribute this partly to our growing experience in handling anticoagulants. The effect of this anticoagulant persists for 2–4 days after the final dose, but the hypoprothrombinæmia can be rapidly corrected by vitamin K_1. Phenylindanedione has still to be subjected to the searching trial that tromexan has had; we need to know especially whether control of its action is steadier and more easily achieved than with tromexan. Meanwhile the observation by DOUGLAS [14] that tromexan depresses "factor VII" rather than prothrombin suggests that we still too easily assume that a prolonged prothrombin-time exactly reflects pure hypoprothrombinæmia. These different substances may act on different coagulation factors; and more research into their pharmacology is likely to be needed before we find the ideal anticoagulant.

From Teaching to Learning

FOR years we have been telling one another what is wrong with the medical curriculum; and now some American medical schools, backed by the moral and financial support of the Commonwealth Fund,[15] are looking into the facts. In these schools the emphasis is shifting, so the annual report of the fund says, "from teaching to learning, from the department to the school, and from the specialty to the patient." The history of medical education is seen in three stages. The first, the age of scientific medicine, has already lasted forty years; but we are now at the opening, the report suggests, of the second or transitional stage "in which the concept of comprehensive medicine is beginning to modify the definition of scientific medicine"—a reaction, in fact, against extreme specialisation. The third stage, it is hoped, will be a reconciliation of scientific and general medicine, of the specialist and the general practitioner, and a new integration in both medical education and medical care. To achieve this end the medical curriculum will have to be reoriented; for it is in the nature of specialists to teach passionately their specialties, and they do not take easily to what the report calls "a whittling down of departmental prerogatives." Yet, to the credit of the profession, the demand for a broader approach comes primarily from physicians and surgeons; and these American experiments have been undertaken on the assumption (still to be verified, as the report justly notes) that "medical teaching organised around the student's need to learn and the patient's need for care will prepare students to meet the responsibilities of medicine as a social institution more effectively than medical teaching organised around the preoccupation of teachers with what they as specialists think they ought to teach."

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[8] Scott, R. A. M. *Lancet*, 1952, i, 488.

[9] Douglas, A. S., Brown, A. *Brit. med. J.* 1952, i, 412.

[10] Toohey, M. *Ibid*, Sept. 27, 1952, p. 687.

[11] Soulier, J. P., Gueguen, J. *C.R. Soc. Biol., Paris*, 1947, 141, 1007.

[12] Blaustein, A. U., Croce, J. J. jun., Alberian, M., Richey, N. *Circulation*, 1950, 1, 1195.

[13] Preston, F. W., O'Connor, W. R., Thompson, C. E., Christensen, E. N. *Ibid*, 1952, 6, 515.

[14] See *Lancet*, Oct. 18, 1952, p. 761.

[15] Annual Report, 1952. New York: Harkness House, 1, East Seventy-Fifth Street. See also *Lancet*, 1951, ii, 1171.

One important enterprise has been maturing at Western Reserve School of Medicine since 1950, when the fund made a 5-year grant towards it; and the new teaching plan was put into effect for the class entering in September this year.

> The 4-year course covers our preclinical and clinical periods, and has been divided into three phases. Phase I "orients the student to medicine and to the patient and presents the fundamental principles of man's structure, *function, growth, behaviour, and relation to his* environment; phase II deals with disease, first in general principles and then by organ and site; phase III deals with the care of sick people."

The first two phases occupy together 2½ years, and teaching is to be done not by the departments separately but by inter-departmental teams. Moreover, to help the student to feel that he is studying medicine as a whole, all his laboratory work (except anatomical dissection) is done in his "home room"—an all-purposes laboratory where the instructors come to him. Some additional building has been necessary, but in the main the extra space has been found by rearranging existing laboratories. Under the departmental system many laboratories stand idle for much of the time: the new system has made them fully active throughout the day. The final result is that students have more room to work and also, it is believed, a far better opportunity for coherent learning. Those trained in the English tradition of bedside teaching may wonder whether phases II and III of this scheme can really be separated; and, if they can, whether they should. Detailed plans for these two phases have not yet been worked out.

If Western Reserve has approached its problem by way of the student and what he is to learn, Harvard approaches it by way of the teacher and how he is to teach. Twenty graduates working in the medical division of the Graduate School of Arts and Sciences (which is closely linked with the medical school of the university) are taking a PH.D. course in the fundamentals of medical science—including not only the functions and structure of cells, organs, and systems, but also techniques—with a view to becoming "integrated teachers" in the medical school. It is not easy to tell from the brief account in the report exactly what kind of rare birds will be fledged from this unique nest, but the fact that the fund has provided a substantial 3-year grant gives grounds for confidence in their value.

Experiments of another kind are in progress at Colorado, Cornell, and Tennessee Universities. At Colorado and Cornell the aim has been to bring students into closer touch with the lives of their patients, and also to measure accurately the effects of whatever changes this produces in the students. In each of these schools a young physician has been put in charge of a new kind of clinic which places "a premium on continuity and comprehensiveness in medical care." At Cornell a period of experience in the clinic is being given to senior students, while at Colorado undergraduates and house-officers are being exposed to "a reasonably general point of view" throughout their clinical years. Which will prove the more effective? To decide the question Cornell is investigating the student's attitudes, expectations, judgment, and scale of values by getting him to fill in, at the end of his last academic year, an adroitly worded 26-page questionary; while at Colorado a psychologist has collaborated with the educational testing service of Princeton in developing devices to study short-term changes in student behaviour. By using these and other methods on successive classes of students both schools hope to measure their success in teaching good medicine.

In Tennessee people have a preference, very natural as it seems to us, for family doctors; so in the autumn of 1951 the Tennessee medical school started, with the help of the fund, a "family general practice clinic," designed to resemble the practice of a good family doctor. All senior students spend a short time in it, under the continuous supervision of a staff of general practitioners. Every fifth patient who comes to the hospital outpatient department is assigned to this clinic, and four out of five of these are treated in the clinic without the direct help of specialists. Students are given plenty of responsibility and often take their own radiographs and do their own laboratory work. Again the effects of the experience on the developing doctor are to be studied. A more thoroughgoing effort to bring the student face to face with the patient and his family is being made at the University of Pennsylvania, where the freshman is assigned to a family as an "adviser"—not as an adviser on medical matters, for which he is not competent, but rather as an intermediary between the family and the hospital. He visits their home as "a doctor-in-training," is present when any of them comes to the hospital, is consulted by his seniors about the home situation, helps members of the family when they are anxious or puzzled by explaining hospital procedure to them, and in fact learns to maintain "a constructive relationship with the patient, which is half the doctor's job." And he thrives on the responsibility. Under a similar plan at Boston University, the student has a year of family study and a month of home calls on the district. It is noteworthy that teachers of social science and of nursing have begun to follow this lead, and are now giving their students similar experience.

The University of Florida has been given, by the State legislature, a most unusual opportunity to develop schools of medicine and nursing in a medical centre, and has begun a study of the existing university resources which can be woven into the pattern of medical education. These include a university college giving a 2-year course in general education built round the social sciences, an agricultural experiment station undertaking research into nutrition, a cancer research laboratory, a centre for clinical services with a special interest in psychology, and a student health service with a large medical staff. A research group have been appointed "to think out what a medical school ought to be and do, before a staff is hired and building plans are fixed," and they are to report in the spring of 1953. The fund has made a large grant towards the expenses of this study. Finally, at Columbia University the bureau of applied social research is making a pilot study, financed by the fund, of "the character of the social and psychological environment comprised by the medical school and the bearing of that environment upon the acquisition of knowledge and skills, attitudes, and values by medical students." If this proves informative, it may lead to a 4-year full-scale study of one or more medical schools.

The results of these varied types of study will be as instructive for us as for the Americans; and, as the report points out, many other American medical schools and universities besides those in which the fund is interested are now making experiments. Medical education can never be static or defined: its content changes constantly with our growing knowledge. This is well recognised; but we have been slow perhaps to admit that even the structural pattern of teaching should be pliable—a tent, easily pitched and struck, rather than a classic fane.

Annotations

A EUROPEAN HEALTH COMMUNITY?

THE latest proposals of the French government for a European Health Community were discussed at a meeting in Paris this month. The plan of M. Ribeyre, the minister of public health and population, is based, like the Schuman plan for coal and steel, on the assumption that certain supranational powers should be given to a new health organisation representing a Community of those European nations wishing to join. As in the case of the Schuman and similar plans, the British Government made it clear at the meeting that it was not prepared to join such a Community on those terms, though it would wish to be very closely associated with it. Further, if such a new health organisation was to be considered without supranational powers, the Government felt that careful examination was needed to see whether the existing intergovernmental organisations—the World Health Organisation with its Regional Organisation for Europe, the Brussels Treaty Organisation, and the Council of Europe—could not do the job themselves. It was therefore agreed that a committee of experts should examine the proposals and report back to the conference as early as possible next year.

The proposals themselves fall into two groups: (1) obligations or restrictions incumbent on all members of the Community, such as the abolition of customs dues on pharmaceutical products or medical appliances, and the abolition of unfair competitive practices in these fields; and (2) common tasks and objectives, such as the pooling of medical products and facilities and the results of research, as well as uniformity in social-security legislation. Such objectives might lead to the establishment of laboratories by the Community and of centres for research into such questions as silicosis or the treatment of burns or of cancer by high-voltage apparatus. The suggested organisation would perhaps consist of a high authority, a council of ministers, and an expert advisory committee; and the facilities set up under the Schuman plan might be used.

This is not the first proposal to give executive powers to an international health organisation. There were the old sanitary councils of Egypt, Constantinople, and Tangier. The fourth International Sanitary Conference in Vienna in 1874, discussing the function of an international commission on epidemics, rejected a suggestion to give the commission executive as well as advisory powers, because it seemed unlikely that many governments would agree and because the step might prejudice "the scientific nature of the commission." These arguments hold good today, particularly since a much greater variety of activities is now proposed. No doubt a careful examination of the proposals by experts is proper, but without supranational powers, which few countries seem disposed to give, there would have to be a very strong case indeed to warrant yet another international health organisation.

TREATMENT OF SHOCK IN CARDIAC INFARCTION

WHEN cardiac infarction is accompanied by shock, the precise mechanism by which the blood-pressure falls is not at all clear. On the one hand, a large part of a ventricle may be rendered suddenly ischæmic and consequently non-contractile, and the effective myocardium remaining may well be unequal to the circulatory burden; disturbances of rhythm may supervene; under such conditions the cardiac output falls,[1 2] and this alone may contribute largely to the hypotension. On the other hand, there is evidence of peripheral vascular collapse as well. To some extent, this may be compensatory, for a reduced load is then imposed upon the damaged heart. At all events, the prominent feature of traumatic shock—namely, a fall in volume of the circulating blood—is of no great significance in cardiac infarction, and there is no justification at all for intravenous infusions of blood or plasma. Nevertheless, persistent hypotension carries its own dangers—impaired coronary flow, aggravated myocardial depression, the risk of further coronary occlusions, and a deprivation of blood-supply to the brain, kidneys, and liver. No ingenious statistics are required to demonstrate convincingly that, when shock occurs with cardiac infarction, the prognosis is much more serious than when the blood-pressure is scarcely affected.

A direct therapeutic attack on the infarcted heart is clearly out of the question with the resources at present at our disposal. But it can be relieved as far as possible of all unnecessary loads, and the hypotension which often follows infarction certainly contributes in this way. If, however, the hypotension is so profound or prolonged that it becomes a danger in itself, then its correction by improving peripheral vascular tone may be justified in principle. Now orthodox teaching is against such a step: Wood[3] says that, because of the increased risk of ventricular fibrillation, "adrenaline, ephedrine and other adrenergic substances should be avoided . . . no matter how low the blood pressure." This, of course, underlines the real difficulty—namely, to find a drug that will bring about satisfactory peripheral vasoconstriction without, at the same time, stimulating the heart itself.

American workers, who remark that the use of "pressor amines" for the treatment of shock following cardiac infarction is a "relatively new concept," have lately subjected the idea to clinical trial. Kurland and Malach[4] have reported their results with 14 patients. Noradrenaline, given as an intravenous infusion, brought about a rise in blood-pressure in most cases; and, unlike the other sympathomimetic amines that have been tried, it had no effect on heart-rate, cardiac irritability, or the central nervous system. Disappointingly, however, the proportion of survivors was not convincingly higher than would have been expected with conventional treatment. In another series, Hellerstein et al.[5] used mephentermine, a synthetic pressor amine, giving it intravenously to 18 patients with acute cardiac infarction in whom there was unequivocal evidence of shock; and of these patients, 7 recovered sufficiently to leave hospital. As Hellerstein et al. consider that the usual mortality in patients of this kind is about 80%, they feel, perhaps a little optimistically, that their results show a significant improvement. Unfortunately, neither of these reports gives full details about the course of events in the individual patients, so it is impossible to make a direct comparison between what happens when shock is not treated and the developments when the blood-pressure is deliberately raised. Certainly, before we can agree with Hellerstein et al.

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1. Grishman, A., Master, A. M. *Proc. Soc. exp. Biol., N.Y.* 1941, 48, 207.
2. Fishberg, A. M., Hitzig, W. M., King, F. H. *Arch. intern. Med.* 1934, 54, 997.
3. Wood, P. *In* Medical Treatment. London, 1952; p. 185.
4. Kurland, G. S., Malach, M. *New Engl. J. Med.* 1952, 247, 383.
5. Hellerstein, H. K., Brofman, B. L., Caskey, W. H. *Amer. Heart J.* 1952, 44, 407.

that the "more favourable results of pressor therapy in comparison to other methods justify further clinical application in the treatment of shock accompanying myocardial infarction," we should like to have more information about the way in which their patients responded and the precise mode of death in the fatal cases.

PERSISTENT HICCUPS

A MILD attack of hiccups may amuse or embarrass, according to temperament or circumstances. A severe and prolonged attack is a serious disorder calling for energetic treatment to save the patient from dangerous exhaustion. Nearly every year one or more papers are published on the subject—a fact which shows how little we know of the cause or treatment. Hiccups has been described as intermittent clonic spasm of the diaphragm, but the latest observations cast doubt on the accuracy of this definition. Samuels[1] has made repeated fluoroscopic examinations of patients suffering from severe hiccups, and he concludes that the type of diaphragmatic contraction differs from patient to patient, but that one pattern of contraction leads to the next if treatment is delayed or unsuccessful. The transition from the milder attack to the more severe is especially rapid in debilitated patients. In the mildest form the spasm is a unilateral pyramid-like contraction. After five to eight days of hiccuping the pyramid becomes flatter, and wavy contractions appear at the outer segment on the same side. Finally these contractions spread across the whole dome. Rarely the hiccups may be bilateral from the start. Samuels considers that complete flattening of the whole dome with wavy contractions at the outer segments is a grave sign indicating muscular exhaustion.

The muscular spasms are of reflex origin; and the efferent path is most commonly the phrenic nerve, at any rate in the early stages. But other nerves and muscles of respiration may be involved, for in a patient of Campbell's the hiccups persisted in spite of bilateral phrenicectomy.[2] Moreover, Samuels's observations on the innervation of the various parts of the diaphragm showed that the peripheral areas, which could be involved in the contractions, interdigitated with bundles from the transversus abdominis muscles and were supplied by the anterior branches of the lower three thoracic nerves, with few or no fibres from the phrenic. The crura, too, have a limited phrenic supply, and are innervated mainly from the last two thoracic and the first two lumbar nerves. The phrenic itself, on reaching the diaphragm, fans out from the central area into a plexus formed by its own subperitoneal branches and by sympathetic nerves arising mainly from the cœliac plexuses and travelling to the diaphragm along the inferior phrenic artery. Vagus fibres are said to join the plexus as well. The anatomy of the upper parts of the phrenic nerves is of considerable surgical importance. The phrenic originates from T3, 4, and 5 in 70–80% of cases, while in the remainder it may come from some or all of T2, 3, 4, 5, and 6. This would matter little to the surgeon were it not that the 5th thoracic root often forms a fine separate nerve which runs its own course until it joins the main trunk in the superior mediastinum. Occasionally the same is true of the 3rd thoracic root. In addition to its variable origin, the phrenic is a mixed nerve and may be joined by fibres from the superior and inferior cervical ganglia, the vagus, the spinal accessory, and the hypoglossal nerves. An interesting anatomical finding by Funaoka[3] is that communicating strands with the vagus are more common on the right side than the left. This may, or may not, have any connection with the fact that hiccup spasm occurs more often on the left side than the right.

The afferent side of the hiccup reflex can arise almost anywhere in the viscera, or where nerves containing fibres of the visceral sensory system are involved by disease process; and it can also originate in the central nervous system. The cause may be physical, such as pressure, or chemical, as in uræmia; alcohol, too, may be classed as a chemical irritant. Bailey[4] says that he has not seen a single case of persistent postoperative hiccup among over 1500 patients who had operations on the stomach or gall-bladder, including repair of perforated gastric ulcer. He is, therefore, convinced that irritation of the lower surface of the diaphragm is not an important cause of hiccups. By contrast, the condition often followed operation on the bladder or prostate, even in the absence of uræmia. He comments on the rarity with which severe hiccups developed in women. There are many possible peripheral causes, including acute dilatation of the stomach, irritation of the peritoneum and infections or tumours in the respiratory tract or the mediastinum. Hiccups may be initiated centrally by pressure changes due to tumours or hydrocephalus, or by bacterial or parasitic infections, including neurosyphilis and neuromalaria. It has been reported in the fœtus,[5-7] where it presumably results from passage of a chemical substance across the placental barrier. Samuels[1] stresses the importance of psychogenic disorders, whether overt or latent.

If there is no removable or evident cause, some of the many suggested remedies must be tried. Carminatives produce a sense of gastric comfort, and are sometimes of more than temporary benefit. Gigot and Flynn[8] found that occasionally so simple a manœuvre as slightly painful pressure on the eyeballs, maintained for at least a minute, was successful. Many sedatives have been tried, with about equal degrees of success and failure. General anæsthesia and psychiatric treatment are both said to be useless. Antispasmodics have their supporters. Carbon dioxide inhalation, used within the first few days, is often a success, either by the homely method of rebreathing into a paper bag, or by using more expensive apparatus. The important point is that inhalation must be continued to the stage of moderate discomfort. Barnard[9] had good results with the application of sinusoidal galvanic current. Another method, spraying of the posterior cervical triangle with ethyl chloride, is inadvisable, for it can too easily lead to necrosis of the skin and deeper tissues. If no simple method works, the phrenic nerve can be crushed; and this operation, performed under local anæsthesia, nearly always produces a complete and permanent cure.

The phrenic-circle test can be used to determine on which side the spasms occur or which is the pacemaker side. Firm pressure by the fingers is applied over the phrenic nerve just above the clavicle, and any spasms on that side usually stop within a minute. Hiccups is far more often left-sided than right, and unless there are indications to the contrary the left phrenic nerve should be dealt with first, because further measures may then be unnecessary. In the rare cases in which bilateral crushing fails, Samuels recommends that the sympathetic and the lower thoracic and upper lumbar nerves be interrupted. As a precaution in all operations, Gigot and Flynn[8] advise the use of antiparasympathetic drugs during anæsthesia.

But we are still in the dark about many questions. We do not know why severe hiccups is sometimes seen after operation, how or where uræmia facilitates the reflex arc, why persistent hiccups is uncommon in women, or whether the parasympathetic system bears a special responsibility.

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2. Campbell, M. F. *Amer. J. Surg.* 1940, 48, 449.
3. Funaoka, S. *Acta Sch. med. Univ. Kioto*, 1928, 10, 287.
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7. Norman, H. N. *J. comp. Psychol.* 1942, 34, 65.
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9. Barnard, F. G. *Amer. J. Surg.* 1940, 77, 230.

AN OSSEOMUSCULAR CIRCULATION

THE histopathological foundations on which the clinical diagnosis of fibrositis rests are for the most part obscure. Stockman's definition[1] of fibrositis as "a condition of chronic inflammation of the white fibrous tissue . . . of muscles" (and other connective-tissue entities) is often refuted by biopsy of the nodules, which may show no characteristic changes.[2 3] Surgical exploration of a fibrositic trigger-point sometimes discloses herniation of a fat lobule through a gap in the fascia, but Copeman[4] pointed out that this explanation certainly does not account for all cases. When the clearly mechanical reasons for muscular pains of fibrositic type—prolapsed intervertebral disc, spondylitis, and trauma—and infective and parasitic causes have been excluded, a number of cases (perhaps the majority) are left without a satisfactory explanation, although Cyriax[5] does not think that such a group exists.

In these circumstances investigations of the anatomy of the muscles and the muscle attachments to bone are of particular interest; and Cecchi and Fiumicelli,[6] following up Heald's observations,[7] have turned their attention to the circulatory paths between bone and muscle. Heald's work showed that local injections of a mixture containing benzyl salicylate were most effective in relieving primary fibrositis when the injection was made near the bony origins of the affected muscles. Indeed, the best clinical results were obtained when the injection was made into the cortex of the metaphyses of the bones from which the painful muscles arose. The distribution of the injected material was traced by including a radio-opaque oil in the mixture. Injected into the cortex of the humeral metaphysis, the oil quickly left the bone as a fine spray, apparently within the deltoid muscle.

Cecchi and Fiumicelli have now confirmed these findings. They used a similar technique and they obtained radiographs which show fasciculated strands of oil running in the direction of the muscle-fibres like the warp on a loom. On the other hand, oil injected directly into the muscle belly gave a localised fusiform opacity of quite different appearance; and an injection into a region of the metaphysis devoid of muscular attachments gave no indication of any communications between the bone and the adjacent muscle. From these results they suggest that there is a humoral osseomuscular circulation, related to the sites of muscular attachments, and they think that it may be of physiological importance. In support of this view they quote Cretin's finding[8] that an area of bone stripped of its muscular insertions shows an underlying osteoporosis, and they point out that fractures involving a bare region of bone heal more slowly than those involving the regions of muscular attachments. They imply, therefore, that the nutrition of both bone and muscle depends in part on this circulation between them. Wood-Jones, quoted by Heald, thought that a dye injected into a fresh femur post mortem left the cortex by multiple fine openings alongside Sharpey's fibres; and histological findings in similar experimental injections of bone support the view that these communications between bone and extra-osseous tissues are vascular.

These two sets of observations are convincing evidence for the existence of these osseomuscular channels. It is conceivable that they are of physiological significance, but at present this is far from certain. It would be attractive to postulate that primary fibrositis is due to a disturbance of muscle nutrition associated with a derangement of function of these vascular channels. The periostial thickening which Stockman described in fibrositis has been found by Heald and his colleagues in about half the cases submitted to biopsy, but there is nothing yet to suggest that this thickening has anything to do with the vascular channels. Until more is known of the function of these vessels, their importance will remain in doubt.

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3. Copeman, W. S. C., Ackerman, W. L. *Arch. intern. Med.* 1947, 79, 22.
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5. Cyriax, J. *Ibid*, 1948, ii, 251.
6. Cecchi, E., Fiumicelli, A. *Reumatismo*, 1952, 4, 371.
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8. Cretin, Z. *Praxis*, 1951, 40, 862.

ALMONERS

HOSPITALS took a long time to grasp the value and proper uses of almoners, but once they had accepted the idea they took to almoners warmly—and now literally cannot get enough of them. There are always well over 100 vacancies going. The Secretary of the Institute of Almoners, the *Manchester Guardian* of Dec. 5 reports, puts the numbers now working in England and Wales at about 1000, but estimates the numbers needed for a full service at double or treble that figure. In Scotland[1] the situation is considerably worse; only 75 almoners are employed, whereas a full service is estimated at 500. Moreover, since they are mainly concentrated in the general hospitals, there are many hospitals in rural areas with no almoners at all; indeed, of the 346 hospitals in Scotland, only 35 have an almoner on the staff, and though there are 25,202 beds with almoner service there are still 12,323 without; and the scarcity is particularly noticeable in the tuberculosis hospitals.

The haphazard distribution is partly the outcome of the way the almoner service has developed. Voluntary hospitals first employed almoners to assess the capacity of the patient to contribute to his maintenance in hospital. The development, by almoners themselves, of the medicosocial side of their work has led to a complete reorientation of their position, and a special type of training. But there are still hospitals where the medical staff, never having worked with almoners, have not realised the value of their work. Even now recruitment to the profession is very small: the numbers coming forward are barely sufficient to make good the annual wastage, let alone to provide for extension of the service. A fresh blow to recruitment has been the withdrawal, by the Ministry of Health this year, of its grant towards training; which has meant that the institute has had to raise its fees from 30 to 85 guineas. Grants from local authorities vary widely in amount, and are not easy to get; moreover there are often delays in payment and uncertainty about the amount, even when grants are promised. Again, Home Office grants towards training in other branches of social work, such as child care, divert candidates who might otherwise enter almoning. The Scottish subcommittee regard the withdrawal of the Government grant as a retrograde step, and suggest that the attention of local education authorities should be drawn to the fact that they may make grants to students wishing to train for this profession.

Meanwhile they propose that the best possible use should be made of the almoners already in the service, by staffing hospitals serving industrial areas, especially teaching hospitals (which have to train medical students in social medicine), other general hospitals and chronic sick hospitals in these areas, and tuberculosis hospitals and sanatoria. Hospitals in country districts, where the sense of community is usually well developed, can afford more easily to wait for better times. To ease the shortage they also propose that the service should be diluted by a second grade of "almoners' assistants," or "almoners' apprentices," analogous to enrolled assistant nurses; and they recommend the Institute of Almoners to consider a scheme of recruitment and training of such a grade. This question of dilution is always very difficult. It is serving well in nursing because that is a profession

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1. Report by the Subcommittee on the Almoner Service to the Scottish Health Services Council. Department of Health for Scotland, 1952. Pp. 13.

which offers scope for widely different talents. Almoning, however, demands, as well as humanity and a gift for making good relationships with people and with public and voluntary bodies, a special kind of shrewdness, ability, and judgment; and it is doubtful whether those training for a second grade would bring quite these qualities to the task. It would surely be better, as a first step, to consider the factors which are hindering recruitment of almoners of our present high standard.

CHEMOTHERAPY OF TUBERCULOSIS

Sir Howard Florey, F.R.S., opening a symposium held by the Royal Society of Medicine on Dec. 10, suggested that in the attack on tuberculosis we must study not only the parasite and the host but the influence of each of these on the other. In developing chemotherapy both in-vivo and in-vitro techniques could be of great value. A striking feature of subsequent papers was the close agreement between the assessment of antituberculous drugs by these two techniques.

Dr. A. G. Sanders and Dr. L. F. Dodson have used a specially prepared chamber in the rabbit's ear for studying the development of tuberculous lesions and the effect of drugs on them; while Dr. G. B. Mackaness has studied the survival of tubercle bacilli both in laboratory media and inside macrophages by an elegant and useful technique. Prof. J. M. Robson gave an account of results obtained by the intracorneal inoculation of tubercle bacilli in mice and rabbits; and Prof. Robert Knox described in-vitro studies of sensitivity and resistance to isoniazid, including an agar-plate culture technique using *Mycobacterium smegmatis* as a test organism. Dr. D. A. Mitchison discussed the value of different techniques used in the laboratory for determining sensitivity and resistance of tubercle bacilli to drugs such as isoniazid.

The general conclusions from this group of papers were remarkably harmonious—that isoniazid has an undoubted inhibitory effect on the growth of tubercle bacilli, which in some ways is greater than the effect of streptomycin; that the initial effect is short-lived; that drug resistance rapidly develops; that isoniazid and streptomycin combined are much more effective than either alone; and that drug resistance can be greatly delayed by this combination. Dr. Mackaness suggested that in any long-standing tuberculous lesion there may be large numbers of "dormant" organisms which are relatively insusceptible to the action of drugs. This concept recalls the views of the late Prof. J. W. Bigger on the part played by "persisters" in the development of penicillin resistance by staphylococci, and is well supported by the observations of other workers that many antibiotics are especially effective against actively dividing organisms. Professor Knox and his colleagues observed that the action of isoniazid was profoundly modified by quite small changes in the temperature of incubation, and suggested that perhaps increase in temperature of incubation or combination of isoniazid with other drugs make it more powerfully bactericidal. This observation may perhaps help to explain Professor Robson's finding that isoniazid alone is much more effective in the treatment of corneal tuberculosis in the rabbit than in the mouse, whose mean corneal temperature is several degrees lower than the rabbit's. It may also partly explain the dramatic response to isoniazid by patients with high temperatures. Dr. Mitchison, who has handled the large amount of reference work in the bacteriology of the Medical Research Council tuberculosis trials, suggested that an in-vitro resistance of about 1 µg. per ml. was likely to indicat clinically significant resistance.

This rather satisfactory correlation between in-vitro and in-vivo results was somewhat disturbed by Dr. P. D'Arcy Hart and Dr. R. J. W. Rees, who have found a baffling but extremely interesting group of surface-active agents most of which show powerful antituberculous activity in vivo, but none in vitro. As Sir Howard Florey suggested, these observations, though puzzling at present, may lead to new ideas on chemotherapy.

In the second part of the symposium Dr. Wallace Fox gave an interim account, prepared in collaboration with Dr. Marc Daniels, of the M.R.C. trial of isoniazid alone and in various combinations, in the treatment of pulmonary tuberculosis. The present [illegible] (1) a comparison of isoniazid with [illegible] (P.A.S.) plus streptomycin; (2) a comparison between isoniazid, P.A.S. plus streptomycin, and isoniazid plus streptomycin; and (3) a comparison between isoniazid plus different doses of streptomycin, and isoniazid plus P.A.S. Preliminary results for the first two groups, up to the end of three months' treatment, suggest that on the whole isoniazid plus streptomycin will prove the most valuable combination; it has shown itself strikingly superior to streptomycin plus P.A.S. or to isoniazid alone in the type of case where chemotherapy is expected to give little benefit.

Other aspects were discussed by Prof. John Crofton Sir Clement Price Thomas, and Dr. Honor Smith. In conclusion Sir Geoffrey Marshall suggested that isoniazid should clearly not be used alone; but a combination of isoniazid with other drugs might prove superior to any other known combination.

SCREENING FOR DISEASE

"SCREENING" is a military term that was borrowed some years ago to describe the process by which people in danger of infection are sifted for the earliest signs of such diseases as tuberculosis and syphilis, and the source of infection is traced. Public-health measures devised with this aim have been very successful. Such measures are now termed "monophasic" because they deal with one aspect of illness. Lately American workers have been testing "multiphasic" screening, which has included a questionary completed by the patient, blood-pressure reading, radiograph of the chest, electrocardiogram, urine-analysis, Wassermann reaction, and hæmoglobin and blood-sugar estimations.

The advantages and deficiencies of multiphasic screening have lately been discussed by the Medical Society of New York.[1] The conditions for which screening is carried out, it was argued, should be remediable; and they should not be so common that screening is inappropriate, nor so rare that the return is disproportionate to the cost and labour. The accuracy of methods also needs careful scrutiny; for whereas a false positive result may be corrected by the patient's physician who receives the technical report, missed diagnoses can lead to a false sense of security. Two different types of multiphasic screening have been tried. In one a large number of presumably healthy adults was submitted to clinical test; the results were compiled and reviewed by a physician, who did not interview the patients, and those with possibly abnormal findings were urged to see their family doctor. Dr. V. A. Getting described his experience of this method at two pilot health-protection clinics in Massachusetts. Dr. M. L. Levin, of the New York State department of health, described a rather different plan, by which the health department provided a series of diagnostic aids to help practising physicians. This is akin to the help offered by public-health laboratories in this country, though the American tests were directed towards early detection of degenerative disorders no less than of infectious diseases.

In this country multiphasic screening might eventually be undertaken at health centres. With the present restriction on expenditure, however, there is little hope of an extensive trial of this technique in the National Health Service.

Dr. GIBBON FITZGIBBON, who was Master of the Rotunda Hospital from 1919 to 1926, died in Dublin on Dec. 1, at the age 75.

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[1] N.Y. St. J. Med. 1952, 52, 2599.

Points of View

THE SIEGE ECONOMY AND THE WELFARE STATE OF MIND *

Sir Geoffrey Vickers
V.C., M.A. Oxfd
MEMBER OF THE NATIONAL COAL BOARD AND OF THE MEDICAL RESEARCH COUNCIL

During our lifetime the economic stability of this country has declined to a startling degree. For some decades of the 19th century we enjoyed a pre-eminence, in some fields almost a monopoly, in the arts of turning raw materials into manufactured goods. Raw materials were abundant, the accumulations of capital and skill needed for manufacture were scarce, and, as pioneers in the field, we reaped the benefit of their scarcity. We multiplied our population five times in 150 years; raised our standard of living for the few and took it as our target for the many; and became dependent on the rest of the world for half our food.

Meantime, the monopoly passed and some of the natural advantages on which the pre-eminence was based —the early importance of coal, for example, in the world's carrying trade—dwindled in importance. Other manufacturing nations arose, their later start being in some ways an advantage rather than a handicap; and each addition to the world's manufacturing power increased still further the power to expand manufactures both there and elsewhere. For many years this power has been rising far more rapidly than the power to increase the production of natural resources, even if we include the power to bring new raw materials into use. The pressure of rising populations tilts the balance still further in favour of primary and against secondary production. We share with other manufacturing nations the loss of a differential advantage, in addition to losing our particular advantages over them. The terms of trade move on the whole against us—we have to export today nearly twice the value in manufactures which would have sufficed in 1938 to secure the same return in raw materials—and we are warned on all hands that this deterioration is bound to go on. We shall be stemming the tide for the rest of our lives and perhaps our children's also; and if we are to hold our own with those whom that tide now favours, or even to avoid being carried backwards on to the rocks, it can only be by virtue of some differential in our favour created by our own energy and skill.

Yet collectively we are not, I think, fully aware of what has come to us, still less of what is coming.

THE SIEGE ECONOMY

One result of our economic decline is the increase in planning and in policy-making and in control. This is inevitable in a siege economy. Whenever anything becomes so scarce that its distribution cannot be left to the market, someone is saddled with an inescapable responsibility for settling priorities. Who shall buy what with our limited foreign exchange? Who shall make what with our limited timber and steel? Deliberate policy must decide the answers; deliberate control must enforce them.

This tendency affects relations not only between industry and Government but also throughout industry itself. A siege economy makes policy more dominant, control more anxious and pervasive; and the effect is much the same whether an industry is organised as a single corporation, like the coal industry, or whether many units, still formally independent, coördinate their policies through an association. Standardisation, to take a simple example, can bring savings in money and labour and material; and it claims much attention in the nationalised coal industry; but I gather that it claims even more in the non-nationalised motor-car industry.

Even when the advantages of "coördination" are obvious, we all view the process itself with a suspicious eye, alert to attack bureaucracy, centralisation, and other [illegible]h sinister growths; and it is right that we should. But, on the other hand, we should not deceive ourselves about the result. If nothing were ever decided one single level higher than the lowest which would do; if no "return" ever called for a single piece of information which was not really wanted; if no committee ever sat unfruitfully, or reported unnecessarily, or advised ineffectively; above all, if no-one were ever asked to conform with anyone else about anything without good and sufficient cause—even in that perfect world, we should still find ourselves being "coördinated" much more than we ever were before.

A siege economy demands more solidarity, makes more demands on undeveloped loyalties, assumes a common understanding and a common will which only the demand can create. It thus provokes conflicting responses and breeds the frustration which is their inescapable (though, let us hope, temporary) result.

Frustration is a sign of the times, and a sign which is easy to misread. You have probably noticed the curious fact that many Englishmen will accept a much worse deal from Providence than they will from their fellow men, or at least from any of their fellow men with whom they stand in any sort of relationship. If they are ruined because the bottom falls out of a free market, they may possibly blame themselves but they will at least blame no-one else. But if they are even mildly mulcted by the award of some price-fixing body, they are likely to feel much deeper indignation. They can accept stoically the uncertainties and unfairnesses of an uncontrolled world, but they cannot accept without fury the shortcomings and vagaries of a controller, even though in sum his results are more good than bad. This seems to me both odd and important; and if it were a permanent shortcoming of human nature, the outlook would be sombre.

Happily we can most of us call to mind "combined operations," whether in peace or in war, in which groups of men, dispersed, exhausted, ill informed, have none the less managed to carry out a common plan. I recall an offensive in France in 1915, carefully planned, elaboratel[illegible] rehearsed—it failed. I recall other operations three yea[illegible] later, more difficult, far less prepared, which succeed[illegible] The men engaged were not better or better trai[illegible] Things went wrong just as often—but the organism [illegible]d developed the power to put them right. Som[illegible]ing subtle and unexplained had happened. There ha[illegible]ome into being among all levels of command a mutua[illegible]der-standing not wholly dependent on the telephon[illegible]

I think this illustrates the general truth th[illegible] men are to accept common direction without har[illegible]o their springs of energy and initiative, there must ex[illegible] between them a particular kind of mutual rapport. [illegible]ustration is the sign of its absence and it is a dange[illegible]gnal. [illegible] remedy is either to relax the intensity o[illegible] the direction or to increase the sensitiveness of the r[illegible]port. [illegible] siege economy prohibits the first, the [illegible]ond becom[illegible] the more important.

Reflecting then on the effect of t[illegible] siege economy I am led to conclude that it is bou[illegible] to lead [illegible] situation which will make great dema[illegible]s on our [illegible]tions and our morals, as well as on [illegible]ur brains [illegible]

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* From an address, entitled Background to Management, which was delivered in opening the autumn conference of the British Institute of Management on Nov. 13, 1952, and which has appeared in full in the December issue of the institute's journal, *The Manager*.

the task of adapting ourselves to new relations with people is an imaginative and a moral test, not merely an intellectual exercise. I conclude, too, that this is *the aspect of organisation which is likely to try us most highly.*

I would not, however, attribute this demand for closer rapport exclusively to the siege economy. It stems in part from the sheer growth in size of industrial units, which has been a feature of the whole industrial age and which would of itself have set us the same problem in the end, though more slowly. I agree also that our collectivism did not begin as an effort to close the dollar gap. Dicey, writing in 1905, dated the beginning of collectivist legislation at 1856, on the occasion when the House of Commons for the first time threw out a Bill for enclosing a common and thereby registered the opinion—rank heresy at that date—that at least that bit of our English heritage was better left in common ownership. In 1902 the present Lord Samuel wrote a book to explain why the Liberal Party had abandoned unqualified laissez-faire in favour of such collective projects as accessible higher education and publicly provided housing. Neither Dicey the old-fashioned Whig nor Samuel the new-fangled Liberal based their views on the country's impending bankruptcy. Nothing was further from the thoughts of either. To Samuel in 1902, and to many like him, the perplexing portent of their time was that in the richest country in the world a fifth of the population were too poor to keep themselves in health. The Welfare State can trace its lineage further back than 1902, and its developments had begun to quicken the pace of national integration, with all its strains and rewards, long before the economic blizzard brought its chilly emphasis.

The fact remains that the economic controls which today coördinate British industry and set so many of its problems are products of the siege economy, and that the policies which are affected through those controls are policies aimed primarily at economic defence and economic survival.

THE WELFARE STATE OF MIND

I am concerned here not with the substance of the Welfare State but with the state of mind which it connotes.

The Welfare State connotes a demand by the citizen for security; for status; and to a less extent for opportunity. The character and emphasis of these demands were generated over the last hundred years by way of reaction to the experiences of that time, and they crystallised in the depression of the early '30s; but they may well persist long after the circumstances of their birth have passed away. Any Government in this country must do its best to satisfy this complex of aspirations and expectations; and the management of any industry must do likewise. For the same citizens who press these demands on Governments make the same demands as workers on their employers. Indeed, they are more concerned with the life of the workplace than with the life outside. It is in the workplace that these demands matter most today, and it is there that they are hardest to meet. Industry needs efficiency and mobility of labour; men need status and security; and both demands have somehow to be satisfied.

Thus in facing nationally an unfamiliar and dangerous situation, we bring to it a national state of mind formed in a situation which was very different. Our aspirations, our expectations, and our fears are a response not to the situation we are in now, still less to the situation to which we can look forward, but to a situation which we have left. Our economic situation calls for a great increase in productivity and hence for quick adaptation and a rapid increase of effective energy, both mental and physical. At the same time it calls for more coördination of policy, with greater attention to ends and closer economy of means—two demands which in themselves are hard to reconcile. Our psychological situation, on the other hand, calls for a more assured status for each producer, more attention to the impact on him of each new decision, more consultation with him, more security for him, more leisure, and a greater individual return for effort.

At first sight this would seem to be a mental inheritance perfectly unsuited to our needs. Yet I believe that it is at least a stage along the road to becoming the sort of community which we need to be—a community which is informed throughout by so great a capacity for sensitive response that it can meet without confusion or disruption the sort of challenges which are coming to us. Whether we shall achieve such a community in time only time itself can show. But if we are still unprepared for the next ten years, we are at least better prepared than we were fifty years ago.

The great coal strike of 1893 was settled by the Foreign Secretary at a conference held at the Foreign Office. Seen from the 1950s it seems a strange choice of mediators. Was it prompted perhaps by the sense that here the two nations of which Disraeli spoke were at issue and that mediation between nations was a Foreign Office job? Little more than fifty years later the Foreign Secretary was himself a great trade-union leader. We should not suppose on that account that the two nations have completely fused. They have not. But they are immeasurably nearer to fusion. Our attitude of mind is itself partly the product and partly the cause of that mutual penetration of two once separate worlds, and as such it is precious past telling. For the task ahead is a task for one nation, not two. As two nations we should be doomed from the outset. As one we have a chance.

The chief difficulty about the welfare state of mind today is that collective security cushions the effect of national insecurity in the mind of the individual citizen and makes it harder for him to recognise or to respond to it. In a simpler economy the peasant knows whether his efforts are winning him a livelihood. He knows how much it is. He knows that it is not necessarily as much as his efforts "deserve." He knows that whatever it is he cannot both have his cake and eat it. All these homely truths are still true of our national economy, but they are not wholly true of any individual one of us. How are we to produce a national response to a national situation, if what is wanted is something different from the sum of our individual responses to our individual situations?

Fifty years ago it seemed a paradox that there should be so much individual insecurity within a situation which was nationally so secure. Today the paradox is reversed. How can we reconcile collective security with national insecurity? Fundamentally, the paradox is, I think, unreal. The harder the times, the more important it is that the load shall be fairly shared, that such security as there is shall be spread as it may best be borne, that everyone shall count and that nobody shall be wasted. So we can say with truth that fundamentally a siege economy calls for a Welfare State. The danger lies not in the Welfare State but in some aspects of the welfare state of mind. In a real siege, every citizen can see the besetting dangers, and every private life is altered by it. In our situation it might be that the individual first felt the impact on his own life after the walls had been breached. Unless we can respond individually to a group situation, collective security will damp down our responses until they are too late.

THE BURDEN OF BEING SOCIALLY MINDED

Well, there are my two facts—the siege economy on the one hand, the welfare state of mind on the other. The roads from them have converged on a single problem.

Both demand that we shall learn individually to respond to a situation much wider than the one which we can directly know. This is a most difficult [illegible] indeed unnatural thing to do.

Much has been talked and written about the passing of the old many-skilled craftsman and his replacement by the specialist or the semi-skilled man on the assembly line. The old craftsman, they say, was better placed, partly because he had more scope to plan, execute, and finish a complete job, and partly because he was more independent of other people. I have watched a Scottish quarryman working alone in the section of face which was allotted to him—his "motion" in local parlance. He had his tools and unlimited stone, periodically blown down for him; and every week they came and took away the sets and kerbs and borders which he had made and paid him for them. He kept his own hours, worked at his own pace, waited for no man, hurried for no man, neither received nor gave an order. . . . He was a perfect example of the type with whom we are accustomed to contrast the man on the assembly belt.

What is the essential difference which we instinctively feel and deplore? To appreciate the answer, we need to think of action as response to a situation. The satisfaction which we get from acting depends very much on how free we are to respond to the situation as we see it; and the effectiveness of our response depends on how adequate our appreciation is. My quarryman was completely free to respond as he pleased to every situation which arose; and he was aware intuitively of almost everything which he needed to know in order to respond effectively. He scarcely needed conscious thought. The same may be true of men working in a small team. But the man on the assembly line and the specialist whose work is part of a still wider synthesis tends to be pulled back, pushed on, or pushed about by events to which he cannot effectively respond—the stoppage of the conveyor belt, for instance—or by decisions with which he cannot identify himself; and he needs a profound change of mind if he is to be happy and effective.

Like my quarryman, the proprietor of the one-man business had the world for his oyster and was free to respond to it as he pleased. The manager of today is making part of a collective response to a situation wider than he can know and much wider than he can feel; and in so far as he does know the new features in this situation they are often the harder to accept, because they seem irrelevant to his job. Most of them stem either from the siege economy or from the welfare state of mind; and neither of them shows the slightest tendency to abate.

Clearly both managing and being managed are getting more difficult, and in at least three ways. First, it is difficult to assemble all the relevant facts for the broad decisions. Next, it is more difficult still to make the decisions acceptable to those who are to act on them—I do not mean difficult to exact their obedience but difficult to get them to put it into effect with the same lively initiative which they would put behind a response of their own. These are difficulties of communication. Finally, there are difficulties inherent in the act of decision itself.

THE ART OF DECIDING

My quarryman's decisions were barely conscious; he seldom needed to weigh the pro and con, for the whole situation was present to him and his response was almost instinctive. So were mine when I practised as a lawyer; so are most of the responses of an independent manager so long as the scale of his operations is not too big for him to apprehend his situations directly. But in industry today decisions have to be taken over a field too wide to be within the intuitive grasp of anyone. Even in policy-making, therefore, we are up against the difficulties which specialisation always involves. No-one enjoys either the satisfaction or the certainty of responding directly to the situation. The processes of rational decision have to be dragged up into the light of day. Intuitive assurance of what to do—which is the best sort of assurance—plays an ever smaller part in major decisions and the part it does play becomes ever less helpful, for it tends only to exaggerate the importance of those parts of the situation which are intuitively known.

There is a point at which the scale of management changes its problems not only in degree but in kind. Men successful and experienced in what would have been called large-scale management thirty years ago have to learn new and irksome tasks when they come to what is large-scale management today. They have to learn to accept the limitations of remoteness, to learn the infinitely difficult art of helping to make up a collective mind instead of merely making up their own.

THE ART OF BEING INFORMED

They have today some remarkable technical aids. The mechanical means now at our disposal for collecting, classifying, and handling facts—especially facts which can be expressed as figures—already far exceeds our human abilities for using them. Calculating machines and card-punching machines occupy even more of our offices; within a generation we shall all have an electronic brain in the basement. All these devices will give us the right answers if we feed them with the right facts and ask them the right questions; but they do not help us with those two "ifs"; and they make it harder for us to proceed by trial and error, because they give a certain rigidity to the questions which they are set to answer. No doubt in the future we shall have to know more about the methods, the possibilities, and the limitations of statistical science; but this in itself will not help us in deciding what questions to ask or, if you like, what indices to watch.

Here again times change. In a private undertaking the primary criterion of efficiency is whether it pays; and of this its accounts provide a clear and reliable index. In an undertaking with statutory duties, like the National Coal Board, the proper criterion of efficiency is to inquire how well it is doing the job which it was set up to do, having regard to all the circumstances. In judging this, how are we to weigh the indices of output, of productivity, of cost, and of price, and with what standards are we to compare them? Under these new and exacting conditions, how are we to measure and to audit efficiency?

THE ART OF COMMUNICATING

In the art of communicating there is much more than merely passing information, and communications is itself a wider term than is always recognised, even by its exponents.

Human communication has nearly always a double effect and usually a double object. When A and B talk, they may or may not learn something from each other but they certainly create or modify a mutual relationship. "Did you meet A?" I say to B.—"Yes," says B. "What did he say?"—"He agreed that the weather was warm." "Did you like him?"—"No." How are we to explain "communications" of this kind? B has apparently received some information but it was not about the weather and it was not what A meant to convey. Is it not clear that the technique of speech is being used not to exchange information but to establish a rapport?

A man who spent part of the war in Fighter Control told me that the tone of voice was as essential to success as the speed and accuracy and relevance of the information passed. The fighter pilot, you may say, wanted information and nothing else; but it could only travel along a bond of human confidence.

What happens in the course of industrial consultation? Is its value measured by the information which is imparted? If so, we must widen the meaning which we give to information. In the coal industry since Vesting Day we have closed 137 pits, for various technical reasons: and each closure has meant the breakup of a social group, often with a long history. In 5 cases the closure was not agreed by all concerned without reference to headquarters, and on each of these 5 occasions the process of consultation was repeated at national level. Everyone came, and the whole decision was reviewed. So far as I know, nothing new was said and nothing previously overlooked emerged. Every fact and every argument had already been used at other levels. No information passed which had not passed before. I am not even sure that anyone changed his opinion. In all but one of these cases the final decision was the same as the original proposal. Yet something happened in those cases, no less than in the one where a change was made. A decision, previously unacceptable, was accepted. There was a change, not in opinion, but in relationship and hence in attitude.

THE LIMITATIONS OF HUMAN NATURE

I have invited you to agree that both the siege economy and the welfare state of mind call for a very high degree of coördination in our actions and consequently in our understanding and our sympathy. I have pointed out that this requires us to share individually in forming a common view of the situation and in responding to it, in making up our collective mind and in carrying out its decisions as if they were our own. The logic of all this seems to me to be disagreeably cogent; but the still unasked question is—have we any reason at all to suppose that human beings are capable of a relationship of this sort?

The answer is emphatically "No." We are committed to a social exploration far ahead of the bounds mapped by any previous group of adventurers. We should not on that account despair; but it is only common prudence to make a realistic assessment of our resources. We have no assurance at all that human nature is capable of the sort of collective response for which the situation calls.

I sometimes think that we are in danger of inventing a Social Man capable of doing almost as much damage in our day as the Economic Man did in the days of our grandfathers. It is important, certainly, not to think of men as things or as cogs in a machine; but it is equally important not to think of them as gods or as cells in an organism. We still tend to start from the assumption of man with all the rational character that the 19th century gave him and then let the psychologists and the sociologists explain why he is neither so rational nor so individualistic as on that showing he ought to be. I think we should do better to start with the zoologists and speculate how it is that we humans are on the whole so much more socially adaptable than our fellow creatures and how we can best respond to this new and sterner challenge to adaptation.

If we look at behaviour throughout the animal world, we see the same picture constantly repeated. We see creatures producing beautifully apt and quick responses to the kinds of situation which they normally meet, yet thrown into utter confusion if the situation is unfamiliar or if it awakens two different responses at the same time. We see, too, that situations are recognised by one or two conspicuous features rather than by their essentials. The young of the mallard, I understand, will accept as "mother" any creature whatever which makes the right quack at the right moment—even if it be a zoologist! We see the power of habits which have survived their usefulness to imprison the creature which they once served and often to bring it to destruction, by confining it to a definite sequence of responses. Well, this nature is part of our human heritage also. Men also tend to recognise situations by superficial labels and to respond to them by stock reactions. Men also are often ready to follow the wrong leaders in the wrong directions, so long as they make the same old quack. And is not the history of industrial relations littered with unhappy memorials to men who become imprisoned in "a definite sequence of responses" by habits of mind forged how many years before?

Yet we have far outstripped the rest of the animate world in adaptability. How we do this is by no means clear; but it seems to include at least three processes. We come to understand our situation; we realise it imaginatively in our heads; and we respond to it perhaps with as much liveliness as if it was before our eyes. This is magic indeed. It enables us sometimes, though rarely and with great difficulty, to break our own habits before they break us. We do not know how far this faculty can be developed; so we do not know for certain that the adventure on which we are embarked is impossible.

What we have somehow to do is to build up in our imaginations a picture of our common situation so lively and so accurate that we can respond to it willingly and effectively. We have to recondition ourselves to respond differently to new situations, even though their conspicuous features do not change; and thus to change our habits, without losing them. We have to establish by these means a sufficient common element in our inner worlds to ensure that our responses will be coherent in themselves and consistent with those of others; and on this basis we have to build within industry and to the measure of its expanding needs a social relationship equally remote from the law of the jungle and from the law of the hive.

Public Health

The National Diet

THE original purpose of the National Food Survey, which has been keeping an eye on the country's diet since 1940, was to examine food consumption and expenditure in war-time, and so to measure the effectiveness of the Government's food policy. But the Ministry of Food's worries certainly did not end with the war, and the survey has continued its work. Last year it reported on the changes in the diets of urban working-class households between 1940 and 1949[1]; and now the first of a series of annual reports has been published.[2] An important change in method has been introduced: by choosing a representative sample of the country's households the survey has extended its scope, which has hitherto been confined to urban working-class families; and it is now possible to look at a much more comprehensive picture of our menus and food bills.

The report says that as a nation we now show a much greater uniformity in what we eat and in what we spend on eating than we did before the late war. During the winter of 1950 the average expenditure on food was 14*s.* 6½*d.* per head, per week; and the better-off households (those whose principal wage-earner received £13 a week or more) spent 4*s.* 1*d.* a week more per head than families living on £4 10*s.* a week or less. The most closely comparable pre-war figures (for 1936–37) gave an average of 8*s.* 11½*d.* per head per week and a class range of 10*s.* 10*d.* In those days the top social class spent three times as much on eggs, butter, and fresh meat as the lowest income group; in 1950 there was little difference. This change, however, was not confined to rationed foods; expenditure on fresh milk, vegetables, and fruit showed the same trend.

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[1] See *Lancet*, 1951, ii, 1032.

[2] Domestic Food Consumption and Expenditure, 1950. Annual Report of the National Food Survey Committee. H.M. Stationery Office. 1952. Pp. 131. 4*s.* 6*d.*

More bacon, butter, fresh rationed meat, and eggs went into our larders in 1950 than in 1949, but the increased consumption of meat only took us back to the 1946 level. Analysing the constituents of the national diet, the report finds that it contained more fat and protein than before, though its energy value remained much the same. The average value, for all households, of a day's diet in 1950 was 2474 calories per head; and energy needs seem to have been met by more bacon, meat, eggs, milk, cheese, and fats, offset by less bread and other cereals, potatoes and other vegetables, sugar, and jam.

Care of Old People

In his report for 1951, Dr. George Nisbet, county medical officer for the Soke of Peterborough, mentions the county's plans for a hostel for old people. His chief aim, however, has been to help the elderly folk to stay in their own homes; and he has been surprised how often his department has had to arrange for district nurses, home helps, and voluntary workers to help these people because the relatives have made little effort to do anything themselves. The relatives' attitude is partly explained, Dr. Nisbet says, by the fact that nowadays fewer children settle down in houses close to their parents' homes; many of them move out to new estates on the outskirts of the town. But, in Dr. Nisbet's experience, complete disinterest, and even blatant coldheartedness, often mean that old people have to depend on assistance from the local health authority; and this assistance, though of considerable value to them, can never be a complete answer to their difficulties.

The Third Quarter in Scotland

In Scotland during the September quarter of this year[1] the infant-mortality rate was the lowest ever recorded in any quarter—30 per 1000 registered births. The birth-rate was 17·3 per 1000 population; this was 0·3 more than in the same quarter of 1951, but 1·0 less than the average for the past five years. The still-birth-rate was 24 per 1000 total births; and the neonatal death-rate was 21 per 1000 live births, which was the same as in the corresponding quarter of 1951. The death-rate of 10 per 1000 population was below recent and pre-war averages.

Public-health Administration

The first report of the W.H.O. expert committee on public-health administration has now been published.[2] The report pays particular attention to the personnel of health services. The committee thinks that the needs of the public-health services are at present insufficiently considered both by the authorities who plan undergraduate and postgraduate courses in medicine and other subjects connected with health work, and by the graduates themselves. More stress should be laid in curricula on the preventive and social aspects of medicine. If more doctors are to be persuaded to take up this work, better pay and prospects of promotion must be provided.

Traffic in Dangerous Drugs

The Government's report to the United Nations on the traffic in opium and other dangerous drugs in 1951 shows that seizures of hemp in this country increased over previous years, while the quantity of opium seized continued to diminish. The majority of hemp users were between 20 and 30 years of age, and were men of West African and West Indian origin; and nearly all the persons prosecuted for the illegal possession of opium or opium-smoking utensils were Chinese. Of the known drug addicts in this country in 1951, 67% took morphine either alone or in combination with other drugs. Pethidine was used by 18%, as compared with 12% in 1950. The report says that there is no evidence to suggest organised trafficking in this country, and that drug addiction is not a serious problem, though very strict supervision continues to be exercised.

Special Articles

THE WORLD'S FOOD-SUPPLY

THE difficulties of maintaining the food-supply of the world and ways of solving them were discussed at a meeting of the food group (nutrition panel) of the Society of Chemical Industry on Dec. 10. Mr. J. I. M. JONES, M.SC., chairman of the nutrition panel, presided. This was the first of four discussions to be held by the group on this subject during the present session.

Mr. F. LE GROS CLARK said that a revolution in farming methods was necessary. There had been agrarian transformations before—the enclosure movement in this country and the coöperative movement in Denmark. The process of starting and carrying through such a revolution should have begun at least fifty years ago, when the pressure of population was not so great. If we did not make up for the delay, we should be condemned by future generations; for today we knew the facts. Discussing population increase, Mr. Le Gros Clark said that we could not expect Asians and Africans to take kindly to advice on birth control. "Is it not obvious," they would say, "that you preach to us only when you grow tired of your own fecundity?" But this did not mean that in time the world population would not reach some measure of stability. From a demographic point of view the world's history fell into three phases. In the first, the population of the world, after its primary growth, was held almost stable by high death-rates. There was then a period of accelerating increase, followed by a gradual control of the infectious diseases. If the birth-rate slowly declined, there must come a stage beyond which this growth could advance no further; and if by that time methods of birth control had been widely adopted, we might at last be in a position to suit our numbers to our own convenience. Referring to the need for more research in plant pathology, meteorology, hydrology, and plant genetics, Mr. Le Gros Clark said that most nations were not giving the agricultural scientist and the food chemist half the chance they should have. As to the human factor, turn the peasant into an alert modern farmer, and there was some prospect of getting him and his family to think in terms of scientific family control. But the order could not be reversed. Clearly, the transformation of a largely illiterate peasantry could not be completed for a century or so, but it was high time to plan our grand strategy.

Mr. E. W. RUSSELL, of the department of agriculture in the University of Oxford, discussed the factors limiting food production in this country. It was no answer just to say: "Get rid of all the less good farmers." Who was to take their place? Farmers were a cross-section of the community and, like every other cross-section, included good, mediocre, and bad; and we could only achieve uniform excellence in farming by taking good men from other occupations. The intractable difficulty in the way of increasing productivity in the hills was to get more men with new farming skills into these areas, and to improve the skills of those already there. Yet these were the very areas where the more enterprising and intelligent men were unwilling to live; and therefore the amenities would have to be vastly improved. In the world at large, food production was limited by three sets of conditions—those due to site, those due to disease, and those due to the characteristics of the people living in a particular area. The plant-breeder was helping to reduce the effect of a short growing-season; irrigation could sometimes make good a lack of water; and manuring and a suitable system of crop rotation could alleviate soil poverty. Animal production was limited mainly by the lack of land available for growing animal food; but disease, and particularly insect-

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1. Quarterly Return of the Registrar-General, Scotland: Births, Deaths and Marriages Registered in the Quarter ended Sept. 30, 1952. H.M. Stationery Office. Pp. 30. 2s. 6d.
2. *World Hlth Org. techn. Rep. Ser.* 1952, no. 55. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 41. 2s. 3d.

borne and mite-borne disease, could be very important. The scientist, the agriculturalist, and the social worker or anthropologist should combine to persuade the farmers to adopt new methods. Another important limitation, particularly in the subtropics and tropics, was the hindrance caused by debilitating diseases, such as malaria and those due to intestinal parasites, which sapped the desire and ability to do much work in a day.

Mr. **Norman Wright**, d.sc., chief scientific adviser to the Ministry of Food, asked whether greater production was to be expected by increasing the cultivatable area or by increasing the production of the existing cultivatable area. He had understood that the general pattern of food habits was related to economic conditions—for example, meat consumption was high where meat production was plentiful. What would be the increase in food available if people lived on the crops which could be most suitably cultivated in the area where they lived?

Mr. **Russell** replied that many acres were certainly not being cultivated, but it was not known how to cultivate them. He considered that increase would come from raising the yield per acre. As to food habits, the Scotsman used to eat oatmeal—now he ate bread and just a dash of oatmeal to show his nationality.

Mr. **Le Gros Clark** commented on the suggestion that if we eradicated malaria and other mass diseases, the population would grow more rapidly than ever. But he thought that there was no alternative. More human beings might lead to a famine. Very well, he said, there would have to be a famine.

Mr. F. **Wokes**, ph.d., had hopes that young green leaves, whose protein content was greater than that of older leaves, could make a significant contribution to diet in some parts of the world. The plants that grew in profusion in the tropics were a possible source; and he thought that the date palm should be grown more widely.

Mr. R. **Braude**, ph.d., said that the potential food-producing areas of America could support 500 million people; and some parts of the Middle East could also feed a far greater population than they did at present. Mr. **Russell** pointed out that American irrigation schemes in Arizona had often failed because they tried to irrigate too much land with the available water.

Prof. J. **Yudkin** remarked on the number of subjects involved in the study of nutrition: two of these were psychology and politics. Glass and other psychologists and sociologists had emphasised the fact that much intellectual ability was being cramped by inadequate education and poor social conditions. With a radical change in methods of education, it should be possible to raise the standards of the worst farmers. Professor Yudkin pointed out that there were countries where the question was not how to increase food production but how to limit it—Canada, for instance, would produce more wheat if she could only sell it.

Mr. D. M. **Freeland** spoke of the difficulty of young people who were unable to get farms when they left an agricultural college. Would it not be possible, with all the lands in the possession of the National Trust, to hire out some farms to these men? But Mr. **Russell** did not want young men straight from college to be given charge of farms. The farms of the "surtax farmers" were on the whole in the best class; and these farmers employed keen young men as managers. He thought that it was better for a man from college to spend a few years as manager or assistant manager.

Mr. A. E. **Bender** said that scientists could no longer sit down and say they had done all they could, and that now it was up to the politicians; for chemists were also citizens. Technically the problem had been solved; but success could not be achieved by scientists acting as scientists, but only by scientists acting as politicians.

Mr. A. L. **Bacharach** wondered whether the drive for self-sufficiency in agriculture in this country was economically and socially sound. There was little alternative during the present state of international tension, but a vast amount of time and money was wasted by some countries in producing things which could be much more efficiently produced elsewhere. It was nice for scientists to congratulate themselves and say, "we have solved all the problems, if only the politicians would get on with it." But that was not quite true. Fundamental research was essential, but during the past fifty years there had been a revolution in the attitude towards training in chemistry and possibly also in physics—a realisation that most students would enter the applied branches—and other sciences could with advantage follow the example. Mr. Bacharach found hope in the expectation that the birth-rate would drop as standards of living rose and the value of the child as a labourer decreased.

BIOLOGICAL WARFARE

In a statement on biological warfare the executive committee of the Medical Association for Prevention of War declares that the effect of other weapons cannot be concealed or simulated and the fact of their use is bound in the long run to become public; bacteriological warfare is exceptional in that its use or non-use in a particular theatre of war can be open to dispute.

> "It must now be evident how serious a psychological effect the knowledge that an insidious and inconspicuous weapon of this kind is being stock-piled, must exert on international tension. It seems plain to us that, so long as the development of bacteriological weapons continues unchecked, no official protestations about their defensive character will prevent the dangers which they involve. Accusations that they have been used will recur; these may be true, false or based on genuine error. Such accusations carry a continual risk of reprisal in kind. They can rarely be verified or disproved to the satisfaction of everyone and, in an atmosphere of international tension, the knowledge that such weapons exist, and that their exact nature is secret, will contribute to public anxiety, damage still further the repute of science, and might provide the spark to kindle a new world war."

The association points out that an instrument for international agreement for the prohibition of bacteriological weapons already exists in the Geneva protocol of 1925, which has been ratified by all the major states except the U.S.A. and Japan. The 1952 International Conference of Red Cross Societies appealed to all nations to adhere to the protocol. The association welcomes this appeal, but does not believe that an international agreement not to use a weapon is, in itself, an adequate guarantee that the weapon will not be used. The association does, however, believe that such an agreement would be a significant step towards attaining international confidence, would facilitate future agreement on methods of ensuring that the undertaking is honoured, and would bring nearer the eventual renunciation of all forms of war.

The association urges the governments concerned to view the issue as a problem of fundamental human importance, and not as an opportunity for propaganda; and it proposes the following measures:

1. That all governments publicly state that they will not in any circumstances resort to this form of warfare.

2. That those governments which are not signatories to the existing undertakings on this subject should sign them.

3. That secrecy in the field of bacteriological research should be replaced by full publication, and that all research stations engaged in such research should be opened to international inspection by an agreed authority.

4. That pending the realisation of these requirements medical and scientific workers should decline to participate in any secret research which appears to them to be directed toward the further development of these weapons.

In England Now

unning Commentary by Peripatetic Correspondents

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My wife and I are going on a trip abroad from which she must return before I do, and we have had our single passport converted into two. This was done by extending its availability and deleting my wife, who was given a brand-new shiny passport of her own. We now find, on inspecting the newly arrived documents, that my wife can go to the Canary Islands, Iceland, Madeira, or the Azores, and I cannot follow her. It is little consolation to know that we may visit Algeria or the United States in company, and that neither of us can go to Peru; nor does it soften the blow that I have a Foreign Secretary's autograph while she has none. Since the passports came I have noticed my wife thinking, and there is a gleam in her eye I do not like.

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News from School.—"On Monday we had a debate to decide whether animals should be kept in zoos or not. It was decided that they did not like it, but nobody said anything about what zoos would be for if there weren't the animals in them."

borne and mite-borne disease, could be very important. The scientist, the agriculturalist, and the social worker or anthropologist should combine to persuade the farmers to adopt new methods. Another important limitation, particularly in the subtropics and tropics, was the hindrance caused by debilitating diseases, such as malaria and those due to intestinal parasites, which sapped the desire and ability to do much work in a day.

Mr. **Norman Wright**, D.SC., chief scientific adviser to the Ministry of Food, asked whether greater production was to be expected by increasing the cultivatable area or by increasing the production of the existing cultivatable area. He had understood that the general pattern of food habits was related to economic conditions—for example, meat consumption was high where meat production was plentiful. What would be the increase in food available if people lived on the crops which could be most suitably cultivated in the area where they lived ?

Mr. **Russell** replied that many acres were certainly not being cultivated, but it was not known how to cultivate them. He considered that increase would come from raising the yield per acre. As to food habits, the Scotsman used to eat oatmeal—now he ate bread and just a dash of oatmeal to show his nationality.

Mr. **Le Gros Clark** commented on the suggestion that if we eradicated malaria and other mass diseases, the population would grow more rapidly than ever. But he thought that there was no alternative. More human beings might lead to a famine. Very well, he said, there would have to be a famine.

Mr. **F. Wokes**, PH.D., had hopes that young green leaves, whose protein content was greater than that of older leaves, could make a significant contribution to diet in some parts of the world. The plants that grew in profusion in the tropics were a possible source ; and he thought that the date palm should be grown more widely.

Mr. **R. Braude**, PH.D., said that the potential food-producing areas of America could support 500 million people ; and some parts of the Middle East could also feed a far greater population than they did at present. Mr. **Russell** pointed out that American irrigation schemes in Arizona had often failed because they tried to irrigate too much land with the available water.

Prof. **J. Yudkin** remarked on the number of subjects involved in the study of nutrition : two of these were psychology and politics. Glass and other psychologists and sociologists had emphasised the fact that much intellectual ability was being cramped by inadequate education and poor social conditions. With a radical change in methods of education, it should be possible to raise the standards of the worst farmers. Professor Yudkin pointed out that there were countries where the question was not how to increase food production but how to limit it—Canada, for instance, would produce more wheat if she could only sell it.

Mr. **D. M. Freeland** spoke of the difficulty of young people who were unable to get farms when they left an agricultural college. Would it not be possible, with all the lands in the possession of the National Trust, to hire out some farms to these men ? But Mr. **Russell** did not want young men straight from college to be given charge of farms. The farms of the "surtax farmers" were on the whole in the best class ; and these farmers employed keen young men as managers. He thought it was better for a man from college to spend a few s as manager or assistant manager.

. A. E. **Bender** said that scientists could no longer own and say they had done all they could, and that it was up to the politicians ; for chemists were also izens. Technically the problem had been solved ; ut success could not be achieved by scientists acting as scientists, but only by scientists acting as politicians.

Mr. **A. L. Bacharach** wondered whether the drive for self-sufficiency in agriculture in this county was economically and socially sound. There was little alternat during the present state of international tension, but a vast amount of time and money was wasted by some countries in producing things which could be much more efficiently produced elsewhere. It was nice for scientists to congratulate themselves and say, "we have solved all the problems, if only the politicians would get on with it." But that was not quite true. Fundamental research was essential, but during the past fifty years there had been a revolution in the attitude towards training in chemistry and possibly also in physics—a realisation that most students would enter the applied branches—and other sciences could with advantage follow the example. Mr. Bacharach found hope in the expectation that the birth-rate would drop as standards of living rose and the value of the child as a labourer decreased.

BIOLOGICAL WARFARE

In a statement on biological warfare the executive committee of the Medical Association for Prevention of War declares that the effect of other weapons cannot be concealed or simulated and the fact of their use is bound in the long run to become public ; bacteriological warfare is exceptional in that its use or non-use in a particular theatre of war can be open to dispute.

> "It must now be evident how serious a psychological effect the knowledge that an insidious and inconspicuous weapon of this kind is being stock-piled, must exert on international tension. It seems plain to us that, so long as the development of bacteriological weapons continues unchecked, no official protestations about their defensive character will prevent the dangers which they involve. Accusations that they have been used will recur ; these may be true, false or based on genuine error. Such accusations carry a continual risk of reprisal in kind. They can rarely be verified or disproved to the satisfaction of everyone and, in an atmosphere of international tension, the knowledge that such weapons exist, and that their exact nature is secret, will contribute to public anxiety, damage still further the repute of science, and might provide the spark to kindle a new world war."

The association points out that an instrument for international agreement for the prohibition of bacteriological weapons already exists in the Geneva protocol of 1925, which has been ratified by all the major states except the U.S.A. and Japan. The 1952 International Conference of Red Cross Societies appealed to all nations to adhere to the protocol. The association welcomes this appeal, but does not believe that an international agreement not to use a weapon is, in itself, an adequate guarantee that the weapon will not be used. The association does, however, believe that such an agreement would be a significant step towards attaining international confidence, would facilitate future agreement on methods of ensuring that the undertaking is honoured, and would bring nearer the eventual renunciation of all forms of war.

The association urges the governments concerned to view the issue as a problem of fundamental human importance, and not as an opportunity for propaganda ; and it proposes the following measures :

1. That all governments publicly state that they will not in any circumstances resort to this form of warfare.

2. That those governments which are not signatories to the existing undertakings on this subject should sign them.

3. That secrecy in the field of bacteriological research should be replaced by full publication, and that all research stations engaged in such research should be opened to international inspection by an agreed authority.

4. That pending the realisation of these requirements medical and scientific workers should decline to participate in any secret research which appears to them to be directed toward the further development of these weapons.

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Letters to the Editor

RESECTION FOR PULMONARY TUBERCULOSIS

SIR,—Your leading article of Dec. 6 indicates a startling revolutionary change in medical and surgical practice which calls for the strictest examination.

The logic of the argument, that patients, who have made a good recovery and have been proved to have consistently negative sputum are the fitter and more likely to tolerate surgery well, must be conceded as correct; but to subject such patients to the risks and the mutilation of resection of the lung and thoracoplasty would appear to be as indefensible as, and to a degree the same as, to remove healthy lungs or other structures to prevent disease developing in them at a subsequent date.

Pathologists have taught us for a century or more that unknowingly the majority of us have had tuberculous foci in some part of the body, and for the past fifty years radiologists have demonstrated the very common occurrence of old tuberculous foci in the chest and abdomen. Prior to the introduction of mass radiography these calcified masses were merely recorded by the radiologist and were ignored by the clinician, since they were unassociated with any clinical signs or symptoms. Even with the introduction of mass radiography in this country the directors were advised to ignore them.[1] But in view of these developments it is as well to note the original instructions to the directors of these units, which I criticised[2]: "It is important to avoid creating the impression that Mass Radiography (1) is intended for those already ill, or (2) there is danger in his work or life."

In support of the removal of these calcified lesions from healthy people it is stated that some showed a lamellated structure; and liquefaction of the focus with discharge of its contents, teeming with bacilli, is a common cause of relapse. But the former is a characteristic protective feature of the chronic inflammatory process which prevents the latter. I have seen the massive gumma and the chronic abscess and its sequestra in bone disappear with effective medication.

One might conclude that tuberculosis was a localised lesion which could readily be eradicated by resection, and that we had no means to combat it; but this is not true. One has seen resection of one lesion when many others were present, and resection followed by dissemination of the disease; but today with the aid of chemotherapy widespread lesions are healed and the lung cleared entirely—occasionally localised calcified foci have been left, but even these have been resected. I have watched calcified lesions for many years and seen no change. If the condition of the patient suggests a possible reactivity and radiography confirms it, surely chemotherapy, and not surgery, is indicated. I am not overlooking the fact that the coroner has inquired into the death of a young man who died of extensive pulmonary tuberculosis without any signs or symptoms.

If the patient can overcome the generalised disease of tuberculosis with the mutilations of surgery he can overcome it more readily without. Not all patients who were living useful lives survive the operation; and, as your leader indicates, not all cease to spit up tubercle bacilli, [illegible] not all fail to develop progressive fatal disease.

Formerly the argument for resection and thoracoplasty was that it was a preventive measure, but now the patient must not have the lung resected until he has ceased to be infective and is happy and well; the fitter he is the better he will stand the operation. These operative measures are opposed to the teaching of established medicine: Never remove the normal, for in attempting to remove the localised [illegible] tissue is removed and other structures are [illegible] no little risk to the patient.

As far as the radiography is concerned, I [illegible] at the satisfaction with work, producing gr and extensive changes in the chest, whi undertaken because of lesions such as one shrink and cease to mar the course of a long life.

We now see the admittance of failure measures of all degrees of severity—artific thorax, pneumoperitoneum, phrenic avulsion, crush—thoracoplasty, and more recently resection. To think of it: "30 wedge or s resections, with bilateral resections in 3 patien had 9 wedges removed)." If mass radiogra used to detect the unknown healed lesions people—i.e. "surgeons' radar"—the sooner it the better.

With the advent of beneficial chemotherap claim for improved housing and standards o the reinstatement of the patient into the h general practitioner would appear to be the for the patient and the eradication of the dis

Birmingham. JAMES F. BR

CURE OF TOBACCO-SMOKING

SIR,—I can assure your readers in ge *Dr. Joullié (Nov. 1) in particular, that* t mention in the *Koran* of the tobacco plant o The tobacco plant was introduced into E Arabia after the discovery of America—abou after the death of Mohammed.

Bagdad, Iraq. BAHJAT AL

BOVINE TUBERCULOSIS AND HU TUBERCULOSIS

SIR,—There are several statistical points wh be made with regard to Mr. Pitcher's lette in which he shows that in certain Scottish where the proportion of attested herds is gre 50%, the annual number of pulmonary tu notifications per 100,000 population has in m increased, *and that other counties where attes* number less than 16½% show on the whole tuberculosis notifications.

If the counties for which Mr. Pitcher gives f classified according to whether the popul increased or decreased between the 1931 a censuses, it is found that the division is almost with that made by Mr. Pitcher on the basis o centage of attested herds. The counties with 50% attested herds all show an increased except Zetland (where incidentally tuberculos tions have decreased). Moreover the counties Perth for which only old figures are given by M with less than 16½% attested herds have populations, with the exception of Kincardine, and Inverness (the increase being small in th counties).

Therefore, without some additional eviden Mr. Pitcher does not supply), it is as reasonab bute the changes in tuberculosis notifications population density as to reduction in bovine This statement must not be interpreted as a increased population density "causes" increa culosis notifications; it merely shows that at alternative hypothesis fits Mr. Pitcher's facts could be suggested. The point I wish to ma something more than an apparent statistical r is required before any such hypothesis can *be* as true.

It seems very doubtful that the proportion o herds in each county today is a suitable meas ich has taken place, over the past 20 or 30 the proportion of tuberculous cattle in that hich is what Mr. Pitcher wants to measure. ole, in his original letter[1] he stated that when of Zetland were tuberculin-tested in 1945 there ly any reactors. Thus the introduction of the attle scheme can have made little difference to but what [illegible] the position 20 years earlier? ss the percentage of attested herds represents of an examination of all the cattle in the gives only a doubtful indication of the prevaovine tuberculosis; and this applies particularly percentages.

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[1] Advisory Report on the Working of a Mass Radiography Unit. London, 1943.

[2] *Postgrad. med. J.* 1944, 20, 135; *Med. World, Lond.* March 31, 1944.

cher gives figures for only 20 of the 33 Scottish How do the others fit in with his theory?

Ir. Pitcher's arguments unconvincing, but this is tant matter and it seems to me that some or medical evidence is required before any ns can be drawn. The national statistics are by too many extraneous influences to provide more than indications for further research.

Middlesex. R. H. DAW.

ESTHESIA FOR TONSILLECTOMY IN CHILDREN

rightened children, as seen in hospital outinics, often fall into one of two classes:

toddler whose only contact with a doctor in a at has been in the diphtheria prophylaxis clinic d of a needle, with other children crying round. Results might be happier, though less hygienic, if its were abandoned in such clinics.

post-tonsillectomy "smash and grab" child who has hyxiated into unconsciousness beneath the glare of light or the beam of the throat raider's headlight.

e visited hospitals and departments where the ed child is placed on the operating-table "so o start the anæsthetic outside." Induction takes the ever-increasing roar of running water and the f stainless-steel buckets.

ll who operate upon the young make it their l business to see that no conscious child ever he anæsthetic room. Light premedication is not ; for it merely makes the child unable to accept urances (so freely given) of the nurse "that the is not going to hurt."

ds, sights, and smells of surgery must not be to enter the child's absorptive memory. In such ve anæsthesia there is only one danger— ence.

1, W.1. D. F. ELLISON NASH.

HÆMORRHAGIC FEVER IN KOREA

I was interested to read Captain Rowe's review s on this subject (Nov. 15). All the cases among Commonwealth troops in 1951 and the onths of 1952 were seen in the 29th British Hospital, now known as the British Commoneneral Hospital, in Kure, Japan, where I lately

sease, which first appeared among troops in Korea 1951, is now known both there and in Japan rrhagic fever, for there is no certain evidence isease is epidemic. In our experience the age occurred nearer the tenth day than the it was often heralded, and sometimes manily, by epistaxis. It is generally agreed that he early signs of the "bleeding tendency" seen t four or five days of the disease are attributable ontinuous and violent vomiting and retching. more emphasis should be laid on the albumich is a characteristic feature—so much so that me it was only in exceptional circumstances that a diagnosis of hæmorrhagic fever was mad absence, and even then some doubted the valid such a diagnosis.

Of the other points one in particular is both important and interesting. Patients with hæmorrhagic fever travel extremely badly, and quite often the journey from the forward medical units in the field to the base hospital in Japan was a major factor in the severity of their illness. Since the introduction of helicopters by the U.S. medical services to evacuate patients with hæmorrhagic fever from forward to rear medical units, there has been a reduction in the mortality of the disease and in the severity of the individual case.

Finally, I would like to mention the excellent work performed by the regimental medical officers of forward units in diagnosing the disease in its early stages.

London, N.W.1. C. BERNSTEIN.

ESTIMATION OF BLOOD-DEXTROSE

SIR,—I have read with great interest Mr. Sheridan's comments (Dec. 13) on the theory of my method for rapid blood-sugar estimation. While I respect his views, I am unable to agree with him for the following reasons:

(1) A consideration of the formula concerned will show that for the usual concentrations of dextrose in the blood and for a vessel of the length of the eye the optical rotation produced would be extremely minute—a fraction of a degree.

(2) Light which has been rotated on entering the eye would be rotated back again to an equal and opposite extent on reflection.

(3) We have been able to reproduce the results using a series of stops to measure light intensity without polarising the light.

The London Hospital,
Whitechapel, E.1. D. W. VERE.

DEATH AFTER ANÆSTHETIC WITH HYPOTENSION

SIR,—Dr. Bodman (Nov. 29) draws attention to the slower recovery following the use of the methonium compounds. I agree that such is quite often the case. I feel, however, that the cause lies in the lowered metabolic rate and, therefore, the slower elimination of the drugs used, rather than in stagnant anoxia. If anoxia were present it would surely have shown itself by now by an increase in postoperative morbidity.

It is unfortunate when an able anæsthetist has such an experience in a short series of cases using a particular technique. I would cross swords at once with Dr. Belfrage for his uncomprehending letter (Dec. 13) condemning Dr. Bodman for his choice of drugs and technique.

Rather let us congratulate Dr. Bodman on his courage in reporting a death which he believes was associated with hypotension. I suggest that his technique may, in fact, have been responsible, not only for a bloodless field, but for getting the patient off the operating-table alive. It could be argued that hexamethonium bromide may well have dilated, and temporarily relieved, the diseased arterial circulation. Blood-loss with an ordinary anæsthetic could easily have caused compensatory vasoconstriction and thrombosis during the operation in such a case.

Queen Victoria Hospital,
East Grinstead, Sussex. JOHN F. PELMOR[illegible]

SIR,—I was glad to read the spirited protest by [illegible] Belfrage (Dec. 13) against the indiscriminate use of hypotensive techniques in anæsthesia. There is no doubt that these techniques, especially when associated with the head-up position, carry a serious risk, and can only be justifiable in those few cases in which the *possible benefit* to the surgeon outweighs the *certain risk* to the patient.

In the first article on the use of methonium compounds in anæsthesia,[1] I uttered a caution which I repeated plified on several occasions, particularly at a ng of the section of anæsthetics of the Royal ety of Medicine in March, 1951,[2] but with small port from the body of anæsthetists. No new techie should be introduced into anæsthetic practice ss it brings with it greater safety for the patient: ppears from the reported fatalities that the methonium pounds, used to produce hypotension, fail by this, and their use should be abandoned, save in very and carefully selected cases.

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[1] *Lancet*, 1951, ii, 786.

[1] Davison, M. H. A. *Lancet*, 1950, i, 252.

ewcastle upon Tyne. M. H. ARMSTRONG DAVISON.

DEALING WITH DISASTER

IR,—I should like to make some points arising from r editorial (Dec. 6) on the organisation and treatit *of casualties in a major accident.*

he so-called "general surgeon" no longer exists. is a specialist in abdominal surgery and surgery of the k and of a few other areas, and is as much a specialist for example, an orthopædic surgeon. It is therefore gical to suggest that a surgeon with such specialised erience should lead a team to deal with accidents re 90% of the casualties are orthopædic.

esuscitation in the form of blood-transfusion should vailable on the spot in an accident of this kind, where re is delay in extricating people who are trapped.

f, however, the injured can be readily transported hospital then this is the best course to take. But in the sorting and decision as to the immediate tment would be best made by an accident or orthodic surgeon who is constantly meeting this problem is daily routine work.

indsor. G. P. ARDEN.

HE WHOLE-TIME OFFICER AND MILEAGE ALLOWANCES FOR HOSPITAL STAFFS

IR,—In the Supplement of the *British Medical Journal* Dec. 6 (p. 220) we are given the impression that at concessions have been secured for whole-time cers by the agreement reached on mileage allowances the General Whitley Council. Let us examine these oncessions" more closely.

irst, the new mileage allowances will be introduced only the employing authority by resolution so decide." They not national awards, but depend on the charity or whim he employing authority. They may vary from region to on and be terminated at a moment's notice. Unforately *the matter does not end* with the sacrifice of a vital iciple. When the Staff Side of Whitley "B," in their ecent haste to secure better *terms for their part-time* eagues, agreed to the imposition on whole-time consultants egulations that had hitherto been applied only to *clerical* manual workers, they opened the door to the application nore of these regulations and the further degradation of status of whole-time consultants. Our chances of getting Spens report implemented have been gravely impaired reby.

econdly, the "concessions" are so restricted in their lication that they do not "benefit" more than 1–5% of ole-time medical staff. How many whole-time consultants e a *definite commitment* to visit a second hospital or ic every day? Does this include Saturdays and Sundays? *st consultants* with these *commitments* have, where the ional boards would allow it, gone part-time, as they then a *higher net income* for possibly less work and they are e of their travelling allowances.

he other alternative, where the *liability of being called* to make emergency visits is "so extensive and the journeys practice so frequent," depends for its application on the erpretation of "extensive" and "frequent." They can given such a restricted application that they apply *only* hypothetical cases; and, of course, the employing authority s the last word.

The average whole-time consultant who does a few ergency visits or makes some other official journeys each week, and who must run a car (for which he c claim no income-tax allowances), is still worse off un *the new regulations* than he was under the old if he u his car routinely to travel from home to hospital sol in the interests of the employing authority.

These facts prove conclusively that the negotiat committee, and those who "b[illegible]f" them, are competent to speak for whole-time medical staff. ask once more for adequate representation of who time consultants and specialists on the Staff Side Whitley "B."

EO GILCHRIST
OUIS L. GRIFFITHS
). P. VAN MEURS
KEITH RANDALL
. Y. D. WAKEHAM
. G. WILLIAMS.

Farnborough Hospital,
Kent.

THE PROSPECT OF GENERAL PRACTICE

SIR,—Having spent forty-one years in general practic I read with interest the comments on this subject i your columns.

The general practitioner's work is attractive becaus of his privileged position as the family doctor wh advises and befriends all the members of the family I reject outright your correspondent's reproach (Aug. 16 of "*low professional standard* and lack of opportunit for good work." In my practice I had at hand a electrocardiograph, X-ray apparatus, *polarimeters*, microscope, and so on; and I could investigate ever case thoroughly. Certainly such investigation require *time and patience*; and one regrets that the genera introduction of health insurance has lowered the standar of care, for the doctor now has simply not enoug time, and the fountain-pen has become the most impor tant instrument in the consulting-room.

The general practitioner deals with the whole ma and therein lies his gratification.

TH. OLBERT.

Düsseldorf, Germany.

VITAMIN B_{12} IN PRACTICE

SIR,—With reference to your leading *article on* th subject (Dec. 13), we would draw your attention to th fact that we have been misquoted in two respec *Firstly*, we did not say that signs of reversion in th bone-marrow could be detected after *40–50 days*, that signs of reversion in the bone-*marrow* could detected 40–50 days *before* signs were evid in peripheral blood. Secondly, we did not conclude t the technique of massive *single dosage* was not pr ticable; we said[1] that, "while of theoretical a practical interest, these findings do *not* justify, witho further trials, the routine treatment of pernicious anæn by 1 mg. doses of vitamin B_{12} at long intervals."

ROBERT B. HUNTER
W. WALKER.

Department of Pharmacology
and Therapeutics,
Medical School, Dundee.

SIR,—In addition to the investigations mentioned your article, several others have been made into t effect of vitamin B_{12} as a growth *factor* in childr Though some reports describe a failure to improve t growth of premature infants,[2–4] attempts with ol children have proved *more* successful.[5 6] We are parti larly impressed with the results just published by Wetzel and his colleagues[7]; *for great* care was taken assess their statistical significance. We believe that reason for his success lies in the choice *of* children th whom he worked." Another colleague tells of od judgment as a surgeon and of his amiable and l nature; and a third writes: "Without being ically brilliant he possessed a good intellect; self-discipline he rose above trials and frustrations might have weighed down a lesser man."

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[2] *Proc. R. Soc. Med.* 1951, 44, 382.

[1] Walker, W., Hunter, R. B. *Brit. med. J.* Sept. 13, 1952, p.
[2] Downing, D. F. *Science*, 1950, 112, 181.
[3] Rascoff, H., Dunewitz, A., Norton, F. *J. Pediat.* 1951, 39,
[4] Mitchell, T., Etteldorf, J. N., Tuttle, A. H., Clayton, G. W. *Pediatrics, N.Y.* 1951, 8, 821.
[5] O'Neil, G. C., Lombardo, A. J. *J. Omaha clin. Soc.* 1951, 12,
[6] Wilde, E. *J. Pediat.* 1952, 40, 565.
[7] Wetzel, N. C., Hopwood, H. H., Kuechle, M. E., Gruenin R. M. *J. clin. Nutr.* 1952, 1, 17.

e and Mrs. Wostenholm are survived by three

JOHN HENDERSON SMITH

B.A. Oxfd, M.B. Edin.

Henderson Smith, who died at his home at nden on Nov. 26, had a distinguished career. a bacteriology and later in plant pathology.

n Henderson Smith was born in Edinburgh in He was educated at Fettes and went on to ol College, Oxford, where he read classics. After ating with first-class honours in Greats in 1898, ook up medicine and qualified at Edinburgh in . Thereafter he returned to Oxford, where he held ilip Walker studentship in pathology.

t this time pathology was developing very rapidly, its scope was being enlarged beyond the study of bid anatomy. The advances in physiology and the discoveries in bacteriology were creating almost a discipline in pathology; and one of the most active res of this work was in Oxford, where J. S. Haldane James Ritchie were training a rising group of ologists.

enderson Smith was chiefly attracted by bacterio- and immunology, and at the end of his studentship went abroad and spent some time in Germany and mark. In Denmark he worked with Professor lsen, and was much influenced by the attempts there find a physicochemical basis for the principles of unity which were being gradually uncovered by eriments along biological lines.

n 1907 he was appointed assistant bacteriologist he Lister Institute, then under the directorship of Charles Martin. Here he worked chiefly on the hoid-coli group of bacteria; on complement devia-, as it was then called; and on the Wassermann tion. In the early months of 1913 he was appointed etary to the Government Advisory Commission on gue in India. Late in that same year, however, his lth deteriorated; and from then onwards his life e a struggle with ill health.

fter his first illness he returned to work and gave llent service as head of the bacteriological depart-nt at the Lister Institute in 1915. Early in 1916, ver, he was again seriously ill, and he resigned from nstitute.

a pathologist he carried out his work with excellent ique, and expressed his findings in clear, logical age. He was always highly critical of his own oc.

1919, after he had made a more solid recovery of h, he was appointed assistant mycologist at amsted Experimental Station. Thus at the age of began a new scientific career; and it says much f is intellectual capacity and his courage that he e a distinguished reputation in this new field.

is first work at Rothamsted was an excellent research he death-rate of spores of moulds killed by heat and henol. He then took up the study of virus diseases, icularly the mosaic diseases of tomatoes. He ved that the streak mosaic of tomatoes could be oduced in plants grown aseptically and was not, d been believed, a bacterial disease.

a result of his successful work in this field a research was appointed in 1929 to work on these diseases r his leadership. In 1933 he was appointed head e department, which was re-named the department ant pathology. He was one of the first to recognise alue of the chemical work on plant viruses carried during the 1930s. In his presidential addresses to Association of Applied Biologists in 1938, and to the section of the International Congress of Micro-gy in New York in 1939, he accepted the view that of the viruses at least were proteins. He retired his post at Rothamsted in 1940.

took pleasure in outdoor things and played games particularly golf and tennis. Apart from his work, his main interest was his collection of the heraldry associated with them.

M. R., to whom we are indebted for th writes: "Henderson Smith brought to his work scholarly appreciation of the logic of facts. W fine capacity for exposition he was an admirable te and it was a pity that he never held a chair. He ha kind, friendly disposition and was always willing to give any point of view a hearing."

Dr. Henderson Smith married Miss Alice Robinson, who survives him.

Appointments

Bisset, C. M., B.M. Oxfd: asst. school M.O. and asst. M.O.H. Croydon.

Braithwaite, D. W., M.B. Durh.: M.O., Colonial Medical Service, Northern Rhodesia.

De Winter, Edith, M.D. Prague, D.A neurosurgical unit, Atkinson M

Elliott, R. W., M.D. Lond., D.P.H.:

Fenton, John, M.B. N.U.I., D.P.H.: M.O.H., Hackney.

Mitchell, Robert, M.B., B.Sc. Edin., D.P.H.: M.O.H. and school M.O., Burton upon Trent.

O'Meara, P. B., M.B. N.U.I., D.P.H.: M.O., co. Mayo.

Perry, J. F., M.D. Belf., D.P.M.: consultant psychiatrist, Holywell Hospital, co. Antrim.

Warren, M. D., M.D. Lond., D.P.H., D.I.H.: asst. M.O., L.C public health department, and deputy M.O.H., Hampstead.

Birmingham Regional Hospital Board:

Adams, E. F., M.R.C.S., D.A.: consultant anæsthetist, Dudley Stourbridge group of hospitals.

Brown, D. E. M., M.B. Lond., D.M.R.: consultant radiotherap Wolverhampton and Stoke-on-Trent groups of hospitals

Duthie, D. A., M.B. Edin., M.R.C.P.E.: consultant dermatolog Stoke-on-Trent and Stafford groups of hospitals.

Hoult, J. G., M.B. Birm., D.C.H.: asst. pathologist, Birmingham (Selly Oak) group of hospitals.

Kalinowski, Stanislaw, M.D. Bologna: asst. chest physic South Worcestershire group of hospitals.

Knappett, C. R., M.D. Lond., consultant pathologist, Stoke Trent group of hospitals.

Wilson, J. R. E., M.B. Lpool: asst. psychiatrist, St. Ge s Hospital, Stafford.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but cand es may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

Betts.—On Dec. 9, at the London Hospital, to Mary, wife of Dr. Anthony Betts—a daughter.

Chalmers.—On Dec. 10, to Doreen (née Boorman), wife of Dr. Theodore Chalmers, of St. Mellons, near Cardiff—a son.

Lewis.—On Dec. 13, at the Barratt Maternity Home, Northampton, to Kathleen (née Seely), wife of Dr. M. Peebles Lewis—a daughter.

Lockyer.—On Dec. 9, to Cicely (née Nelson), wife of Dr. J. C. G. Lockyer, Colonial Medical Service, Tanganyika—a daughter.

Nicholl.—On Dec. 12, at The Castle Lodge, Lewes, to Margaret (née Pippett), wife of Dr. Patrick Nicholl—a son.

Richards.—On Nov. 16, in Birmingham, the wife of Dr. D. G. Richards—a son.

MARRIAGES

Taylor—Sanderson.—On Dec. 13, Joseph Taylor, M.B., of Chislehurst, to Joan Agnes Sanderson, of East Grinstead.

DEATHS

Craig Mooney.—On Dec. 6, at Yelverton, South Devon, A Craig Mooney, M.B. Lpool, D.M.R.E., F.F.R., aged 62.

Evans.—On Dec. 13, Alfred Ernest Evans, M.B. Glasg. of Kingston Hill, Surrey, aged 82.

Evans.—On Dec. 11, at Edmonton, London, Charles Evans, L.R.C.P.E., aged 85.

FitzGibbon.—On Dec. 1, at Clonskeagh, Dublin, Gibbon, M.D. Dubl., F.R.C.P.I., late Master of the Hospital, aged 75.

Hessey.—On Dec. 13, James Dodson Hessey, M.R.C.P., of ton, and late of St. Leonards-on-Sea.

Hunt.—On Dec. 15, Edmund Henderson Hunt, M F.R.C.S., of Farnham, Surrey, formerly of Secunderabad aged 78.

Johnson.—On Dec. 12, at Bassingham, Lincs, Osborne L.R.C.P.E., aged 91.

Kay-Mouat.—On Dec. 11, John Richard Kay-Mou D.P.H., late professor Singapore Medical Colleg New South Wales, aged 71.

Keates.—On Dec. 13, in London, Henry Crewe Kea lieut.-colonel, I.M.S. retd, aged 73.

Kellaway.—On Dec. 13, in London, Charles Ha M.C., F.R.C.P., F.R.S.

Knowles.—On Dec. 9, at Crieff, Kate Knowles,

Porter.—On Dec. 15, in London, Charles Porter, M.R.C.P.E., D.P.H., barrister-at-law, of Clift N.W.8.

Wostenholm.—On Dec. 12, Maurice Humph F.R.C.S., aged 37, of Harpenden, Herts.

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We know that we can remove the disorganised tissue in some of the less active and more localised growth disorders so that the patient lives his normal span of life without recurrence, but we also know that he may harbour a tumour focus for twenty or thirty years without knowing it, only for it to wake to activity at last to cause his death. The wonder is not that disorganisation of the normal processes of growth and repair occur, or that their manifestations are so varied, but that we maintain so long as we do our wonderful steady state despite our extraordinary internal turmoil. We had to wait for radioactive isotopes to tell us just how extraordinary that ordered turmoil is.

The wide variety of degree of incoördination of growth which we cover by the vague word cancer is one of the universal ways in which living things decay and die. As accidents and infections are warded off and life is prolonged, death depends more and more on the degenerative diseases for its necessary toll. The more we understand about the particular relaxations, stresses, strains, and irritations which chiefly predispose to the disorganisation of growth control in various tissues, the better shall we be able to postpone the day when restraint breaks down. The more we learn about the earliest manifestations of such disorganisations, the more quickly shall we be able to deal with the situation before it has got out of hand. The more we know of the natural history of growth disorders at different sites and can assess the degree of disorder and extent of spread reached, the more efficiently shall we be able to choose and apply our treatment methods.

PRESCRIBING TREATMENT

In a general discussion of this kind a detailed account of a treatment plan for patients with cancer of the breast would be out of place. Such an account needs setting in a framework of general principles, the reasons for accepting which are given, together with the evidence on which each one is based. These principles must be interpreted in the light of the needs of each individual patient. Patients vary as much in personality and circumstances as they do in the type of tumour and degree of advancement of the disease with which they present themselves. There is as much difference from one to another in the confidence with which we can rely upon our clinical assessment of the extent of the disease as in the reliance we can place on the history that they give. These things may have an important bearing on the treatment we prescribe. I propose merely to make a few short statements here as illustrations of the kind which I think should colour our view of this treatment problem. They seem to me at the present time to fit in well with the evidence available and to provide a guide to help us make the best use of all the proved treatment methods available. Since several hospitals employing only one or other of these methods as their main treatment plan produce survival-rates of the same order, when allowance is made for differences in material treated, we must either conclude that all these methods have some merit, chiefly exercised in different groups, or that the treatment method used makes little difference to survival, which we know to be untrue for the later cases and which we have good reason to believe to be untrue for the earlier cases also. Patients in the same clinical stage of advancement may still be clearly distinguishable as having a different prognosis and in needing different treatment plans. Radical mastectomy (with postoperative irradiation where indicated), local mastectomy with irradiation of the regional lymph-node regions, and radiotherapy alone or preoperatively, may all have their place within one clinical stage.

The few short statements about the treatment of patients with breast cancer which I would put forward at present to illustrate an approach to the problem are as follows:

1. The outcome of any treatment for patients with breast cancer depends more on the degree of advancement of the disease, which is largely dependent on the nature of the tumours they develop, than on any other factor.
2. Only surgery, radiotherapy, and occasionally hormones, have been shown to modify the course of the disease.
3. Surgery is generally more effective than radiotherapy in eradicating breast cancer, both in the primary site and in the axilla; but unsuccessful surgery usually makes matters worse, whereas radiotherapy normally provides at least some degree of improvement and may lead to complete clinical tumour regression lasting many years.
4. The first consideration in treatment is what chance there is that surgery will be successful. When the chance of complete removal of the tumour by surgery does not seem to be good, or the assessment of that chance is difficult, radiotherapy is to be preferred. The breast and the axilla should be considered separately in making this decision. In some of the doubtful cases operation is best performed after radiotherapy.
5. A worth-while estimate of the nature of the tumour, on which the chance of success with treatment so much depends, can usually be made by considering the length of history, good sense of the patient, size of the tumour, and clinical evidence of spread in relation to the ease of making the examination.
6. A sensible patient with a small hard tumour in the outer half of the breast which has been noticed for some months, who is reasonably thin and easy to feel, and has no more than one or two hard mobile nodes low down on the medial wall of the axilla (stage II), *is usually best treated by radical mastectomy.* Postoperative irradiation should be reserved for those patients in whom detailed pathological examination of the specimen removed suggests that local recurrence is likely, and that the clinical judgment was at fault.
7. A patient with a small hard mobile primary tumour who is either too fat for adequate palpation of th axilla, or who on palpation has several sma nodes extending high up into the apex (stage II is usually best treated by local mastectomy an radiotherapy to the lymph-node regions, especiall if the history is short.
8. A patient with a short history and a large tumou in the inner half of the breast with several har nodes palpable in the axilla (stage II) has a ba prognosis, may never be suitable for operation, an is usually best treated by radiotherapy alone.
9. The more differentiated, slow growing, and localise the tumour, the more reason for primary surgic treatment. The more undifferentiated, rapidl growing, and disseminating, the more reason fo primary radiotherapy. In the middle group, whe in doubt, it is wise to use radiotherapy first wit a view to using surgery later; but if the conditio is still doubtful after irradiation, surgery is stil to be avoided and reliance placed on radiotherap and hormones.
10. *Careful management* and energetic treatment o patients with more advanced disease, avoiding surgery in regions where it is likely that all th abnormal tissue cannot be removed, is often wel worth while.
11. In elderly patients with slowly progressive ulcerating breast tumours, œstrogen therapy may be completely successful—i.e., enable them to live their normal span of *life* without discomfort. Premenopausal women with metastases may be helped, sometimes *dramatically*, by *surgical* or *X-ray castration*. Androgens may sometimes be of value when the castration effect has worn off, or for debilitated patients of any age with widespread deposits especially in bone. In general,

hormone response is infrequent and uncertain and the treatment is at present best reserved for patients with symptoms due to multiple metastases no longer controlled by irradiation. Its combination with X-ray therapy holds out a real prospect of improvement in results as we learn more about their joint action on both the tumour cells and their environment.

12. The most successful palliative treatment may take as much time and care as that designed with a more ambitious aim. At the mere mention of the word palliation the extremes of either giving some easy, quick, ineffectual treatment and then sending the patient home to die under someone else's care, or of pushing treatment till it adds to the patient's discomfort while merely prolonging the act of dying, are still far too often adopted.

Envoy

We can now at times eradicate, we can often delay progress, and usually we can relieve suffering for a time at least; but it seems that more is expected of us not only in the quality of the work we do, which is reasonable, but in its very purpose. The purpose of medicine is surely not to change the whole face of Nature. It is good to set ambition high but not to let our thoughts get out of hand.

> "Couldst thou make men to live eternally
> Or, being dead, raise them to life again,
> Then this profession were to be esteemed."

It was thoughts like this which led Dr. Faustus straight to the devil saying "Physic farewell." Is not the pursuit of a "universal cancer cure" dangerously near to the desire to be "a sound magician" and "a mighty god"? This is for the quacks, a few of whom are no less earnest and well-meaning than we are, but who nevertheless impose on the pitiful anxiety of the public, supported by an ill-advised press at times and quite often sustained by doctors who see and know little of the fine variability of growth disorders, and who, by endorsing their spurious remedies, monotonously expose their own inexperience as one after another they announce that they have never seen anything like it happen before. Credulity, in many fields other than medicine, is due less to lack of brains than to lack of knowledge; it is often easier to fool the intellectual when he is out of his depth than it is to take in the illiterate.

The necessity for cancer treatment is an indication of our failure to prevent, or marks the limit of our ability to postpone; and treatment itself is designed to keep a man healthy for his normal span of life if that be possible and to relieve his suffering if it be not. This seems to me to be the very stuff and heart of medicine, just as universal cures are the stock-in-trade of magicians. Sir William Jenner said that the three essential qualities of a doctor were that he must be honest, that he must be dogmatic, and that he must be kind; he did not say that he must work miracles. Familiarity with the advances that have been made in the knowledge of cancer, and of the effects produced by the treatment methods that are used, will help us to offer our patients the best advice and treatment that is procurable for them at the time. A close study of each individual, to assess both the activity and degree of advancement of the disease and the particular suffering, mental and physical, which that patient is experiencing, will help us to decide what we want to achieve. The difficult things that sound so simple, like a clear idea both of what we want to do and what is possible, are more likely to lead to progress in the treatment of breast cancer than the easy things that sound so grand, like either sitting waiting for someone else to find "a cure" or reassuring ourselves that what we have always done is still the best.

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SURVIVAL OF TRANSFUSED RED CELLS

PREVIOUSLY STORED FOR LONG PERIODS IN THE FROZEN STATE

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RED cells in 15% glycerol can be frozen and thawed with the production of only slight hæmolysis (Smith 1950). The glycerol can be removed from such cells by dialysis, and the recovered red cells can then be used for transfusion (Sloviter 1951). Human red cells, recovered in this way after having been kept at −79°C for two hours, survive normally in the recipient after transfusion (Mollison and Sloviter 1951). Red cells stored at −79°C for up to eight months appear normal (Sloviter 1952a), and it is shown here that such red cells survive normally after transfusion.

In a study of the behaviour of red cells at temperatures between 0°C and −79°C it was found that a considerable proportion of the red cells could be recovered after storage in 15% glycerol at −15°C for several weeks (Sloviter 1952b). The percentage of red cells which can be recovered after storage at −15°C is much lower than after storage at −79°C. Nevertheless transfusion experiments were made to determine whether −15°C is a sufficiently low storage temperature to prevent those changes (presumably due to metabolic activity) which shorten the survival of the red cell after transfusion. The results show that red cells recovered after storage at −15°C for eighty days have an approximately normal survival in vivo.

METHODS

Storage of Blood

Pilot tubes obtained at a routine blood collection of the National Blood Transfusion Service were tested and bottles of group-A type-N blood selected. The bottles of blood had been stored for three or four days at + 4°C by the time they were selected. Before mixing with the glycerol solution, about 150 ml. of plasma was removed to prepare a concentrated suspension of red cells. The procedure for freezing and recovery of the red cells was exactly the same as that described by Mollison and Sloviter (1951), except that the red cells were stored at −79°C (solid carbon dioxide-alcohol) for periods up to eight months. As before, the red cells were transfused seven or eight days after thawing; this delay was due mainly to making sterility tests on the red-cell suspensions before transfusion.

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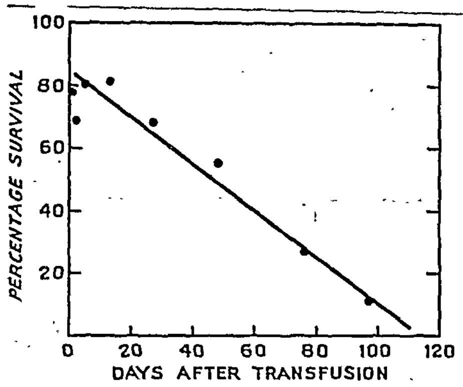

Fig. 1—Survival after transfusion of red cells stored at −79°C for three months and at +4°C for eleven days (case 1).

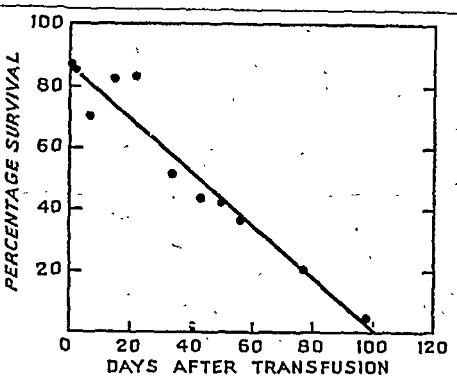

Fig. 2—Survival after transfusion of red cells stored at −79°C for six months and at +4°C for eleven days (case 2).

In further experiments blood was stored at −15°C. In these experiments the procedure was similar, except that the blood-glycerol mixture was simply placed in an ordinary deep freezing cabinet and in some instances solidified quite slowly (many hours). Thawing was carried out by placing the bottles in a water-bath at +37°C. Thereafter the procedure was the same as for blood stored at −79°C.

In the present work the volume of red cells frozen was determined by measuring the volume and hæmatocrit of the original suspension; and this was compared with the final volume of red cells recovered after freezing, thawing, dialysis, and washing. Thus the estimations of the percentage recovery of red cells include losses during dialysis and washing.

Control Blood

On the day of transfusion a donor of group O, type M, was obtained and blood was drawn into acid-citrate-dextrose about an hour before the time arranged for transfusion. A and B substance (Sharp & Dohme) was added in the proportion of 1 ml. to every 50 ml. of blood to reduce the anti-A activity of the donor plasma.

Choice of Recipients

Ten patients were transfused, each receiving both stored (previously frozen) and fresh (control) red cells. All the patients belonged to group A (Rh-positive) and were M-positive. All but one of the patients were women, and most of them had iron-deficiency anæmia connected with pregnancy.

Measurement of Survival of Transfused Red Cells

The concentration of surviving cells was estimated by differential agglutination, Dacie and Mollison's (1943) modification of Ashby's method being used. The method was further modified because of the rather small quantities of red cells transfused in some experiments. The modification consisted simply in using a more concentrated suspension of red cells, so that the final concentration of blood in the tests (after adding the agglutinating serum) was 1 in 42. For counts of O cells highly potent anti-A sera produced in rabbits were used; for counts of N cells anti-M powdered globulin (Lederle) was used (Ebert and Emerson 1946).

"Blank" (pre-transfusion) counts with anti-A serum were 4000–11,000 cells per c.mm. in nine cases, and 21,000 in the remaining case; with anti-M sera the blank counts were all between 2000 and 7000 cells per c.mm. On the day after transfusion the counts of previously frozen cells were 128,000–254,000 per c.mm. in eight cases, and 67,000 and 478,000 per c.mm. in the remaining two. *Counts of control cells were higher; 126,000–280,000* per c.mm. in five cases, and 408,000–862,000 per c.mm. in the remaining three.

For each population of transfused cells, estimates on the day after transfusion were based on counts of 4000 cells; most other estimates were based on counts of 2000 cells; but, when very few cells were left, only 1000 cells were counted.

The volume of cell suspension transfused was measured by weighing the bottle with its contents before and after transfusion and determining the specific gravity of the blood mixture. Any cell suspension left in the giving set was returned to the bottle before the final weighing.

The red-cell count of a well-mixed sample from each bottle was determined by counting not less than 4000 red cells. From these data the "expected" ratio of test cells to control cells was calculated—i.e., the ratio expected if the previously frozen and the freshly drawn red cells survived equally well. For convenience the ratios actually found have in each case been expressed as percentages of the expected ratio (see table I).

These "percentage survivals" express simply the survival of the stored cells relative to the control cells; thus, "100% survival" implies that the stored cells are surviving exactly as well as the control cells, and not that all the stored cells are surviving.

The absolute percentage survival was estimated in the following way. First, the concentration of test cells expected on the day after transfusion, if the test cells survived just as well as the control cells, was:

$$\text{Observed count of control cells, Day}_1 \times \frac{\text{No. of test cells transfused}}{\text{No. of control cells transfused}}$$

This figure was considered as 100% survival of the test cells, and the observed count of test cells on any day

TABLE I—PROTOCOL OF CASE 2

(The method of obtaining the figures in columns 4–8 is described in the text)

(1) Days after transfusion	(2) Test (prev. frozen) red cells (×10³ per c.mm.)	(3) Control (fresh) red cells (×10³ per c.mm.)	(4) Observed ratio: test/control	(5) Ratio observed/Ratio expected (%)	(6) % Survival of test cells (uncorrected)	(7) "Expected" counts of control cells (×10³ per c.mm.)	(8) "Absolute" survival of test cells (%)
1	123	136	0·91	87	87	136	87
2	120	137	0·88	84	85	135	83
7	100	127	0·79	76	70	128	71
15	116	135	0·86	82	82	119	73
22	117	126	0·93	89	83	111	66
34	72	93	0·78	75	51	97	53
43	61	74	0·83	80	43	87	51
50	60	67	0·90	86	42	79	50
56	51	58	0·88	84	36	72	44
77	28	31	0·90	86	20	49	31
98	6	8	—	—	4	25	13
119	3	—	—	—	—	—	—

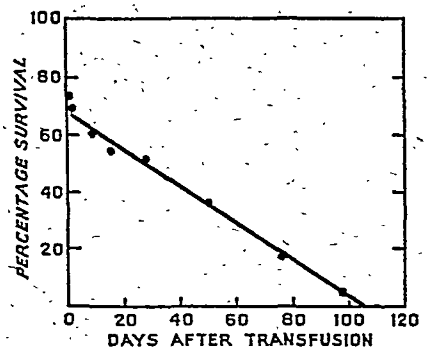

Fig. 3—Survival after transfusion of red cells stored at −79°C for six months and at +4°C for ten days (case 3).

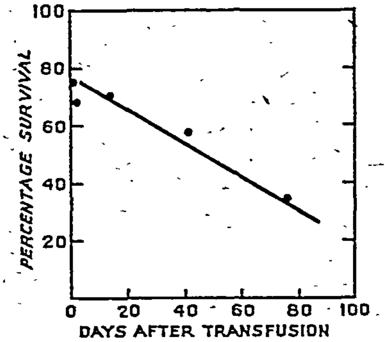

Fig. 4—Survival after transfusion of red cells stored at −79°C for six months and at +4°C for eleven days (case 4).

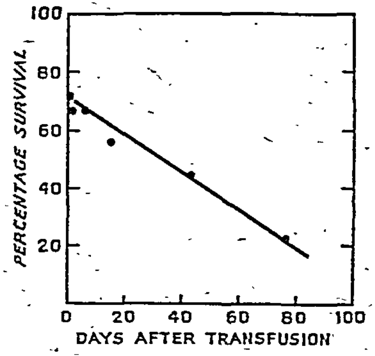

Fig. 5—Survival after transfusion of red cells stored at −79°C for six months and at +4°C for ten days (case 5).

(Day$_n$) could then be expressed as a percentage of this figure.

A correction for fluctuations of plasma volume was made by taking into account the difference on any day between the observed count of control cells and that expected if their number decreased by exactly $^1/_{110}$ a day. (All but one of the recipients were female: in the one male recipient a loss rate of $^1/_{120}$ a day was assumed.) The expected count of control cells on Day$_n$ is thus:

$$\text{Count of control cells, Day}_1 \times \frac{(110 - n)}{110}$$

where n = no. of days after transfusion

Thus an estimate of the absolute survival of the test cells on Day$_n$, as a percentage, is given by the formula:

$$\frac{\text{Observed count of test cells, Day}_n}{\text{Count of test cells equiv. to 100\% survival}} \times \frac{\text{Expected count of control cells, Day}_n}{\text{Observed count of control cells, Day}_n} \times 100$$

RESULTS

Clinical Observations

No febrile reactions were noted after the transfusions. One of the patients developed transient mild urticaria, but in the remainder no untoward effects were observed.

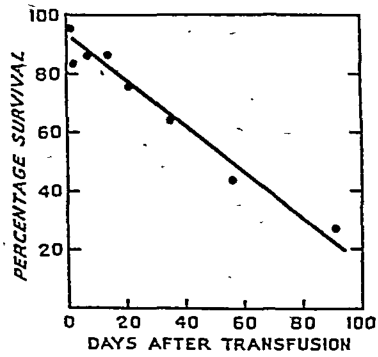

Fig. 6—Survival after transfusion of red cells stored at −15°C for seventy-seven days and at +4°C for ten days (case 9).

Loss of Red Cells during Storage and "Processing"

As previously reported, experiments with small quantities of red cells stored at −79°C have shown that the proportion of red cells recovered after thawing diminishes with time (Sloviter 1952a). In the present experiments with larger quantities of red cells the amount of red cells recovered after storage and processing was in most cases about 50% of the amount originally frozen. There were considerable variations between one batch and another. For example, in the present series the best yield (80%) was obtained from the blood which had been stored the longest time (eight to nine months). Hæmolysis is much greater after storage at −15°C than at −79°C. Thus after twenty-nine days at −15°C the yield was about 50%, and after eighty days about 20%. It must be emphasised that the data presented above relate only to recoveries of cells before transfusion and bear no relation to the results presented below, which deal with the survival in the circulation of those red cells which were transfused.

Survival of Red Cells in Vivo

To illustrate the method of calculation of results, the full protocol of a case is set out:

Case 2.—A man, aged 49, had severe hypochromic anæmia secondary to previous bleeding from gastric ulcer. Hb 6·4 g. per 100 ml. Blood group A, type M. Transfused with previously frozen red cells and with freshly drawn red cells.

Previously frozen red cells.—Group-A type-N blood drawn from donors on June 2, 1951; kept at + 4°C till June 5; then frozen and kept at − 79°C till Dec. 4; then thawed; cells recovered in the usual way and held at + 4°C till Dec. 12, 1951; then transfused. Amount transfused: 275 ml.; red-cell count 2,680,000 per c.mm.

Fresh red cells.—Group-O type-M blood drawn from donor one hour before transfusion; AB substance added. Amount transfused: 227 ml.; red-cell count 3,110,000 per c.mm.

Expected ratio of surviving cells:

$$\frac{\text{No. of test cells transfused}}{\text{No. of control cells transfused}} = \frac{275 \times 2{\cdot}68}{227 \times 3{\cdot}11} = 1{\cdot}044$$

Blank counts.—Before transfusion, when a suspension of the patient's red cells was mixed with an anti-A serum, all but 4000 red cells per c.mm. were agglutinated; with an anti-M serum all but 2000 red cells per c.mm. were agglutinated. These "blank" counts have been subtracted from the results which follow.

Ratio found, Day$_1$ (see column 4, table I):

$$\frac{\text{Count of test cells, Day}_1}{\text{Count of control cells, Day}_1} = \frac{123{,}000}{136{,}000} = 0{\cdot}91$$

Relative percentage survival, Day$_1$ (see column 5, table I):

$$\frac{\text{Ratio found, Day}_1}{\text{Ratio expected}} = \frac{0{\cdot}91}{1{\cdot}044} \times 100 = 87\%$$

Count of test cells expected on Day$_1$, if 100% survived:

$$\text{Count of control cells, Day}_1 \times \text{“Expected ratio”} \left(\text{i.e., } \frac{\text{No. of test cells transfused}}{\text{No. of control cells transfused}}\right)$$

i.e., 136,000 × 1·044 = 142,000 per c.mm.

Absolute survival of test cells, Day$_{50}$, uncorrected (see column 6, table I):

$$\frac{\text{Observed count of test cells, Day}_{50}}{\text{Expected count of test cells, Day}_1} = \frac{60{,}000}{142{,}000} = 42\%$$

Expected count of control cells, Day$_{50}$ (see column 7, table I):

$$\text{Count of control cells, Day}_1 \times \frac{120-50}{120} = 136{,}000 \times \frac{70}{120} = 79{,}000$$

Absolute survival of test cells, Day$_{50}$, corrected (see column 8, table I):

$$\text{Observed survival test cells, Day}_{50} \times \frac{\text{Exp. count control cells, Day}_{50}}{\text{Obs. count control cells, Day}_{50}}$$

$$= 42 \times \frac{79{,}000}{67{,}000} = 50\%$$

Further results are set out in table II and figs. 1–6.

To consider first the post-transfusion survival of red cells stored at −79°C relative to the survival of the

TABLE II—SURVIVAL OF PREVIOUSLY FROZEN RED CELLS AT VARIOUS TIMES AFTER TRANSFUSION, EXPRESSED AS A PERCENTAGE OF THE SURVIVAL OF A CONTROL POPULATION OF FRESHLY DRAWN RED CELLS

(No allowance has been made for the fact that the test cells were stored for 11 days at + 4°C whereas the control cells were freshly drawn; the values in this table should be increased by approximately 10% to allow for this)

Case	Length of storage	frozen red cells survival of freshly ous intervals after transfusion						
		Immed.	1 day	2 days	6–9 days	13–16 days	35–56 days	76–91 days
	Stored @ −79°C							
1	3 months	93	78	71	79	92	96	89
2	6 months	93	87	84	76	82	83	86
3	6 months	78	73	69	66	65	62	56
4	6 months	88	75	70	..	80	90	110
5	6 months	85	72	69	71	66	72	73
6	3 months	..	92	90	..	..	..	..
7	8½ months	82	76	77	71	40	0	..
	Mean (Cases 1–7)		79·0	75·7				
	(Cases 1–5)	87·4	77·0	72·6	73·0	77·0	80·6	82·8
	Stored @ −15°C							
8	29 days	82	77	76	74	..	88	..
9	77 days	100	95	86	92	98	89	*
10	84 days	106	75	70	70	82	91	*
	Mean (Cases 8–10)	96·0	82·3	77·3	78·7	..	89·3	..

* Definite evidence of survival but number of cells too small for accurate estimation of ratio.

control red cells (see table II): immediately after transfusion survival was 78–93%, mean 87%; at twenty-four hours it was 72–92%, mean 79%; in six out of seven cases there was a slight further fall at forty-eight hours, with a mean survival of 76%. Thereafter there was no tendency to fall any further—i.e., the test cells were removed from the circulation at about the same rate as the control cells. In one exceptional case (case 7) both test and control cells were eliminated within sixty days of transfusion (see below).

In the three cases in which blood stored at −15°C was transfused the results were similar to those in blood stored at −79°C (table II). Survival fell from 96% immediately after transfusion to 82% at twenty-four hours, and to 77% at forty-eight hours. Thereafter there was no increased loss of previously frozen red cells relative to that of fresh red cells.

Estimates of the absolute survival of the stored cells in cases 1–5 and 9 are plotted in figs. 1–6. The method of correcting the observed values to obtain estimates for "absolute survival" has already been described. It will be seen that the estimates from forty-eight hours onwards fit straight lines cutting the time axis at about a hundred and ten days after transfusion.

In the one exceptional case (case 7) referred to above, the number of previously frozen red cells fell rather rapidly after about the first week, with the result that at fourteen days the percentage survival was much lower than that of the control. However, the next blood sample taken from the recipient, forty-two days after transfusion, showed that the fresh red cells were also disappearing rapidly; the survival of the previously frozen red cells was now nil, and that of the fresh red cells, relative to their initial concentration, was less than 10%. A sample taken two months after transfusion contained no transfused cells at all. It was now apparent that the abnormality lay in the recipient rather than in the donor, and that the case was very like those described by Loutit et al. (1943), of which some further details were given by Mollison (1951). It is not proposed to discuss the matter further at present, except to say that it seems clear that the rapid disappearance of the red cells in this case was not due to any effects of storage.

DISCUSSION

The post-transfusion survival of the previously frozen red cells is expected to be lower than that of the fresh red cells because the frozen red cells were stored for ten or eleven days at + 4°C in addition to the period of storage in the frozen state. From previous work it may be estimated that the red cells of blood stored in *acid-citrate-dextrose* for ten or eleven days have about a 90% survival at twenty-four hours after transfusion (Gibson et al. 1947, Ross et al. 1947, Mollison and Sloviter 1951).

Another factor which would tend to make the survival values for the previously frozen cells low was the presence of an appreciable number of "ghosts" in the suspension of red cells transfused. These ghosts are not completely removed during the washing of the recovered cells after dialysis. In the present work, in determining the number of previously frozen red cells in the suspension prepared for transfusion, all red cells were counted even when they were ghost-like. It was estimated that less than 5% of the cells were ghosts.

When allowance is made for these two factors (eleven days' storage at + 4°C and the presence of ghosts), it is evident that the expected survival of the previously frozen red cells is about 85%, *if storage in the frozen state* has had no deleterious effect on the cells. The survival of the frozen cells at forty-eight hours after transfusion was in fact 70–90%. It seems therefore that very little, if any, irreversible change takes place during storage at −79°C in those cells which escape lysis. There is good reason to believe that the lysis which occurs during storage and processing is due to physical rather than biochemical processes. Biochemical activity at −79°C is expected to be negligible; and this belief is supported by the observation that those previously frozen red cells which are present in the circulation forty-eight hours after transfusion are capable of a normal life-span. As figs. 1–6 show, the estimates from forty-eight hours onwards, when plotted against time, fall on straight lines cutting the time axis at about a hundred and ten days.

The *advantage of comparing* the survival of one population of red cells with another is well illustrated by case 2 (table I). During the first twenty-two days after transfusion there was no apparent decrease in the survival of either population, owing presumably to shrinkage of the recipient's plasma volume. Confidence in the validity of the results is greatly increased by showing that the survival of one population relative to the other remained constant both during this period and during the subsequent period when the *concentration* of both populations started to diminish. In the present series it was particularly important to have a control population of red cells, since many of the recipients were recently delivered women in whom considerable changes of plasma volume were to be expected. The advantages of a control population are further illustrated by case 7: in this case the bad survival of the previously frozen red cells might have been ascribed to damage during freezing, had it not been possible to show that the same recipient rapidly destroyed fresh red cells.

It is a very interesting feature of the results obtained with red cells stored at −15°C that, although relatively few red cells were recovered after storage, these were capable of a normal life-span. Evidently, if appreciable ageing of the red cells took place at −15°C, cells recovered after storage for eighty days would be expected to be incapable of surviving for as long as a hundred days after transfusion. In fact, as clearly illustrated in fig. 6, those cells which are present in the recipient's circulation twenty-four hours after transfusion disappear at a rate indistinguishable from that of fresh red cells.

Practical Value of Storing Red Cells in Frozen State

At present there are two main obstacles to be overcome before storage of red cells in the frozen state can be of practical value in the field of blood-transfusion. First, a simpler and less time-consuming method for the removal of glycerol from the red cells must be devised, because the technique used in these studies is too cumbersome for general use. The process recently described by Lovelock (1952) may be the answer to this problem. Secondly, a higher recovery of red cells after storage at −79°C must be attained before the expense of storage at this low temperature can be justified. At present, after storage at −79°C for several months the recovery may be as low as 50%, and is even lower after storage at −15°C. However, recent work suggests that it may be possible to improve these yields considerably (Chaplin 1952).

The most important conclusion from the present work is that red cells recovered after storage at low temperatures have a normal post-transfusion survival. Therefore, if the number of cells destroyed by physical processes can be reduced, it may become worth while to store red cells in the frozen state for long periods.

SUMMARY

Human red cells stored in 15% glycerol at −79°C for six months are capable of normal survival after transfusion. When they are stored at −15°C for about eighty days, only a small proportion of the red cells can be recovered after thawing; however, these also have a normal post-transfusion survival. The implications of these observations are discussed.

It is a pleasure to thank Sir Charles Harington, F.R.S., and the Medical Research Council for hospitality to one of us (H. A. S.) at the National Institute for Medical Research; Mr. A. S. Parkes, SC.D., F.R.S., for his continued interest and advice; and Dr. A. A. Miles for his generous help on the bacteriological aspects of the present work. Prof. J. McC. Browne kindly allowed us to make observations upon patients in the department of obstetrics, Hammersmith Hospital, and Dr. J. D. James, director of the North London Blood Supply Depot, again arranged for a supply of suitable donors. We are very grateful to Miss Hal Crawford, B.SC., and Miss Marie Cutbush, B.SC., for much help, particularly in doing a great many of the Ashby counts; and to Miss Rita Lyons for skilful assistance in the freezing and processing of the blood.

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"The Long Vacation is becoming in Cambridge an increasingly busy academic period, so much so that it is popularly, and quite improperly, known as the 'Long Vac. Term.' . . . it is a bad organisation of studies which would turn vacation into term; and it presses hardly upon that hard-pressed creature, the teaching don. It is a vivacious myth, that a don has leisure. He has not—the 'older model' don at least, who actually taught as well as studied and who was a characteristic of the older English universities. The chief importance of the Long was that it made possible his way of life. That it should continue to be possible is vital, for it will be catastrophic if the University is broken up into castes of persons who teach, who research and who administer, each of them exclusively."—*Manchester Guardian*, Sept. 3, 1952, p. 4.

OBSERVER ERROR IN THE INTERPRETATION OF CHEST FILMS*

AN INTERNATIONAL INVESTIGATION

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DURING the last five years there has been an increasing interest in methods of measuring, and if possible reducing, the effect of observer error in fields where its existence had previously been ignored. In particular this is true of medicine, although only in the radiological diagnosis of pulmonary tuberculosis, on miniature and on full-sized chest films, has a detailed investigation been made, and this has been done almost exclusively in the United States. It was clearly shown that radiologists and chest physicians, however well trained, show a considerable inter-observer and intra-observer error (Birkelo et al. 1947, Garland 1949, Yerushalmy et al. 1950). As a result, techniques for reducing these errors were found. It is surprising that this work has evoked so little attention in Great Britain. Recent figures suggest that in British mass miniature radiography the observer error should be studied and techniques for its reduction applied (Stewart and Hughes 1951).

In the measurement of observer error in the diagnosis of other respiratory diseases in chest films the British have been the pioneers. Fletcher and Oldham (1949) have noted how physicians varied in their interpretation of coalminers' films. This naturally led the film readers in the Pneumoconiosis Research Unit to treat their diagnosis of tuberculosis with some suspicion. The American work gave additional cause for anxiety, and it was decided, as a preliminary step, to find out how British observer error compared with the American by reading a short series of films which contained an unknown proportion showing reinfection-type tuberculosis. The British readers had every reason to fear the comparison with their American colleagues, and they were therefore pleasantly surprised to find that their errors were rather less than those published in the United States (Cochrane 1951). It was thought that this might be because the films were easier to interpret than those used by the Americans. Later, it was possible for the British films to be read by some of the American investigators.

TABLE Ia—AMERICAN READERS; DISTRIBUTION OF FILMS ACCORDING TO TUBERCULOSIS CLASSIFICATION

Reader	Tuberculosis positive					Tuberculosis negative
	Active	Inactive			Total	
		Clinically significant	Not clinically significant	Total		
A_1 1st reading	20	3	12	15	35	54
2nd ,,	17	6	8	14	31	58
A_2 1st ,,	26	0	9	9	35	54
2nd ,,	23	1	9	10	33	56
A_3 1st ,,	18	..*	..	10	28	61
2nd ,,	20	..	..	10	30	59
Mean	20·7	2·5†	9·5†	11·3	32·0	57·0
Range	17–26	0–6	8–12	9–15	28–35	54–61

* Reader A_3 did not indicate clinical significance.
† Excluding reader A_3.

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* A similar paper is to be published in the U.S.A. in the near future.

TABLE Ib—BRITISH READERS; DISTRIBUTION OF FILMS ACCORDING TO TUBERCULOSIS CLASSIFICATION

Reader	Tuberculosis positive					Tuberculosis negative
	Active	Inactive			Total	
		Clinically significant	Not clinically significant	Total		
B_1 1st reading	11	11	12	23	39	65
2nd ,,	12	6	10	16	28	61
B_2 1st ,,	19	3	2	5	24	65
2nd ,,	18	5	6	11	29	60
B_3 1st ,,	17	4	7	11	28	61
2nd ,,	17	4	8	12	29	60
B_4 1st ,,	20	5	2	7	27	62
2nd ,,	20	7	2	9	29	60
B_5 1st ,,	5	13	3	16	21	68
2nd ,,	5	14	2	16	21	68
B_6 1st ,,	11	9	3	12	23	66
2nd ,,	8	9	7	16	24	65
Mean	13·6	7·5	5·3	12·8	26·4	62·6
Range	5–20	3–14	2–12	5–23	21–34	55–68

The original set of films was not selected with an exhaustive study in view. A short trial was prepared with the simple objective of comparing directly British and American observer error, and in this it was successful. This paper is presented as a report of these findings.

MATERIAL AND TECHNIQUE

The films used for the trials were 14 × 17 in. survey chest films, taken by a mobile unit on a radiography survey, which were very generously put at our disposal by Dr. Norman Tattersall, then medical director of the Welsh National Memorial Association. We asked Dr. Tattersall to provide about 100 chest films of good technical quality, of which between 5 and 30 should show some sign of reinfection-type tuberculosis. From these, 89 films were selected by another doctor, who did not take part in the trial, as technically adequate, and as containing a suitable proportion of films showing minimal disease. Six readers (see Appendix A) then indicated their interpretation on a prepared form (see Appendix B) so arranged that a *comparison* would be possible of the relative reproducibility of classifications based on the diagnosis of "active" tuberculosis and of "clinically significant"† tuberculosis. Readings were made on two separate occasions and were strictly supervised. The films were then mailed to San Francisco, where three members of the Chest [illegible] arch Committee read the films under [illegible]. Both sets of results were analysed in San Francisco and at the Pneumoconiosis Research Unit; the analyses were then exchanged, and agreement was reached on the basic conclusions.

TABLE IIa—AMERICAN READERS; AVERAGE AND RANGE OF "AGREEMENT" AND "DISAGREEMENT" (SEE TEXT) IN PRESENCE OF TUBERCULOSIS

—	Agreement on presence of tuberculosis	Agreement on absence of tuberculosis	Disagreement	Disagreement as % of all films	Disagreement as % of films called positive at least once
Between pairs of readers (inter-individual)	26·7 (24–32)	50·3 (50–51)	12·0 (6–15)	13·5 (6·7–16·9)	31·0 (15·8–38·5)
Between readings of individuals (intra-individual)	29·7 (27–31)	54·7 (52–58)	4·7 (4–6)	5·2 (4·5–6·7)	13·6 (11·4–16·2)

*Contact between the two groups was made when Dr. C. M. Fletcher, director of the Pneumoconiosis Research Unit, visited San Francisco in March, 1950, and Dr. L. H. Garland, chairman of the Chest Radiological Research Committee, visited the research unit in Cardiff in August, 1950. It became clear, in retrospect of course, that contact would have been more valuable before the readings than after. For instance, the Americans interpreted the phrase "*clinically significant*" differently from the British, and this would have been avoided by previous discussion.

ANALYSIS

A convenient way of measuring disagreement is to take each pair of readers in turn and to enumerate the films on which they agreed and disagreed. The number of films on which there was disagreement, averaged over all possible pairs of readers (15 if there are six readers), may be called the mean disagreement of the group, and it can be expressed as a percentage of either the total number of films or the total of films that were called positive by at least one reader.

Intra-individual disagreement is measured similarly by classifying the pairs of readings by each reader into agreements and disagreements, averaging the disagreements over all the readers, and expressing the results as a percentage of either the total number of films or the total number of films called positive at least once. Evaluation of disagreements in assessment of activity is made in an identical manner. Tables Ia, IIa, and IIIa show the results for the American readers, and tables Ib, IIb, and IIIb for the British readers.

TABLE IIb—BRITISH READERS; AVERAGE AND RANGE OF "AGREEMENT" AND "DISAGREEMENT" (SEE TEXT) ON PRESENCE OF TUBERCULOSIS

—	Agreement on presence of tuberculosis	Agreement on absence of tuberculosis	Disagreement	Disagreement as % of all films	Disagreement as % of films called positive at least once
Between pairs of readers (inter-individual)	22·7 (21–27)	59·4 (53–66)	6·9 (2–13)	7·7 (2·2–14·6)	23·2 (8·7–38·2)
Between readings of individuals (intra-individual)	24·5 (21–27)	60·7 55–68)	3·8 (0–8)	4·3 (0–9)	13·5 (0–22·9)

RESULTS

British readers called a smaller proportion of the films positive for tuberculosis than did the American readers, the mean being 26·4 positives for the British and 32·0 for the Americans (*tables* Ia and Ib). Similarly the British read "active tuberculosis" in 13·6 of films on the average, whereas the Americans placed an average of 20·7 films in this category. However, more "inactive but clinically significant" cases were reported by the British than by the Americans. The mean number of "negative for tuberculosis" cases found by the British readers was 62·6, compared with 57·0 by the Americans.

In conferences between representatives of the two groups, held first in San Francisco and subsequently in Cardiff, it became apparent that American readers tended to emphasise minimal abnormal shadows to a greater extent than did British readers. This may be due to the

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† A film is classified as showing "clinically significant" tuberculosis if, in the opinion of the observer, the shadows in the film are such that he would recommend immediate medical action or that the subject should return for a second film in less than six months. Thus the definition can include films which would be classified as "inactive" in a simple "active/inactive" dichotomy.

TABLE IIIa—AMERICAN READERS; AVERAGE AND RANGE OF "AGREEMENT" AND "DISAGREEMENT" (SEE TEXT) ON ACTIVITY OF TUBERCULOSIS IN FILMS IN WHICH TUBERCULOSIS IS AGREED TO BE PRESENT

—	No. of films agreed to show tuberculosis	Agreement on activity of tuberculosis	Agreement on inactivity of tuberculosis	Disagreement	Disagreement as % of no. agreed to show tuberculosis	Gross disagreement; active tuberculosis v. tuberculosis absent
Between pairs of readers (inter-individual)	26·7 (24–32)	17·3 (16–20)	3·7 (1–7)	5·7 (5–7)	21·2 (15·6–29·2)	2·3 (1–5)
Between readings of individuals (intra-individual)	29·7 (27–31)	19·0 (17–23)	8·7 (7–12)	2·0 (1–3)	6·7 (3·2–11·1)	1·3 (1–2)

TABLE IIIb—BRITISH READERS; AVERAGE AND RANGE OF "AGREEMENT" AND "DISAGREEMENT" (SEE TEXT) ON ACTIVITY OF TUBERCULOSIS IN FILMS IN WHICH TUBERCULOSIS IS AGREED TO BE PRESENT

—	No. of films agreed to show tuberculosis	Agreement on activity of tuberculosis	Agreement on inactivity of tuberculosis	Disagreement	Disagreement as % of no. agreed to show tuberculosis	Gross disagreement; active tuberculosis v. tuberculosis absent
Between pairs of readers (inter-individual)	22·7 (21–27)	8·9 (3–17)	4·9 (2–10)	8·9 (4–15)	39·3 (17·4–71·4)	0·9 (0–2)
Between readings of individuals (intra-individual)	24·5 (21–27)	12·0 (4–18)	9·8 (5–15)	2·7 (1–5)	10·9 (4·2–22·7)	0·5 (0–1)

fact that the three American readers had previously conducted extensive studies on minimal pulmonary lesions and had become aware of the potential significance of very small and faint shadows, especially in surveys of groups, such as nurses and medical students. Conversely, in a comparable but unpublished joint study of some films of coalminers, the British readers would interpret certain minimal radiological changes as "category I pneumoconiosis," whereas the American readers tended to report such films as "negative—within normal limits." In this instance the British observers had been conducting extensive surveys on coalminers, and therefore were on the alert for minimal parenchymal alterations which may later develop into definite pneumonoconiosis.

The mean number of inter-individual disagreements on "tuberculosis present" for the British readers in their first set of readings was 7·7% of all the 89 films, or 23·2% of those films which were ever read as showing tuberculosis (table IIb). These figures are lower than those obtained from the American readings, which were 13·5% and 31·0% respectively (table IIa). The intra-individual comparisons, however, were about the same in both groups. The American readers showed inconsistency between their first and second readings on 5·2% of the films, on the average, and the British figure was 4·3%.

Inter-individual disagreement on activity (first readings only) was surprisingly low, but higher for the British readers than for the Americans (tables IIIa and *b*). The mean number of disagreements on activity was 8·9, or 39·3% of the films agreed to show tuberculosis, for the British, compared with 5·7 or 21·2% for the Americans. The inter-individual disagreements were also somewhat greater for the British, with a mean of 2·7 or 10·9%, compared with 2·0 or 6·7% for the Americans. There were fewer complete disagreements—i.e., one reader reporting "active tuberculosis" while the other reported "tuberculosis absent"—by the British readers; the average was 0·9 for such disagreements for pairs of readers and 0·5 comparing each reader with himself. The corresponding American figures were 2·3 and 1·3.

It is a point of interest for British readers that the observer error, when the films are classified on the one hand as "clinically significant" including "active" and "inactive, but clinically significant," and on the other hand as "inactive," is much less than when they are classified simply as "active" and "inactive." This does not hold for American readers, and the reason for this finding among the British readers is obscure; but, if it holds generally in Britain, the adoption of this method of classification might assist in introducing some order into the present chaos in the field of tuberculosis terminology, as well as helping to achieve consistent and

TABLE IV—ANALYSIS OF FILMS ON WHICH BRITISH AND AMERICAN READERS DISAGREED

Film no.	Readings during trial (1st and 2nd occasions)		Comments at joint conference*	Conclusion
	British readers	American readers		
1	12 tuberculosis negative†	3 tuberculosis negative; 3 tuberculosis positive, inactive	Questionable small scar at right first space, laterally (A), negative (B)	Understandable difference of opinion on significance of a small opacity; no major disagreement
2	12 tuberculosis negative	2 tuberculosis negative; 4 tuberculosis positive, inactive	Questionable density right first space, laterally (A), negative (B)	No major disagreement
3 & 4	12 tuberculosis negative	2 tuberculosis negative; 4 tuberculosis positive, inactive (calcified hilar nodes)	Calcified nodes (A), negative (B)	No major disagreement; American readers coded the nodes; British did not
5	6 tuberculosis negative; 3 tuberculosis positive, active; 2 tuberculosis positive, inactive but clinically significant; 1 tuberculosis positive, inactive, not clinically significant	4 tuberculosis negative; 1 tuberculosis positive, active; 1 tuberculosis positive, inactive	Faint opacity left first space, possibly active (A), possible lesion (B)	Difficult case with probable minimal lesion and inevitable difference of opinion among different observers; both groups of readers diverged; no significant international disagreement
6	9 tuberculosis negative; 2 tuberculosis positive, active; 1 tuberculosis positive, inactive, but clinically significant	1 tuberculosis negative; 2 tuberculosis positive; 2 tuberculosis positive, inactive, but clinically significant; 1 tuberculosis positive, inactive and not significant	Lesion, right second rib, dense and probably obsolete; adjacent lesion right second space, soft (active) (A); negative except for healed primary (B)	Difficult case with small soft lesion overshadowed by adjacent small dense one; subsequent review by independent British consultant reported "positive and significant"

* A, American; B, British. † That is, of 12 readings, all were recorded as negative.

reproducible diagnosis. A statistical argument in support of this conclusion is given in Appendix C.

In cross-comparison between British and American readers, first readings alone being used, it was found that of 52 cases called tuberculosis negative unanimously by the British, 42 were also called negative unanimously by the American readers, 6 were called tuberculosis positive by one American reader, and 4 were called tuberculosis positive by two American readers. The 6 films over which major disagreement was apparently occurring were subsequently studied at a joint conference at Cardiff, with the results outlined in table IV. In 5 cases there proved to be no major disagreement; in 1 case there was disagreement on the interpretation of a rather difficult lesion.

CONCLUSION

No considerable difference existed between American and British readers in the accuracy with which they read the films. The greater accuracy with which the series was read, compared with that found in earlier American trials, must have been due to the series as a whole being easier. On the whole it appears that the results of the more detailed American studies already published could be applied to the work of British readers. There is no doubt that the application of their findings would be entirely beneficial.

SUMMARY

Following American work on inter-observer and intra-observer errors in the radiological diagnosis of tuberculosis, a small-scale test of these errors was made by six British readers. Rather smaller errors were found than had been expected.

The films were then sent to a group of radiologists in the U.S.A. Their errors were of a similar magnitude to those of the British group.

The difference from previous results is most probably due to a rather easier group of films having been chosen, and it is concluded that observer error in the radiological diagnosis of tuberculosis should be reduced by application of the methods already fully developed in the United States.

We wish to thank the teams of readers who provided the data, and the statisticians who did the analyses, especially Mr. Oldham, who provided Appendix C.

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Appendices

A.—COMPOSITION OF READER PANELS

The American group consisted of the following three radiologists:

L. H. Garland, M.D., clinical professor of radiology, Stanford University.

E. R. Miller, M.D., associate professor of radiology, University of California.

M. A. Sisson, M.D., clinical instructor in radiology, Stanford University.

The British group consisted of the following members:

L. R. West, M.D., M.R.C.P., consultant physician, Sully Hospital, South Wales.

K. J. Mann, M.D., M.R.C.P., D.P.H., member of the scientific staff of the Medical Research Council.

A. L. Cochrane, M.A., M.B., D.P.H., member of the scientific staff of the Medical Research Council.

V. H. Springett, M.D., Prophit scholar, Royal College of Physicians of London.

I. Davies, M.D., M.R.C.P., D.P.H., member of the scientific staff of the Medical Research Council.

T. W. Davies, B.SC., M.B., B.CH., D.P.H., consultant chest physician to South Wales Regional Hospital Board.

B.—FORM USED FOR CLASSIFICATION OF FILMS

X-ray no.	*Tb absent*	*Tb present*	*Active*	*Inactive stable*	*Of clinical significance*
W5092405	+	..	..	..	..
W0060938	..	+	..	+	+
5091717	..	+	+	..	..
5091760	+	..	..	..	..
0123149	..	+	..	+	..
&c.					

Each observer was asked to place a mark in the appropriate column or columns opposite the reference number of each film.

C.—RELATIVE MERITS OF DIFFERENT WAYS OF READING TUBERCULOSIS

P. D. Oldham
M.A. Oxfd
MEMBER OF PNEUMOCONIOSIS RESEARCH UNIT

In the trial whose results are reported here the readers were required to classify each film under one of the following headings:

A, tuberculosis absent.
B, tuberculosis present, active, and clinically significant.
C, tuberculosis present, inactive, but of clinical significance.
D, tuberculosis present, but inactive and of no clinical significance.

It is more customary to divide films into only two classes, but there is disagreement about where the dividing line is to be drawn. It usually lies between one or other pair of the headings given above, and systems that have been used are three:

(1) tuberculosis present or absent (A or B, C, D).
(2) tuberculosis active or inactive (B or A, C, D).
(3) clinically significant or not significant tuberculosis (B, C or A, D).

The results obtained from the British readers can be used to throw some light on the relative merits of these three systems.

By means of the technique known as analysis of variance, numerical results in a table with multiple headings can be analysed to show the significance of average differences between the different headings. In a table giving the results of multiple tests given to multiple observers the analysis could break down the total variance of the observations into sections corresponding to differences between the observers, differences between the tests, and a remainder. The ratios of the first and second of these to the third represent a measure of the success of the first and second headings in explaining the variation of results throughout the table. If we were to apply this technique to the results obtained from the British readers, our subdivisions of the variance would correspond to differences between the six observers and differences between the 89 films, with a remainder. A large ratio between the first and third could indicate a large inter-observer error, and a large ratio between the second and third, large differences between films. Clearly we would like the results to make the first ratio small and the second large.

The results actually obtained were of course not numbers but the classification referred to as A, B, C, and D above. We can nevertheless carry out the analysis of variance procedure in algebraic terms, the subdivisions of the variance emerging as quadratic expressions in A, B, C, and D. The three possible groupings to be examined can then be introduced by putting

(1) $A = x$, and $B = C = D = y$,
(2) $B = x$, and $A = C = D = y$, and
(3) $B = C = x$, and $A = D = y$.

The observer-error ratio and the film-difference ratio can then be calculated for each suggested grouping in turn, and these ratios will not contain x and y. Thus we may at once examine the merits of the different groupings as revealed by the size of the ratios. They are:

	System 1	2	3
Observer error	7·93	16·74	6·44
Film differences ..	56·50	22·04	65·80

It can be seen at once that system 2, corresponding to reading active tuberculosis only, is the worst. Systems 1 and 3 are very similar, but system 3 shows slightly smaller observer error and slightly better discrimination between different films. We may conclude that on the evidence of the British readings the best results would be obtained if films were classified on the basis of their clinical significance, though the system in which the criterion is the presence or absence of any kind of tuberculosis is almost equally good.

PRODUCTION OF HEPATITIS IN MICE BY THE COMBINED ACTION OF TWO FILTERABLE AGENTS

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A previous publication (Gledhill and Andrewes 1951) gave an account of the isolation from one strain of mice (P. mice) of a virus which caused fatal hepatitis in recently weaned mice of another strain, V.S. Rockefeller (Webster 1937). This mouse-hepatitis virus (M.H.V.) has been isolated from the blood and viscera of more than 50% of normal adult P. mice by 1–6 blind passes in just-weaned V.S. mice. Such passes were made at 7-day intervals with suspensions of liver and other viscera which were injected intraperitoneally. The disease in V.S. mice was prevented by aureomycin or terramycin when these were given not later than 48 hours after inoculation of the virus. Arising out of investigations into the action of terramycin in preventing mouse hepatitis, we made the rather bizarre discovery that the virus causing the disease could be resolved into two agents, each capable of being serially transmitted in susceptible mice. Either one alone rarely produced symptoms or lesions in the mice; yet together they gave rise to the typical disease. Mice infected either with the mixture or with the original M.H.V. died in 4–10—usually 5–7—days after infection when the dose was large. Their livers were necrotic, either uniformly yellow or, more often, strikingly mottled; their spleens were enlarged, the urine was dark, and there was sometimes visible jaundice. After smaller doses the liver damage might occur without death.

METHODS

The techniques used were similar to those described by Gledhill and Andrewes (1951) except that liver and spleen were used as the source of virus in place of liver and kidney. Suspensions and dilutions were made in 10% horse-serum broth with or without an equal volume of saline. The inoculum per mouse for all dilutions was 0·2 ml. given intraperitoneally. Terramycin (2 mg. per ml.) suspended in 5% gum acacia was given subcutaneously in a dose of 0·5 ml. V.S. mice weighing 8–10 g. were used for the experiments to be described.

RESULTS

Discovery of 'S.,' the Stable Component of M.H.V.

In our experiments with terramycin, we found that mice were protected by a single dose of the antibiotic given on the same day as a large dose of M.H.V. (more than 10^3 L.D.$_{50}$). Such a dose of terramycin had no effect when given 24 hours before the virus. It was next observed that mice treated with M.H.V. and terramycin on the same day became refractory to challenge with a large dose of M.H.V. 2 or more days later. In table I an experiment is recorded in which groups of mice were challenged with M.H.V. 1, 2, and 3 days after treatment with M.H.V. and terramycin on day 0; the controls of each group received terramycin only on day 0, followed by the challenge dose of M.H.V. 1, 2, and 3 days later respectively. It will be seen that mice show some refractoriness as early as 24 hours after the M.H.V.-terramycin treatment.

It appeared to us that the refractory state of the mice could possibly be induced by M.H.V. which had been rendered incapable of multiplying by the action of the terramycin. This possibility we showed to be improbable by the type of experiment (table II) in which groups of mice were challenged 8 days after receiving terramycin and falling tenfold dilutions of M.H.V. Since high dilutions of M.H.V. given on the same day as terramycin induced the refractory state, it seemed unlikely to be due to a non-multiplying agent. The rapidity of induction of the resistance suggested that we might be dealing with interference rather than with true immunity, and we therefore wondered whether an avirulent terramycin-resistant variant of M.H.V. could be interfering with the development of the fatal infection.

To test this possibility we killed, on the 5th day, mice which had received M.H.V. and terramycin, and passed liver-spleen extract to other mice, with a view to challenging them later. The unchallenged controls as well as the challenged mice developed hepatitis. When, however, we repeated the experiment giving five daily doses of terramycin, we harvested an extract which was not lethal to mice, yet which made them refractory to challenge 3 or 5 days later. We maintained the avirulent agent for five passes by treating daily with terramycin the pass mice injected with virus. This type of experiment was repeated a number of times with satisfactory results. In one such experiment in which five serial passages were carried out, the mice received a dose of 1 mg. terramycin on the third and again on the fourth day after injection with virus. At each passage another group of mice received virus but no terramycin; these mice were challenged as shown in table III. It will be seen that the mice which received extract and no terramycin at each pass and were challenged 3 and 5 days later mostly survived, whereas nearly all the controls of the challenge virus died. In some experiments the challenge controls received liver-spleen extract from normal V.S. mice, but such were not significantly protected against challenge. If, however, several passes of avirulent virus were made in mice untreated with terramycin, especially if these were made at 7-day intervals, virulent M.H.V. reappeared in some series. Nevertheless we had

TABLE I—PROTECTIVE EFFECT OF M.H.V. AND TERRAMYCIN AGAINST CHALLENGE WITH 1000 L.D.$_{50}$ OF VIRUS

Inoculum	Time of challenge (hours)	Mortality ratios
Terramycin	24	5/5*
	48	5/5
	72	6/6
Terramycin + 1000 L.D.$_{50}$ M.H.V.	24	6/8
	48	0/6
	72	0/4

*5/5 indicates that 5 out of 5 challenged mice died.

TABLE II—EFFECT OF TERRAMYCIN ON MOUSE-HEPATITIS VIRUS

Inoculum	Mortality ratios* at dilution				
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Virus only	5/5	5/5	5/5	5/5	5/5
Virus + terramycin	0/5	0/5	0/4	0/5	0/5
Virus + terramycin challenged on 8th day by approx. 1000 L.D.$_{50}$	0/5	0/5	0/4	1/5	2/5

* Includes mice sacrificed with typical lesions.

TABLE III—RESULTS OF CHALLENGING MICE PREVIOUSLY INJECTED WITH TERRAMYCIN-RESISTANT VIRUS

No. of pass	Days between injection and challenge	Dilution of virus used to immunise	Mortality ratio	
			Challenged group	Control group
2	3	10^{0}	3/5	6/6
3	5	10^{0}	0/6	5/6*
4	5	10^{-2}	0/5	5/6

* 5/6 = death from hepatitis in 5 out of 6 mice.

passed an avirulent but immunising agent sufficiently often to feel moderately confident that our working hypothesis was correct in that we had a transmissible terramycin-resistant agent distinct from M.H.V. Later we found that an agent in no way distinguishable from this could be obtained much more conveniently by allowing M.H.V. tissue extracts to stand on the laboratory bench overnight at about 20°C. This we called "S." because of its relative stability on standing.

Discovery of "L.," the Labile Component of M.H.V.

One doubt remained: could the transmissible immunising agent consist after all of M.H.V. kept down by terramycin to a low level at which it could not produce disease? To test this possibility groups of mice were infected with virulent M.H.V. at dilutions higher than the lethal dilution and challenged several days later to see if they had become refractory; an example of such an experiment is shown in table IV. It was found that mice treated in this way not only did not become refractory but, when challenged several days later, died more quickly than controls. Thus, in table V, the challenged controls died in a mean of 5·9 days as against 4·4 days for the mice which received the double inoculation. The difference between these averages in this single experiment is statistically significant, owing to the small variability in the times of individual deaths. Amongst other experiments carried out when seeking an explanation of this finding, we injected mice which had received a sublethal dose of M.H.V., with S., the avirulent agent obtained from terramycin-treated mice. These mice died of M.H.V. hepatitis whereas the controls did not. Such an experiment is illustrated in table V. Experiments of this kind were successful whether the S. component was mixed with sublethal dilutions of M.H.V. or injected as long as 5 days later.

The high-titred labile component (L.) was obtained from M.H.V. without difficulty by passing at 3-day intervals M.H.V. diluted 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} and finding the highest dilution producing hepatitis when mixed with the S. component; we hoped by this limiting dilution method to identify a preparation free from S. L. so obtained was propagated by passing it alternately undiluted and diluted 10^{-7} at 3-day and 4-day intervals.

Passage in Mice of S. and L. and their Recombination

Many of our earlier experiments gave inconclusive results because we could not guarantee that supposedly pure L. and S. would not kill a few mice. Thus in one such experiment 1 of 25 mice used in six serial passes of "L." died with hepatitis, and 5 of 30 mice died in the course of six serial passes of S.; by contrast, 27 of 27 died when L. and S. were recombined. More recently the method of passing L. twice weekly and diluting 1 : 10^{7} at every other pass has given us L. preparations which have killed none out of 46 mice in the course of twenty-two passes. If, however, such L. is passed at 7-day intervals in V.S. mice without any diluting, hepatitis due to M.H.V. has appeared, for by such a method S. can be picked up from V.S. mice and the virulent combination reconstituted. Similarly by a limiting dilution method we have now obtained from M.H.V. suspensions allowed to stand, an S. preparation which is perhaps pure as no specific deaths have occurred amongst 36 V.S. mice used in six passes. Deliberate recombination of these "pure" L. and S. lines produced fatal hepatitis in 100% of mice: this has occurred after five passes of pure S. and twenty-two passes of pure L.

TABLE IV—POTENTIATING EFFECT OF SUBLETHAL DOSES OF M.H.V. ON SUBSEQUENT CHALLENGE

Dilution of inoculum	Challenge L.D.$_{50}$	Mortality ratio	Average survival-time (days)
10^{-6}	Nil	1/10	6
10^{-6}	1000 (approx.)	10/10	4·4
None	1000 (approx.)	11/11	5·9

Properties of L. and S.

L. seems harmless even to newborn mice. S., on the other hand, will produce hepatitis, often fatal, in mice up to about 1 week of age. Passage from livers of these baby mice yields only S., not the complete M.H.V.

The filterability of L. and S. is still under investigation. S. has several times been passed through a gradocol membrane of 250 mμ average pore diameter (A.P.D.); on one occasion we failed to pass it through one of A.P.D. 110 mμ. L. seems to be somewhat larger; it has passed through a membrane of 350 mμ A.P.D. but failed to pass through one of 250 mμ A.P.D. M.H.V. itself was shown to pass through a membrane of 300 mμ A.P.D. but, like L., not through ones of 250 mμ A.P.D. (Gledhill and Andrewes 1951).

TABLE V—EFFECT OF S. UPON MICE PREVIOUSLY INFECTED WITH SMALL DOSES OF M.H.V.

1st intraperitoneal inoculation	2nd intraperitoneal inoculation 72 hr. later	Mortality ratio	Average survival-time (days) of mice which died
M.H.V. 10^{-6}	..	2/16	8·5
..	S	0/3	..
M.H.V. 10^{-6}	S	6/6	5·0

It is possible to measure the L.D.$_{50}$ of extracts of L. for a constant dose of S. and, likewise, the L.D.$_{50}$ of S. for a constant dose of L. This has been done on several occasions for L. (S. constant) and gave values of between 10^{-7} and 10^{-9} ml. as against 10^{-4} to 10^{-6} ml. for M.H.V. itself. The L.D.$_{50}$ of S. (L. constant) gave values of 10^{-3} to 10^{-4} ml.

L. and S. are both inactivated by heating to 56°C for 30 min.; and by treatment with 20% ethyl ether overnight at +2°C.

DISCUSSION

The experiments reported above are readily reproducible: their interpretation is far from clear. It is uncertain whether L. and S. are two unrelated viruses or whether they are alternative phases of one virus. A third, much less likely, possibility is that M.H.V. is a real entity, not merely a mixture of L. and S., and that L. and S. are variants of it. Our discovery that two components could be obtained from M.H.V. depended upon several fortunate chances, particularly the susceptibility of L. but not S. to terramycin. The demonstration that a virus can be so split may lead others to examine other virus infections from this point of view; if the possibility is not in mind, such a complex ætiology might long be overlooked. Plant pathologists are familiar with the idea that two relatively innocuous viruses may, when they co-exist in a plant, produce a serious disease: the infection of tomatoes by a combination of potato virus X and tobacco mosaic is an example (Bawden 1946).

It seems probable that L. is carried in the blood and tissues of a majority of P. but not V.S. mice. S. is probably carried by both breeds; but if it were present in only a small proportion of V.S. mice one could readily account for the varying number of blind passes necessary to produce hepatitis in the serial passage technique we have used (P.→V.S.→V.S. . . . &c.). Such a state of affairs would account for our failure to keep L. permanently pure and avirulent when passed in V.S. mice, except by the help of special precautions.

The production of hepatitis by inoculating blood of normal mice into other normal mice is an occurrence having obvious possible analogies with homologous-serum jaundice in man. M.H.V. is much more labile than the human virus, but the S. component is fairly stable, though even it does not resist 20% ether nor exposure to 56°C for half an hour: it is also a small virus, though its size has not yet been determined accurately.

The mechanism whereby these two agents act synergically to produce a fatal disease is still under investigation.

SUMMARY

Further work is reported concerning a virus causing fatal hepatitis in mice. This was obtained by taking blood or viscera or normal mice of one strain (P.) and making serial intraperitoneal passages in young mice of another strain (V.S.). The hepatitis could be prevented by a single dose of terramycin or aureomycin.

The mouse-hepatitis virus (M.H.V.) has now been resolved into two components, one relatively stable (S.) and one more labile (L.). S. is obtained from mice inoculated with M.H.V. and treated by terramycin, to which it is resistant; or by allowing suspensions of M.H.V. to stand at about 20°C for 24 hours; the L. then dies out. L. is present in M.H.V. suspensions to higher titre than S. and is obtained by passage at limiting dilutions. Neither L. nor S. when given separately to recently weaned V.S. mice produces any evident disease; when given together they cause fatal hepatitis. L. and S. are both transmissible in series and are presumably viruses—either separate entities or, less probably, phases or variants of one virus. S. is apparently smaller than L.

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THE DIAGNOSTIC VALUE OF ESTIMATIONS OF PROTEIN-BOUND IODINE IN SERUM

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THE blood-iodine level was estimated as long ago as 1900, by Gley and Bourcet, and numerous techniques have been introduced for its measurement since then; but it is only within the past ten years that reliable methods have become available for clinical purposes. Practically all the work in this field has been done in America, and very little has been written about it in this country. The subject is fully reviewed by Rapport and Curtis (1950).

NATURE OF BLOOD-IODINE

The blood-iodine is predominantly bound to the plasma-proteins: 75% of it is present in the albumin fraction; some of it is found in the α-globulin fraction, and a smaller amount in the β-globulin fraction; but the γ-globulins play no part in binding iodine. The inorganic iodine content of the blood is usually negligible, but it varies considerably with the iodine content of the diet and is greatly increased by the administration of iodides (Bassett et al. 1941, Riggs et al. 1942, Taurog and Chaikoff 1948).

There is considerable evidence that the amount of protein-bound iodine in the serum is an index of the amount of circulating thyroxine, as shown by its chemical behaviour and by experiments with radioactive iodine (Chaikoff et al. 1947, Taurog and Chaikoff 1948).

MATERIAL AND METHODS

The series reported here consists of estimations of the level of protein-bound iodine in the serum of 30 normal people and 375 hospital patients. In 317 cases the basal metabolic rate (B.M.R.) was also estimated, and in 243 cases the serum-cholesterol level was determined.

The level of protein-bound iodine in the serum was estimated by the method of Barker (1948); 10 ml. of blood was collected at any convenient time of the day, with no particular time-relationship to meals. Barker's method is very sensitive and 0·01 µg. of iodine may be estimated relatively easily.

The apparatus was modified slightly by Mr. R. A. Adams who introduced a stoppered side-arm just below the condenser, so that sodium-sulphite solution could be introduced into the trap without disturbing the condenser. Our experience with the method agrees well with Barker's, but the following comments should be made: (1) our recoveries of iodine from thyroxine, added before digestion, were about 100% rather than 90%; we do not therefore make any correction for losses during distillation; and we believe that different stills vary slightly in efficiency; (2) The grade of sulphuric acid mentioned by Barker does not seem to be available in this country; in our experience the purity of this reagent is the most important factor in the attainment of low blank values; the most satisfactory grade that we have tried is the 'M.A.R.' grade of Messrs. Hopkins and Williams; this should be boiled with hydrochloric acid, as described by Barker, for at least two hours on the same day as the estimation is made.

The serum-cholesterol level was estimated by the method of Bloor (1916). In practically every case the levels of serum-cholesterol and protein-bound iodine were estimated on the same sample of blood.

The B.M.R. was determined by the method of Robertson (1944). A Kendrick apparatus was used. Estimations were made both on outpatients and on inpatients, and the subject rested for half an hour before each test. Two recordings of ten minutes each were made consecutively in all cases, a trial reading having been made on the preceding day in those cases in which the patient had not previously been tested. In most cases agreement between the two consecutive readings was within 5%. The B.M.R. was determined, so far as possible, on the same day as blood was taken for the estimations of cholesterol and protein-bound iodine, usually within a few days, and always within a week.

All the estimations of protein-bound iodine in the serum that were made in the past two years have been recorded here, except that we have only included those in which satisfactory duplicate readings were obtained, and that we have excluded cases of thyroid disorder in which previous treatment has prevented an adequate assessment of the thyroid state.

NORMAL RANGES

We obtained a range of 4–8 µg. per 100 ml. of serum for protein-bound iodine in 30 normal people, with a mean of 5 µg. per 100 ml. The duplicate determinations usually agreed to within 1 µg. per 100 ml., and the result was not accepted if they differed by more than this amount. Consequently the results have been expressed to the nearest microgramme, the decimal points being ignored. Most other workers have also found a normal range of about 4–8 µg. per 100 ml.

Though we found a range of 4–8 µg. per 100 ml. in normal healthy people, some patients who were clinically euthyroid showed levels as low as 3 µg. per 100 ml., and a few gave figures even lower than this. The lower level is therefore indefinite, and only figures of less than 3 µg. per 100 ml. can be regarded as abnormally low. On the other hand, the upper limit of normal in our series was remarkably well defined; any figure exceeding 8 µg. per 100 ml. could be regarded as significantly high.

The normal range of serum-cholesterol levels determined in our laboratories is 150–350 mg. per 100 ml. (Foote and Merivale 1949); a wider range than is usually recognised.

Our normal range for the B.M.R. is from 0 to −20%. The reason for this difference from the usually accepted range (from +10% to −10%) is probably that the Du Bois standards of height-weight-surface area and oxygen consumption per unit of surface area are calculated from American and not British people.

LIMITATIONS AND SOURCES OF ERROR IN DETERMINATION OF PROTEIN-BOUND IODINE IN SERUM

Administration of Iodine Compounds

The level of protein-bound iodine in the serum may be increased by iodine from various extraneous sources. If meticulous care is taken to exclude traces of iodine from the apparatus, the only important source of confusion is the previous administration of iodine to the patient. Small amounts of inorganic iodine should be eliminated from the serum by repeated and careful washings during the estimation. If large amounts of inorganic iodide are administered, iodine compounds are formed, which are apparently adsorbed on to the serum-proteins and increase the level of protein-bound iodine. This increase may persist for a week after the iodine therapy has been discontinued, and outlasts the rise in inorganic-iodide level in the serum; the thyroxine level is, however, not increased (Bassett et al. 1941, Salter 1947, Danowski and Greenman 1949, Danowski et al. 1950a and b, Starr et al. 1950).

The administration of organic iodine compounds is particularly likely to increase the amount of protein-bound iodine in the serum. This effect may persist for as long as three months or even a year after a cholecystogram (Riggs 1947, Starr et al. 1950), and for as long as five years, and even perhaps permanently, after the intrathecal injection of 'Lipiodol' (Hallman et al. 1951). The level of protein-bound iodine in the serum may also be raised after bronchography or salpingography, or after the injection of sinus tracts with lipiodol. Pyelography may have similar effects, but they are much more short-lived, since the iodine compound is rapidly excreted in the urine and disappears within 1–4 weeks (Riggs 1947, Starr et al. 1950, Hallman et al. 1951).

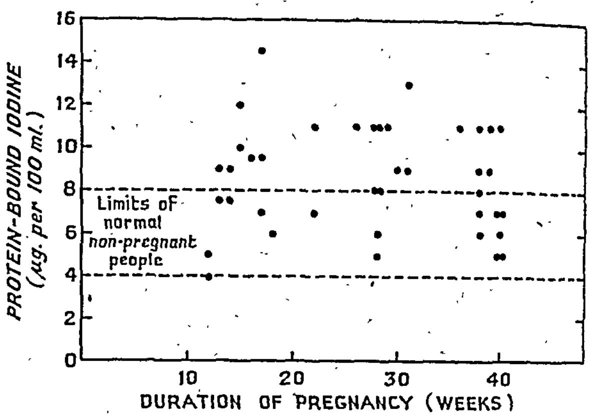

Fig. 1—Levels of protein-bound iodine in serum of 41 normal pregnant women.

Pregnancy

The protein-bound iodine in the serum was estimated in 41 healthy women with normal pregnancies. 22 (54%) of these showed levels exceeding 8 µg. per 100 ml. between the thirteenth and last weeks of pregnancy. The range of values was 4–20 (mean 8·8) µg. per 100 ml. (fig. 1). Similar findings have been made by other workers, who have found that the level may be raised as early as six weeks after conception (Man et al. 1951). It is interesting, in this connection, that the B.M.R. is also raised in normal pregnancy.

RESULTS

The values obtained for protein-bound iodine and cholesterol in the serum and for the B.M.R. in various disorders are recorded in the accompanying table and fig. 2.

Hyperthyroidism

The level of protein-bound iodine in the serum was raised in only 61% of the cases, whereas the B.M.R. was raised in all the cases. The serum-cholesterol level was reduced in only 11% of the cases. Each case was carefully assessed on clinical grounds (resting pulse-rate; tem-

COMPARISON OF LEVELS OF PROTEIN-BOUND IODINE AND CHOLESTEROL IN SERUM AND B.M.R. IN VARIOUS CONDITIONS

Clinical diagnosis	No. of cases tested	Protein-bound iodine (µg. per 100 ml.) >8 (No. of cases)	3–8 (No. of cases)	<3 (No. of cases)	Range	Mean	No. of cases tested	Basal metabolic rate (%) >0 (No. of cases)	From 0 to −20 (No. of cases)	< −20 (No. of cases)	Range	Mean	No. of cases tested	Serum-cholesterol (mg. per 100 ml.) <150 (No. of cases)	150–350 (No. of cases)	>350 (No. of cases)	Range	Mean	Agreement with clinical diagnosis (%) Protein-bound iodine	B.M.R.	Cholesterol
Non-toxic goitre	59	1	53	5	1–11	5·4	43	2	39	2	−24 to +6	−9	37	1	31	5	140–422	266	81	90	86
Hyperthyroidism	64	39	25	0	4–20	10·2	53	53	0	0	+5 to +65	+23	54	6	48	0	109–328	202	61	100	11
Borderline hyperthyroidism	28	12	14	2	2–20	7·4	23	15	8	0	−17 to +37	+5	17	1	15	1	120–400	235	..	..	..
Myxœdema	9	0	1	8	0–3	1·2	9	0	0	10	−24 to −47	−31	9	0	4	5	160–530	391	89	100	56
Doubtful hypothyroidism	9	0	8	1	2–6	4·1	8	1	3	4	−26 to +8	−17	9	0	7	2	231–490	317	..	..	..
Panhypopituitarism ..	3	0	0	3	2	2	3	0	0	3	−31 to −45	−36	3	0	1	2	315–420	381	..	..	..
Anxiety state	13	2	9	2	1–18	5·3	5	0	5	0	−10 to −19	−14	6	0	6	0	214–275	211	69	100	100
Acromegaly	6	1	5	0	3–22	7·2	6	3	2	1	−21 to +11	−2	5	0	5	0	200–400	271	..	..	..
Obesity	51	1	48	2	2–11	5·1	24	0	17	7	zero to −34	−16	17	1	12	4	114–450	241	..	..	..

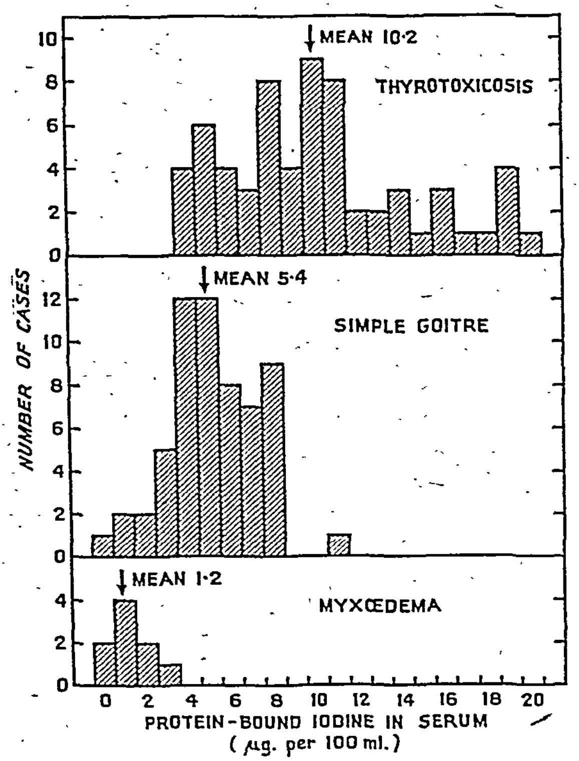

Fig. 2—Distribution of levels of protein-bound iodine in serum in various thyroid disorders.

perature and moisture of the skin; presence or absence of tremor, exophthalmos, or lid retraction; and response to treatment with iodine, thiouracil, or thyroidectomy) and, in surgical cases, by the histology of the thyroid gland. We have included in this group only those cases in which a diagnosis of the hyperthyroidism was established beyond doubt on the basis of these criteria.

In 2 cases with normal initial levels of protein-bound iodine the levels were found to be raised some weeks later, even though both patients had been treated with thiouracil during that period. It is likely that other cases would have shown similar fluctuations if repeated estimations had been made. Random estimations during anti-thyroid treatment gave varied results (fig. 3).

Non-toxic Goitre

The amount of protein-bound iodine in the serum was normal in 81% of the cases, the B.M.R. normal in 90% of the cases, and the serum-cholesterol level normal in 86% of the cases. Apart from the single raised value of protein-bound iodine included in the table, 2 other cases showed raised values attributable to the recent administration of iodine. The finding of levels below 3 µg. per 100 ml. in 8% of the cases is difficult to explain; none of these cases showed any other evidence of hypothyroidism.

Borderline Hypothyroidism

In many of the cases the amount of protein-bound iodine in the serum and the B.M.R. were not in agreement. The B.M.R. was estimated in 11 of the 12 cases with increased amounts of protein-bound iodine, and in only 6 of these was it increased; in only 5 of the 15 cases with a raised B.M.R. was the amount of protein-bound iodine in the serum increased. Since the B.M.R. was increased in all the cases of undoubted hyperthyroidism and was normal in 90% of the cases of non-toxic goitre, and since the amount of protein-bound iodine in the serum was increased in only 61% of the cases of proved hyperthyroidism and was normal in only 81% of the cases of non-toxic goitre, we place more reliance on the B.M.R. in the diagnosis of borderline cases.

Myxœdema

The level of protein-bound iodine in the serum and the B.M.R. was compatible with the diagnosis in all the cases, except one in which the level of protein-bound iodine was in the low normal range (3 µg. per 100 ml.). In another case two separate readings of 0 and 3 µg. per 100 ml. were obtained before treatment was started. The serum-cholesterol level was raised in only 56% of the cases. In another case, not included in the table, the amount of protein-bound iodine in the serum was 15 µg. per 100 ml. This patient had received several courses of thyroid extract in the past, but had had to discontinue the treatment each time after a week because she could not tolerate it. She had received no thyroid treatment since a year before the estimation was made; at that time she had been given crystalline thyroxine 0·2 mg. daily for eight weeks.

Panhypopituitarism

The level of protein-bound iodine in the serum was reduced in each of 3 classical cases of post-partum Simmonds's disease with clinical signs of hypothyroidism, in spite of the fact that 1 of them had been receiving gr. 1 of thyroid extract daily for eight years.

Acromegaly

The levels of protein-bound iodine in the serum were essentially normal in 5 of the 6 cases in spite of a slightly raised B.M.R. in 3 cases. In 1 case the level fluctuated in a most remarkable manner between 22 and 3 µg. per 100 ml. within a few weeks; the B.M.R. ranged between +11% and −4% during this period.

Other Endocrine Disorders

The level of protein-bound iodine in the serum was grossly reduced in 2 out of 12 cases of pituitary infantilism, but was normal in 2 cases of Cushing's syndrome, 1 case of Addison's disease, 2 cases of eunuchoidism, and 2 cases of ovarian agenesis.

Miscellaneous Disorders

The level of protein-bound iodine in the serum was reduced in 9 out of 50 patients with various skin disorders, including alopecia and keratosis pilaris. One of the

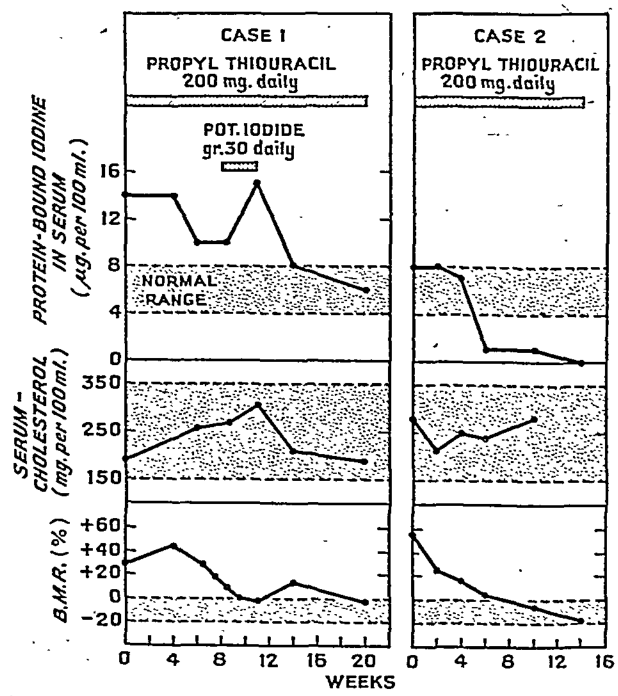

Fig. 3—B.M.R. and levels of protein-bound iodine and of cholesterol in serum in two cases of hyperthyroidism under treatment.

cases of keratosis pilaris was associated with myxœdema, but the other cases showed no evidence of hypothyroidism. Low values for protein-bound iodine were also obtained in 2 out of 52 cases of obesity and in 1 out of 5 cases of dystrophia myotonica. Raised levels were found in 6 other patients, 2 of whom had recently been treated with thyroid extract.

DISCUSSION

The table shows that the level of protein-bound iodine in the serum agrees with the clinical diagnosis less closely than does the B.M.R.: the over-all agreement is only 77% for protein-bound iodine, compared with 97% for the B.M.R. There is a considerable overlap between the values of protein-bound iodine obtained in euthyroid people and those obtained in patients with disorders of thyroid function. Though only about two-thirds of the patients with hyperthyroidism showed raised levels of protein-bound iodine, such raised levels as did occur were practically confined to hyperthyroidism or to pregnancy, or to patients to whom iodine-containing compounds had recently been administered. On the other hand, the level of protein-bound iodine was consistently subnormal in hypothyroidism and panhypopituitarism, though low values were also obtained in some euthyroid people with simple goitres and various non-endocrine disorders. This overlap severely limits the value of the estimation in the diagnosis of borderline cases; in our experience the B.M.R. is more helpful for this purpose.

Our findings therefore disagree with those of most American workers. Salter et al. (1941) found that the level of protein-bound iodine agreed with the clinical diagnosis in 98% of cases, whereas the B.M.R. agreed in only 71%. Riggs (1947) found the level of protein-bound iodine to be compatible with the clinical diagnosis in 85–89% of 325 cases. Winkler et al. (1946) and Salter et al. (1941) found it raised in 95% of cases of hyperthyroidism, and Hallman et al. (1951) in 100%. Starr et al. (1950) found it raised in 94% of cases of hyperthyroidism, but in a few cases they obtained values within the low normal range; in other conditions their findings were similar to ours, and, like us, they found some subnormal values in conditions other than hypothyroidism—e.g., diabetes mellitus, obesity, and heart-failure—in various psychoses, and in some elderly people.

We have found a rough correlation between the amount of protein-bound iodine in the serum and the B.M.R. at various levels of thyroid function, but when one set of values is plotted against the other the scatter is diffuse (fig. 4). Other workers have claimed a closer correlation than this (Salter et al. 1941, Bassett et al. 1941, Lowenstein et al. 1944, Winkler et al. 1946, Tucker and Keys 1951).

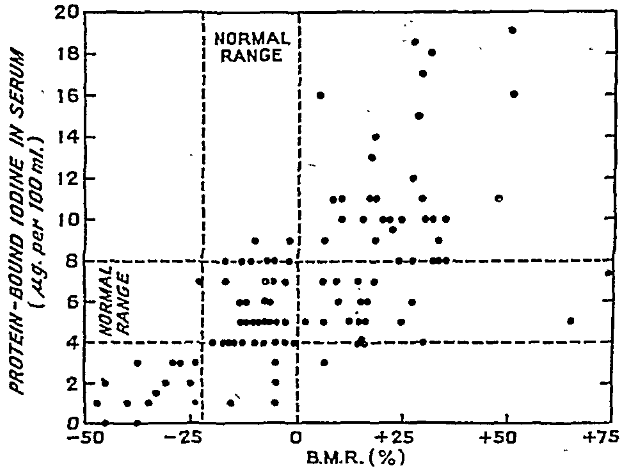

Fig. 4—Correlation of B.M.R. and levels of protein-bound iodine in serum in cases of hyperthyroidism, non-toxic goitre, and hypothyroidism.

There are three possible explanations of the poor correlation between the level of protein-bound iodine and the clinical thyroid state:

(1) It might be due to technical faults. We guarded against this by making duplicate determinations in all the cases, and by repeating the estimation if agreement was not within 1 μg. Moreover our normal range agreed closely with that of other workers, and very few raised levels were found in euthyroid people which could not be explained by previous administration of iodine or of thyroid extract.

(2) We have shown that the level of protein-bound iodine fluctuated in 2 cases of hyperthyroidism, 1 case of myxœdema, and 1 case of acromegaly. It is likely that this fluctuation occurs commonly, and that a single estimation may therefore not give a true reflection of the thyroid state. Since the metabolic response lags behind the changes in circulating thyroxine, fluctuations could occur without any change in the clinical picture. Starr et al. (1950) have shown that fluctuations occur in normal people as well, though these do not extend outside the normal range.

(3) Perhaps some patients will develop hyperthyroidism or hypothyroidism in response to levels of circulating thryoid hormone which would be regarded as normal in most people. Some cases of simple goitre have shown low levels of protein-bound iodine, and in such cases a rise of the level to within the normal range might well be followed by signs of hyperthyroidism. It is well known that endocrine function and dysfunction depend not only on the amount of hormone secreted but also on the response of the "target" organ or tissue.

We have not found the level of protein-bound iodine in the serum to be a reliable guide to treatment. The administration of iodine to patients with hyperthyroidism has tended to raise the level of protein-bound iodine still higher. Under treatment with thiouracil the level has in some cases fallen in parallel with the response of the clinical condition and the B.M.R., though in other cases it has preceded it. In 2 cases the level has actually risen during treatment. The level of protein-bound iodine may actually fall below the normal range without any clinical evidence of hypothyroidism (fig. 3). These findings are again at variance with those of other workers. Man et al. (1942) and Winkler et al. (1946) found that the administration of iodine to patients with hyperthyroidism reduced the level of protein-bound iodine, sometimes to within the normal range, thus reflecting the clinical response. Most workers have found that the fall in the level of protein-bound iodine during thiouracil therapy precedes the clinical response and fall in B.M.R. by some days or even weeks (Lowenstein et al. 1945, Engstrom et al. 1950, Hallman et al. 1951), and Engstrom et al. (1950) regarded a subnormal value of protein-bound iodine, at any stage, as an indication of over-treatment.

In the treatment of myxœdema we have found, as did Robertson and Kirkpatrick (1952), that the B.M.R. is a more accurate guide than the level of protein-bound iodine. The administration of thyroid extract may in itself increase the level of protein-bound iodine in patients who show no signs of over-treatment. A similar increase may follow the administration of thyroid extract to euthyroid people.

Perhaps the chief value of estimating the protein-bound iodine in the serum is in the diagnosis of thyroid disorders where determination of the B.M.R. is impracticable—e.g., in infants and young children, in elderly persons, in cardiac failure and chest disease, and in neurological and mental disease. It may also be helpful in distinguishing thyroid disorders from other conditions with a raised or lowered B.M.R.

There are two disadvantages of the estimation: (1) the technical difficulties are considerable, and it is essential that duplicate determinations should be made by two different people who are practising the technique constantly; and (2) the result may be vitiated by previous administration of iodine-containing compounds. Provided, however, that the latter can be excluded, and that the patient is not pregnant, a raised level of protein-bound iodine practically always indicates hyperthyroidism, though a normal level by no means excludes it. A low level does not necessarily indicate hypothyroidism, but a normal level virtually excludes it.

One could not do better than to sum up in the words of Means (1948):

> "Both the B.M.R. and blood-iodine tell something of thyroid function, but different things. The B.M.R. is an index of the total effect of the thyroid hormone on its end-organs. Its level would depend not only on the amount of hormone discharged, but also on the sensitivity of the end-organs. The protein-bound iodine of the blood merely represents the level of hormone in the blood, which is dependent on the rate of delivery of hormone to, and removal from, the blood. Collection of radioactive iodine is an index of the thyroid's hunger for iodine, which is probably related to its degree of stimulation. Therefore it is not a question of which of these measuring sticks is best. All are of value; the more of them which are used, the more understanding is to be derived from them."

SUMMARY

The levels of protein-bound iodine in the serum were estimated in 30 normal people and 475 hospital patients.

The normal range was 4–8 µg. per 100 ml.

Only 61% of the patients with proved hyperthyroidism showed levels above 8 µg. per 100 ml. With few exceptions, readings of more than 8 µg. per 100 ml. were confined to hyperthyroidism, pregnancy, or cases in which iodine had previously been administered.

The level was consistently reduced in myxœdema and panhypopituitarism, but some low values were obtained where there was no clinical evidence of hypothyroidism.

The B.M.R. was of more value in the diagnosis of thyroid disorders and in assessing the response to treatment.

The serum-cholesterol level was of little value in the diagnosis of hyperthyroidism; it was helpful, but less reliable than the level of protein-bound iodine, in the diagnosis of hypothyroidism.

It is technically difficult to estimate the level of protein-bound iodine in the serum, and the results are liable to be vitiated by previous administration of iodine compounds in any form.

Apparently the value may fluctuate between normal and abnormal levels.

The level of protein-bound iodine in the serum is merely an index of the amount of circulating thyroxine. The response to a given level of hormone apparently varies in different people.

The chief use of the estimation of the level of protein-bound iodine in the serum is in cases in which measurement of the B.M.R. is impracticable or subject to error.

In itself it is not a reliable index of thyroid function but, if used in conjunction with other tests and with sound clinical judgment, it may be of considerable value.

We are grateful to Dr. P. M. F. Bishop and Prof. R H. S. Thompson, in whose departments this work was done, for valuable advice; Mr. R. A. Adams for technical assistance in the estimations of protein-bound iodine; and Dr. W. H. H. Merivale and his technicians in the department of clinical pathology for the cholesterol estimations and for help with the B.M.R. estimations.

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SOME EFFECTS OF LONG-CONTINUED CORTISONE THERAPY IN RHEUMATOID ARTHRITIS

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OF six patients who began continuous cortisone-acetate therapy for rheumatoid arthritis twenty-one months ago, three are well, one is in a worse state than when she started treatment, and two are dead. We report here some revealing observations made on these patients. They do not necessarily detract from the value of cortisone acetate as a therapeutic agent.

THE SIX PATIENTS

The first three are females, aged 16, 22, and 36. They have received and still receive 50–75 mg. of cortisone acetate daily. The first remains well and fully active but has more joints affected now than at the beginning of treatment. The second maintains improvement but is still very thin and has little vitality. The third has so far responded very nearly perfectly. In all three cases the erythrocyte-sedimentation rates and hæmoglobin concentrations approached normal in the early weeks of treatment but have remained respectively above and below normal ever since. The menstrual function and feminine attributes have become and remained normal, suggesting that cortisone acetate, in the doses used, does not suppress adrenal functions which it cannot replace. This may only apply to women in the childbearing years. As so few have been treated in this way for $1^1/_2$ years this tentative conclusion may prove incorrect.

The fourth patient is a woman of 49 who is three years past the menopause.

In the early weeks of treatment an average dose of 50 mg. of cortisone acetate a day brought about really amazing improvement; but, as the months went by, larger doses became necessary. By the ninth month 150 mg. a day was barely sufficient to prevent the return of pain and swelling to all her peripheral joints.

On this high dose abnormal deposits of fat developed, and she became hypertensive (highest recorded blood-pressure 210/120 mm. Hg). Seven months on a lower dose averaging 75 mg. a day has led to the loss of much abnormal fat and the return of blood-pressure to normal, but the rheumatoid disease has increased, generalised stiffness and muscle weakness are pronounced, her knees are more painful and eroded, and her wrists and hands are constantly swollen and hot. Complications have included hæmorrhage from a duodenal ulcer necessitating blood-transfusion (fourth month), the appearance of severe hot flushes (controlled by œstrogen therapy), and at one stage the cortisone-withdrawal phenomenon—painful swollen joints that are eased by rest and made worse by use (rheumatoid symptoms in reverse). An unusual complication, associated with moon-face, has been the floating up of the lower denture.

This kind of response to high doses has been noted by some American physicians in postmenopausal women. In the present state of our knowledge it would be wise to avoid, for rheumatoid patients after the menopause, doses in excess of 75 mg. a day for more than a month. When worth-while control of the disease cannot be achieved with this restricted dosage, it would be best, theoretically, to change over to adrenocorticotropic hormone (A.C.T.H.) before tailing off the treatment. Such a change-over could not be completed for this patient, because she developed gross urticarial reactions to the injections. When A.C.T.H. is available free from carrier protein, this type of reaction may cease to occur.

The pathology of cortisone-withdrawal symptoms, other than those of adrenal insufficiency, has not yet been described. Perhaps some tissues become adapted to the changed environment caused by the prolonged administration of cortisone acetate and, as a consequence, manifest a new disorder when the hormone is withdrawn.

The fifth patient was a man aged 29.

His illness had begun three years previously as pericarditis and acute rheumatism, but this gradually changed to rheumatoid disease. His large joints were damaged, his feet deformed, and his hands practically useless. Six months before cortisone-acetate therapy began, a liver biopsy revealed no sign of amyloid disease.

After three months' therapy he was unwittingly given for three weeks an inactive preparation of A.C.T.H. During this time he became ill, jaundice appeared for a few days, and his liver enlarged rapidly. On the resumption of cortisone-acetate therapy he soon recovered, but his liver did not decrease in size appreciably. In the following nine months he received an average daily dose of 75 mg. At the end of a year's treatment he felt well and his rheumatoid disease was only mildly active, but his liver was enormous and he had little energy. His serum-protein levels were normal. Blood-counts showed leucocytes 20,000–30,000 per c.mm. (polymorphs 85%), hæmoglobin 12 g. per 100 ml.; and his bone-marrow showed an indeterminate picture. In the Congo-red test 99% of the dye was absorbed.

Shortly after this time he became ill suddenly. His blood-pressure fell from about 180/95 to about 80/40 mm. Hg, and he had transient abdominal pain, fever, and tachycardia. On the first day of this terminal illness his blood-electrolyte levels were normal. The dose of cortisone acetate was raised to 100 mg.; blood and, later, glucose saline solution were transfused and terramycin was given. His blood-pressure did not recover, and he died, with a falling heart-rate, on the fourth day, having passed during the four days only some 100 ml. of urine.

The liver weighed 6470 g. and about 95% of it was amyloid substance. The adrenal glands were replaced by amyloid substance save for a narrow rind of zona-glomerulosa cells. The spleen was moderately involved, but the kidneys only very slightly. Sections of the intestine, lung, heart, tongue, brain, thyroid, pituitary, and synovial membrane showed no amyloid deposit.

Many instances of amyloid disease associated with severe rheumatoid arthritis have been described; but as a gross manifestation it is rare. In the extensive literature of amyloid disease we have not found an instance of such an enormous deposition in the liver developing in so short a time. At least it may be said that in this case cortisone acetate did not retard the development of amyloid disease.

Some mice when fed, or given injections of, sodium caseinate develop amyloid disease (Smetana 1925). Our patient received calcium caseinate ('Casilan') daily for nine months. His intestines were not involved, whereas those of the mice were. Unlike man (Gallagher et al. 1951) mice excrete steroids into the intestinal tract (Dobriner 1952). This type of experimental amyloid disease is hastened by cortisone therapy, whereas ascorbic acid has the reverse effect, for in the guineapig a state of scurvy due to ascorbic-acid depletion leads to amyloid deposition (*Lancet* 1951). Our patient received 150 mg. of ascorbic acid daily throughout the cortisone-acetate therapy. One must remember, of course, that amyloid disease is not a definable entity. The name is applied to various states in which accumulations of unknown substances with similar crude staining properties are found between the formed elements of some connective tissues. In the more common secondary varieties the defect seems to belong to the organ affected rather than to the connective tissue. The little that is known of these protein substances and their small polysaccharide moieties suggests that they differ in various diseases and from species to species (Hass et al. 1943).

The terminal event for this patient did not resemble an addisonian crisis, nor was there any evidence of septicæmia. The abdominal pain may have been caused by a small peritoneal hæmorrhage which was found at necropsy. Patients with advanced amyloid disease do not usually die in this way. One is forced to relate his death, and the mode of his dying, in some way to cortisone-acetate therapy.

The sixth patient, a man of 48, had had rheumatoid arthritis for eleven years.

When treatment with cortisone acetate began he was "at the end of his tether." During twelve months' treatment he gained much benefit and was able to keep at work. After the first six months he developed, for the first time, symptoms of a duodenal ulcer. After a further six months the ulcer bled profusely. He responded normally to treatment but stopped taking cortisone acetate twenty-five days after the hæmorrhage. For the preceding six months the dose had been 25 mg. twice daily by mouth. On the thirtieth day, without premonitory symptoms of adrenal insufficiency, he fainted, recovered consciousness for a minute, vomited, and died. At necropsy the only macroscopical abnormality was the duodenal ulcer. It had been large but had healed. Microscopically the adrenal glands were normal; the thrombus in the vessel responsible for the hæmorrhage from the duodenal ulcer was organised and already partially recanalised; and the heart showed severe subendocardial and myocardial fibrosis.

The histologically normal adrenal cortex was a pleasant surprise.

Until more is known of the action of cortisone acetate and of the ætiology of peptic ulceration, it will be advisable to discontinue cortisone-acetate therapy when ulcer symptoms appear. The apparently normal clinical and histological recovery after the ulcer bled suggests that it is not essential to stop cortisone therapy abruptly in this circumstance. To lower the dose of cortisone at any crisis is, of course, unwise in theory. The question has arisen whether, in the presence of a bleeding ulcer, oral therapy should be changed to intramuscular. It was so changed in this case—for no valid reason. Our fourth patient had received only intramuscular cortisone acetate before her ulcer bled, and a year of oral therapy since has not provoked any further bleeding.

Was the fibrosis of the heart muscle sufficient to explain sudden death, or was the cessation of cortisone therapy a necessary adjunct? We do not think that the evidence justifies a conclusion but hope that this account may prompt others to relate their similar or dissimilar experience.

CONCLUSIONS

From these observations, in conjunction with those of other workers, it seems that for women in the child-bearing years, suffering from rheumatoid arthritis, cortisone acetate 50–75 mg. a day for periods up to twenty-one months does not upset normal function.

In women after the menopause 75 mg. of cortisone acetate a day should be the maximum for maintenance therapy.

The administration of cortisone acetate and a high-protein diet in the presence of amyloid disease should be avoided until more is known of their relation to this condition.

Intramuscular cortisone acetate 50 mg. daily does not prevent the healing of a bleeding duodenal ulcer (two cases only).

An average dose of 50 mg. a day of cortisone acetate continued for a year did not lead to any demonstrable abnormality in the adrenal cortex of a man aged 48.

Part of the cortisone used in this study was provided from a gift made jointly to the Medical Research Council and the Nuffield Trust by Messrs. Merck.

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A NEW SYNTHETIC CURARISING AGENT

CLINICAL TRIAL OF COMPOUND 20 (LAUDOLISSIN)

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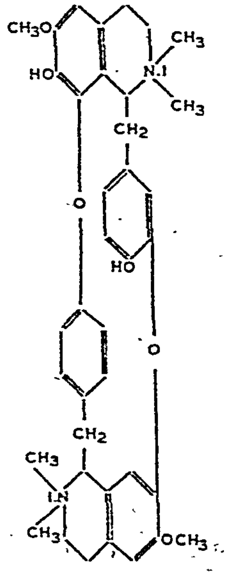
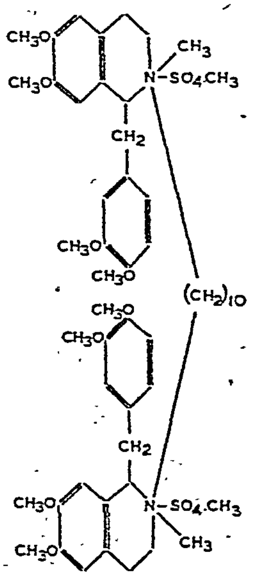
Taylor and Collier (1951), synthesising and investigating the muscle-relaxing properties of heterocyclic decamethylene *bis* quaternary ammonium compounds, produced one (Compound 20) which showed promise of being an effective substitute for *d*-tubocurarine in anæsthesia. This substance has been named 'Laudolissin.' Taylor (1952) described its chemistry, Collier and Macauley (1952) its pharmacology, and Bodman (1952) experiments with it in conscious volunteers. The structures of Compound 20 and *d*-tubocurarine are as follows:



d-Tubocurarine



Compound 20

Briefly, the workers cited above have established that Compound 20 is a true curarising agent, with a potency in man just half that of *d*-tubocurarine but with a duration of action slightly longer, and that it is antagonised by neostigmine.

Since no undesirable side-effects were detected during the work on volunteers, we decided to proceed with a trial in anæsthetised patients, and we record here our impressions of the clinical properties of Compound 20.

Compound 20 was substituted for the established relaxants in 186 procedures, as follows:

Operations	*No. of cases*
Partial gastrectomy	75
Cholecystectomy	14
Abdomino-perineal resection	6
Other major abdominal	47
Pneumonectomy	5
Valvulotomy	5
Other thoracotomies	9
Operations on the head and neck	10
Other major surgery	15
Total	186

Ninety-one patients were anæsthetised with nitrous oxide, with or without pethidine, and the remainder with cyclopropane. Induction was by thiopentone in all the cases.

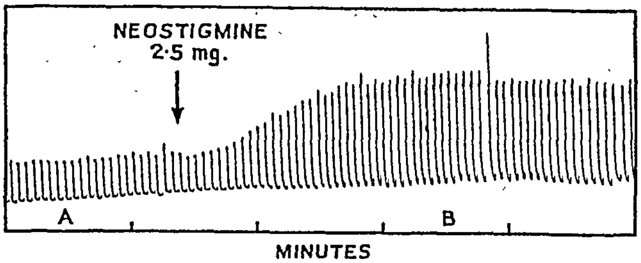
RESULTS

Muscle-relaxing Properties

In general the clinical impression gained has corroborated the experimental findings. A dose of 30 mg. of Compound 20 provided the same relaxation as 15 mg. of *d*-tubocurarine. But where the latter would have been expected to give adequate abdominal relaxation for thirty minutes, the relaxation with Compound 20 lasted forty minutes or more. Maximal abdominal relaxation was not evident until at least five minutes after the injection. The relative action on the abdominal muscles and the diaphragm seemed no different from that of *d*-tubocurarine. "Rectangular respiration" (Morton 1950) was often seen, and carried the same significance as when occurring with the established relaxant drugs.

Another aspect of a relaxant is its ability to paralyse the vocal cords. In a number of cases Compound 20 was given immediately after an initial dose of thiopentone, and intubation was attempted. In some cases relaxation of the cords was not obtained, even after several minutes and with doses which relaxed the abdominal muscles adequately. Conditions for intubating were certainly far less satisfactory than those obtainable with gallamine triethiodide. Consequently one inclined to the use of some other drug or technique for intubating, and reserved Compound 20 for maintaining surgical relaxation. A very satisfactory method was to use succinylcholine (with or without pethidine). Succinylcholine has a very short action, and does not seem to influence the effect of Compound 20 given after it; it has the additional advantage that the patient can breathe spontaneously while the preliminaries are being completed, before the surgeon actually starts the operation.

In experiments on animals Collier and Macauley (1952) demonstrated an antagonism between Compound 20 and succinylcholine, if given in that order: an appropriate dose of succinylcholine rapidly reversed the paralysis caused by Compound 20. With a larger dose a brief paralysis referable to the succinylcholine was followed by a rapid recovery from both drugs. We thus had reason to think that succinylcholine would be an ideal drug for producing additional relaxation for closure of the peritoneum. We have in fact used it with great success, in doses of 20–30 mg., on forty occasions after Compound 20, but as yet have been unable to obtain in anæsthetised patients a convincing demonstration of the antagonism seen in animals. On the other hand, we have seen no evidence of synergy between these two drugs, such as prolonged respiratory paralysis.



Effect of neostigmine on respiration of patient partially paralysed with Compound 20. Spirometer tracing, inspiration upwards. Tidal volume 300 ml. at A, 890 ml. at B.

In 13 cases we used ether for closure of the peritoneum, and it appeared to potentiate Compound 20.

There is no doubt about the antagonism in man between Compound 20 and neostigmine. The latter has been used on 35 occasions with satisfactory results. The accompanying figure illustrates such a case. But our present experience is insufficient for us to say whether this antagonism is greater or less than that between *d*-tubocurarine and neostigmine.

Side-effects and Incidental Properties

In 92 cases the pulse-rate and blood-pressure were recorded at five-minute intervals throughout the operation. In no case was there any change in either which could be attributed to Compound 20. In 3 cases electrocardiograms were made before, during, and after injection; they showed no change.

Of the signs which might be attributable to the release of histamine, bronchoconstriction was never evident, and no sudden or transient falls of blood-pressure were detected in association with the injection.

Experience with other relaxants led us to search for certain undesirable side-effects. Evidence of hæmolysis, such as hæmaturia and hæmoglobinuria, was not seen. The solution did not appear to irritate the vein, and there was no thrombosis or phlebitis. There was no action on the gut that could be seen by direct observation, and there was no ileus.

Compound 20 was not miscible with thiopentone, pethidine, or succinylcholine.

DISCUSSION

The properties of Compound 20 seem to be very similar to those of *d*-tubocurarine. So long as further trials with this drug confirm our findings, we think that Compound 20, of all the relaxants we have had occasion to use since their introduction into anæsthesia, could best take the place of *d*-tubocurarine for surgical relaxation.

The chief advantage of Compound 20 has not concerned us in this trial—it can be synthesised from materials readily available in this country.

SUMMARY

A clinical trial of a new muscle-relaxant has been described—Taylor and Collier's Compound 20, called laudolissin.

It has been used during general anæsthesia in 186 cases.

Its curarising properties are very similar to those of *d*-tubocurarine, except that its action lasts longer.

No important undesirable side-effects were detected.

Messrs. Allen Hanburys supplied the laudolissin used in this trial.

ADDENDUM

Since this paper was written Compound 20 has been used in a further 50 major procedures without incident.

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SPONTANEOUS SEPARATION OF AN INTUSSUSCEPTION

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SPONTANEOUS separation of an intussusception is described in the textbooks as a possibility, but it is rare. The case described here ran a subacute course after the onset, and the pathological processes were verified by recovery of the separated bowel and by laparotomy after the separation. The case was demonstrated at a meeting of the Midland Medical Society on Jan. 31, 1951, and three members at the meeting described other cases of spontaneous separation of an intussusception.

CASE-RECORD

An engineer, aged 74, of sturdy physique and vigorous habit, was taken ill on Sept. 4, 1948. He complained of upper abdominal pain while having his tea. Within a few minutes it became very severe, and he collapsed. He was found by Dr. C. Ramsdale shortly afterwards to be collapsed, grey, cold, with a clammy skin, almost pulseless, and with cyanosis of the lips, nose, ears, and fingers. His abdomen was soft and not tender, and no abnormality could be felt. Coronary thrombosis was provisionally diagnosed, and he was thought to be dying. Nikethamide and morphine were injected, and amyl-nitrite inhalations were given. After an hour he recovered sufficiently for Dr. Ramsdale to leave him.

On examination on Sept. 5 his circulation had fully recovered, but he was vomiting bile-stained fluid, and his abdomen was tense and distended, though not tender. He complained of vague pain in the lower abdomen. The diagnosis was altered to mesenteric thrombosis. I saw him that evening and agreed with this. The patient refused operation, and it was not strongly advised.

Progress.—During the next three days he remained distended, constipated, and vomiting. On one occasion the vomit had a fæcal smell. His temperature rose to 100°F on Sept. 6. On Sept. 10 he was transferred to hospital, and a good result was obtained from an enema. He continued to vomit bile-stained fluid. Dehydration was corrected with saline solution per rectum. I saw him again on Sept. 12 and found him very distended, and considered the possibility of a volvulus. A flatus tube was passed with a good result. His distension decreased, and vomiting became much less. He was walking about the ward after Sept. 24. Up to Oct. 2 he remained in hospital, and a gradual improvement took place, punctuated by occasional attacks of vomiting. Bowel action became regular, and he had a moderate appetite. Pain disappeared, and his abdomen remained slightly distended, but soft and not tender. The day after he went home he had a little diarrhœa, which continued with occasional vomiting. By Oct. 10 he had much improved, and did not vomit. On this day he had an excellent bowel action in the morning, and passed 2 ft. of macerated small intestine. Pathological examination of the gangrenous bowel which was passed showed a simple polypus. Next day vomiting of dark-stained fluid began again, and on Oct. 12 and 13 was profuse. He was now getting intestinal colic, and his abdomen was distended. On admission to hospital on Oct. 14 he was in fair condition, though rather sallow and dehydrated. His blood-pressure was 180/80 mm. Hg, temperature 98°F, and pulse-rate 80. A plain radiograph of the abdomen showed dilated coils of jejunum and ileum.

Operation.—At laparotomy on Oct. 15, distended gut was found. A volvulus of the jejunum was corrected, and the site of an obstruction was discovered 3 or 4 ft. proximal to the ileocæcal valve. At this point a stricture with surrounding adhesions was discovered. Side-to-side anastomosis was done.

Progress.—The patient made an uninterrupted recovery. He drove his own car to the meeting in January, 1951, where his case was demonstrated.

COMMENTS

In the ensuing discussion at the Midland Medical Society, Dr. H. W. Hickman reported that he had seen a young Indian vagrant who was operated on for ileocæcal intussusception which recurred after twenty-four hours. Conservative measures were adopted, and the patient passed the intussusception. A subsequent barium enema showed the appearances of an ileotransverse anastomosis.

Mr. K. O. Parsons reported a case of intussusception of the pelvic colon in a patient who presented with gangrenous bowel protruding from the anus. He had been previously diagnosed elsewhere as a case of prolapse. The patient passed the intussusception five weeks later. A barium enema showed no signs of the anastomotic level.

Mr. Wilfred Mills reported that he had been called to a patient in a mental hospital who was said to be "passing his uterus through his rectum." There was some reason for this description because the prolapsed bowel closely resembled a patulous cervix. Again this intussusception sloughed away, leaving a normally functioning bowel.

In children with intussusception, initial shock is well known, and recognised by quietness and pallor. In the present case in an adult, shock was disproportionate to the pathological condition present. An extreme degree of shock is not commonly seen in acute intestinal obstruction caused by strangulated hernia, or even by impaction of large gall-stones. Acute intestinal obstruction appears in this case not to have been complete until after the separation of the intussusception, when one would have expected recovery. It is possible that complete obstruction was caused by rapid cicatrisation at the site of separation, and was delayed by the presence of the bulky gangrenous mass.

One wonders if diagnosis could have been made in the early stages by barium contrast filling and X rays, but it is doubtful if operation would have been strongly urged even in the presence of an accurate diagnosis, because of the absence of complete obstruction. The total absence of blood from the stools at all times is noteworthy.

Reviews of Books

Eugenics: Galton and After

C. P. Blacker, M.C., G.M., M.A., M.D., F.R.C.P., general secretary, Eugenics Society. London: Duckworth. 1952. Pp. 349. 25*s*.

Dr. Blacker has combined a biography of Sir Francis Galton with a review of the development, after Galton's death in 1911, of the "science, practice and religion" of eugenics. In his description of the person and work of this remarkable cousin of Darwin, Dr. Blacker follows closely Karl Pearson's biography, and the first third of the book is a reliable account of the many interests of a highly gifted and well-connected Victorian gentleman. His account of developments since 1911 gives a better view of what Galton accomplished than can be found anywhere else, and sets it in a framework of modern views about genetics and eugenics. It would be a mistake, however, to regard the book as a detached and academic survey. It is written from a personal standpoint which many do not share. Since eugenics (and even genetics) offer such controversial themes this was inevitable, and the reader must allow for it. In addition, a fair amount of the controversy in this country on national intelligence and kindred issues is reported, and there are informative accounts of the demography of the peoples of the earth, of some recent general developments in genetics (but not in human genetics), and of methods of ascertainment.

The Scientific Paper

2nd ed. Sam F. Trelease, Columbia University. London: Baillière, Tindall, & Cox. 1951. Pp. 163. 20*s*.

Authors who worry about their manuscripts, and would gladly make them less of a burden to editors and more of a joy to readers, will be much helped by this little book. It deals with every aspect of collecting and presenting the results of scientific work: the use of the library, treatment of data, reliability and significance of measurements, the actual writing and the choice of headings, logical presentation, how to maintain interest, revision, typescript, correction, the estimation of length, good usages, tables, illustrations, the ways of editors, and proof-reading. Experienced writers will not find anything unfamiliar, but few books cover the problem so completely as this one. The introduction, Mr. Trelease says, should state the problem, describe its condition at the beginning of the study, tell the reasons for investigating it, and give the purpose, scope, and general method of the investigation. He also thinks it should state clearly and definitely the most significant result of the investigation; for this not only enables the reader to distinguish essential from non-essential evidence, but makes the writer face squarely at the outset what it is that he really wants to say—whether, indeed, he has anything to say. Like other advisers on scientific writing, he emphasises the need for numerous revisions. It is true that a revised manuscript is likely to be better than one which is "dashed off" and dispatched without revision, but there is a limit to the number of useful revisions: some much-revised papers show that their writers have grown sick of the sight of them and are no longer interested in correcting their faults. Before he begins to write, an author should plan his paper so that it conforms to the layout of the journal of his choice. He should then write with a two-inch margin and three spaces between the lines. He can do a great deal of correction on such a script without rendering it illegible to an intelligent typist. Two candid friends of good critical ability, knowledge of the subject, and experience of publishing papers should independently edit and freely comment on copies of the draft; and the author should weigh their observations, think his own second thoughts, and transfer the result to his correction copy. This should be retyped and sent to the editor. If writers would observe these sensible rules it is probable that the editorial staff of scientific journals would live much longer and look much younger than is usual for persons of this kind.

Atlas of Tumor Pathology

Fascicle 9. Rupert A. Willis, M.D., F.R.C.P., professor of pathology, University of Leeds. Pp. 58. 50 cents. Fascicle 16. Philip M. Le Compte, M.D., pathologist, Faulkner Hospital, Boston, Mass. Pp. 40. 45 cents. Fascicle 18. Hans G. Schlumberger, M.D., professor of pathology, Ohio State University. Pp. 88. 75 cents. Fascicle 29. Howard T. Karsner, M.D., medical research adviser, Bureau of Medicine and Surgery, United States Navy. Pp. 60. $1.00. Fascicle 34. Fred W. Stewart, M.D. Pp. 114. $1.10. Washington: Armed Forces Institute of Pathology. 1950 and 1951.

These helpful monographs are published at a reasonable price by the Armed Forces Institute of Pathology, under the auspices of the National Research Council, and are sponsored by various bodies, including the American Cancer Society and the National Cancer Institute of the United States Public Health Service. They form part of an atlas of tumour pathology, and the illustrations are very good though the subject matter is brief. They contain a surprising amount of information nevertheless, and contrive to survey prognosis and treatment into the bargain.

The fascicle by Prof. R. A. Willis is on teratomas, which he defines as neoplasms composed of multiple tissues foreign to the part in which they arise. He believes that they may represent areas of tissue which, during early embryonic development, escaped from the action of the primary organiser, and adduces evidence against the popular view that they are embryomas or distorted fœtuses, derived either from included twins of the bearers or from parthogenetic proliferation of the host's own germ cells.

Dr. Philip M. Le Compte writes on tumours of the carotid body and related structures. Since most carotid-body tumours are both clinically and histologically benign, he favours a diagnostic biopsy only. The surgeon who decides to operate should realise that "he has one chance in three of killing his patient and if the patient survives, about eight chances in ten of leaving him with some kind of temporary or permanent neurological disturbance." For tumours of the glomus jugulare, Le Compte recommends radical tympano-mastoidectomy when the diagnosis is established. He also gives brief accounts of tumours of the aortic bodies, and tumours arising in the *ganglion nodosum* of the vagus, and believes that there are probably two unverified instances of neoplasms arising in the paraganglion ciliare. Tumours of the chemoreceptor system are in general radio-resistant.

In his account of tumours of the mediastinum, Dr. Hans G. Schlumberger does not include an account of tumours of the thymus, œsophagus, heart, or pericardium; but he discusses the histogenesis of the many others met with in this situation, including those arising from misplaced organs. Every mediastinal tumour not known to be metastatic, he says, should be submitted to biopsy before it is irradiated; for this not only establishes the diagnosis but makes it possible to avoid those post-irradiational tissue changes which often increase the difficulty of surgical removal.

Dr. Howard T. Karsner, writing on tumours of the adrenal, includes an account of the tumour-like myelolipoma. He holds that a diagnosis of phæochromocytoma is not valid without a positive chromaffin reaction, because polygonal cells may be numerous in cortical adenoma while cells which resemble those of the cortex occur in phæochromocytoma.

The excellent section on tumours of the breast is written by Dr. Fred W. Stewart. Primary mammary cancer can occur, he says, in any postpubertal breast; in fact, with increasing experience a pathologist may employ the term "pre-cancerous" less and less. The youngest patient he had seen was twenty; the oldest were identical female twins over ninety years of age. Gross anatomy and the extent of disease, he holds, far outweigh in importance microscopical classification, although confirmation of the two may yield significant information. With involvement of the basal axillary group of nodes only, Dr. Stewart has found a 65% survival-rate at 5 years. If the midgroup are involved the survival-rate falls to 45%, while if the apical axillary nodes are affected the survival-rate is only 28%. The so-called medullary type of carcinoma with a lymphoid stroma has a better survival-rate than the average scirrhous cancer: in 5 years only 11·5% had died of their disease in the former group, as against 56% in the latter group.

Management of the Newborn

Arthur Hawley Parmelee, M.D., professor of pediatrics, University of Southern California. Chicago: Yearbook Publishers. 1952. Pp. 358. $7.

This excellent book on the newborn infant will be a welcome addition to the shelves of pædiatricians and obstetricians. Professor Parmelee has had intensive experience of the newborn for many years, and his approach is physiological and clinical. He is a keen and accurate observer, and he has produced a "story of the newborn" which is a pleasure to read. Fully half of the book deals with the normal infant, and the remainder is a comprehensive account of abnormalities and diseases of the newborn. The 83 illustrations are good, but such a valuable book is worthy of many more. It is a pity that American books are now so expensive in this country, but no-one who has regular care of the newborn can afford to be without this one.

Connective Tissues

Transactions of the Second Conference, May 24 and 25, 1951. Editor: Charles Ragan. New York: Josiah Macy, Jr., Foundation. 1952. Pp. 190. $3.50.

The second Josiah Macy conference on connective tissues has produced a volume even more interesting than the first; but when experts confer, new words and unfamiliar concepts, likely to be above the heads of some of us, are often taken for granted. Some small editorial explanatory notes in the present volume are therefore helpful, and more of them would be welcome in later books of the series.

Of the five main topics pain mechanisms in connective tissues, discussed by Travell, is the only one which represents the clinical approach. The other four are of more fundamental nature. Porter's valuable contribution on repair processes in connective tissue is illustrated by a series of beautiful electron micrographs showing the stages of collagen-fibre formation in relation to the cell-surfaces of chick embryo fibroblasts in tissue culture. Morrione deals with the regression of scar-tissue as seen in recovery from experimental cirrhosis of the liver, and advances several ideas which may bear on restoration of the normal state after fibrous-tissue healing in various other maladies, such as rheumatic heart-disease and nephrosclerosis. In discussing the chemical morphology of elastic fibres, Lansing is concerned with the chemistry of the individual fibres and the reasons for their spiral structure, which can be seen under both the light and electron microscopes. Gersh treats mainly of alterations in the appearance and staining reactions of ground substance in relation to the action of hormones or the mechanism of allergy, and also discusses its origin and fate.

Disease in Old Age

Robert T. Monroe, M.D. From the Medical Clinic of the Peter Brent Brigham Hospital and department of medicine, Harvard Medical School, Boston, Massachusetts. Boston: Harvard University Press. *London:* Oxford University Press. 1951. Pp. 407. 32*s.* 6*d.*

Dr. Monroe has made an elaborate analysis of the medical records of 7941 patients over the age of 61 who were admitted to hospital during the years 1913–43. The wealth of the clinical material he describes is impressive; though it would have been more useful if he had compared the incidence of disease in his patients and in those of lower age-groups. He points out that hospital management and practice must nowadays be adjusted to patients in the higher age-groups; for whereas, in 1913, 1 in every 16 patients admitted to hospital was over the age of 61, in 1943, 1 in every 5 patients admitted was of this age—an increase of 200% in 30 years. To those who hold that continued useful employment assists in the maintenance of physical and mental health, Dr. Monroe's figures are depressing, for 92% of men between the ages of 61 and 65 were in employment during the first decade under review, compared with 66% during the last. These figures help to confirm the trend which has been observed in surveys carried out both in this country and in the U.S.A. Dr. Monroe's views on the management of elderly patients are refreshingly humane, and he puts forward a sensible scheme for a comprehensive service for elderly persons, organised by the community, which would ensure an adequate supply of beds of various categories, linked with a central hospital. He emphasises the value of the geriatric clinic, and ends with a plea for an "age centre." This would include a supply of one- and two-roomed flats for about 400 people, where adequate medical and social services would be available.

Hospital Organisation and Management (4th ed. London: Faber & Faber. 1952. Pp. 1782. £8 8*s.*).—This standard work, first published in 1927, is now very portly. Captain J. E. Stone has amplified the facts and data gathered during many years of active work in the hospital field with numerous references to American experience, and to the changes brought about by the National Health Service Act. This has not been offset by sufficient compression and pruning. The appendices, too, which take up as much as 300 pages, could be shortened. Nevertheless this is a very good account of the development of the British hospital system, and of methods of hospital management. All departments of hospital organisation are covered, and the chapters on the law relating to hospitals could not be improved.

Applied Physiology (9th ed. London: Oxford University Press. 1952. Pp. 1190. 50*s.*).—The appearance of the new edition is as startling as that of an old friend who returns from a holiday with an unexpected moustache; but there can be no misgivings about Prof. Samson Wright's book. With the aid of Prof. Montague Maizels and Mr. J. B. Jepson, D.PHIL, he has rewritten more than half the text, and rearranged the presentation in drastic fashion. Though past readers may take time to find their way about again, they will readily agree that the new sequence of subjects is an improvement, starting as it does from "the outstanding generalization of physiology"—the constancy of the internal environment. Some 200 new illustrations have been added. What is virtually a new book will enjoy an even greater popularity.

THE LANCET

LONDON: SATURDAY, SEPT. 13, 1952

Family Size and Natural Selection

From time to time we should turn our attention from the triumphs of sanitary and medical science to consider the ultimate effects of these successes on the evolution of the human species. Bacteriologists and virologists are used to thinking of genetic constitution in terms of variation in the host's resistance and the parasite's virulence; and Sir Macfarlane Burnet, F.R.S.,[1] has sounded a salutary warning to those who think of human health purely in terms of environment. Applied microbiology, he notes, has overcome the high death-rate from infectious disease which has hitherto been a feature of urban civilisation; while the food-shortage that would otherwise have ensued has been largely prevented by deliberate restriction of the number of children.

> "Unfortunately this is not a satisfactory long-term solution of the problem that we have created by abolishing infective disease. If we ensure in general terms that each pair produces two children both of whom reach reproductive age and that the process continues indefinitely, we must inevitably come up against the problem of genetic deterioration. . . . The whole structure of the evolutionary process depends on the fact that mutation is constantly occurring and that only by a highly selective winnowing of the various gene-combinations that arise can evolutionary progress or even maintenance of quality occur. The vast majority of gene changes must of necessity be disadvantageous to the carrier. To maintain the normal character of the species every appearance of a deleterious mutation must be balanced by a 'genetic death.'"

The geneticist expects a constant tendency for the frequency and severity of a disease to return to a level at which the disadvantageous genes predisposing to the disease that are lost in each generation, from the relative infertility of those affected, will balance the new genes of this type appearing in each generation by mutation. Deterioration in environmental conditions will temporarily increase the mortality from the disease, but this fiercer selection will in time decrease the number of genes in the population predisposing to the disease until, without further change in the environment, mortality is brought back to the level which balances the constantly recurring new mutations. In the same way environmental improvement, such as a better method of treatment, will be followed by decreased mortality and accumulation of genes predisposing to the disease until once again the death-rate reaches the equilibrium level. Just how many deaths from diphtheria, for example, represent the equilibrium point it is impossible to say; this point will depend on the number of genes concerned, their mutation-rates, and the specificity of resistance to diphtheria. But, as with several other infectious diseases, deaths from diphtheria in this country are below equilibrium level after a century of adjustment of an originally rural population to city life during which mortality was much above this level. Immunisation against diphtheria is at present effective, but the capacity to respond to the toxin may well depend on past racial selection for resistance to the organism, and may be progressively lost after some generations in which there are no deaths from the disease. Where living organisms are used for immunisation, as in vaccination, the relative safety of the procedure probably depends on generations of selection for resistance; as the effects of this selection are lost, universal vaccination may come to cause as many deaths as did smallpox in a community long and freely exposed to infection by this virus. Few diseases will ever be exactly at the equilibrium point; and changes in bacterial and viral virulence will also for the time being upset the equilibrium. But in the long run environmental improvements, with one exception, are not by themselves likely to alter the mortality from any particular disease; they will merely lead to an increased morbidity-rate balancing a reduced case-mortality. The single exception is the elimination of the agent causing the disease. This is possible with some infectious diseases, and when it has been achieved genetic deterioration for resistance to the disease becomes irrelevant. But the number of diseases which can be controlled in this way seems limited—and this is true even of infectious diseases.

Human genetics is a new science, and little is known about the amount of selection needed to maintain equilibrium against the sum of disadvantageous mutations. One expert guess, by Professor Muller,[2] is that one gamete in five contains a new disadvantageous mutation. Whatever the selection needed, the human species has in the past more than held its own; and so selection must have been adequate. Until recently, however, there has been plenty of material on which selection could operate. At all periods except those of the most rapid population growth, less than half of natural families averaging six or seven children survived to have children in their turn. While some of these deaths may have been purely accidental, most were probably related in some way to the genetic constitution of the child or his parents. It is unthinkable that there should be a voluntary return to natural selection of this intensity. Fortunately, as Galton noted more than fifty years ago, as knowledge of human genetics grows, artificial selection is likely to prove both more humane and more efficient than natural selection; and Galton coined the term "eugenics" for artificial selection of this kind. If genetically ill-endowed individuals, kept alive by medical science or public hygiene, plan a family size 50% below replacement-rate, this gives as much gene-elimination as does the premature death of half of them. Further, artificial selection will be able to take account of the possession of genes in the heterozygous state, which when recessive are not subject to natural selection. In our kind of democracy eugenics must depend on self-selection by responsible parents, influenced in their choice of family size by genetic considerations. The present practice of planning families of only 2–4 children, with large families coming from the diminishing proportion of the population incapable of planning, probably provides insufficient scope for the maintenance of genetic standards, even with the best selection of those who aim at 4 and those who aim at 2 children. Probably even the family-size distribution suggested by the Swedish Commission on Population, with 33% of 3-child families, 27% of 4-child families, and 5% of 5-child families, though it would keep up the size of the population, would not provide adequate differentials to maintain genetic quality. General OSBORN[3] has suggested that, for this, family size should be distributed as follows: 19% 0 children, 15% 1 child, 16% 2 children, 18% 3 children, 18% 4 children, and 14% $5^1/_2$ children.

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[1] *Med. J. Aust.* 1952, i, 801.

[2] Muller, H. J. *Amer. J. hum. Genet.* 1950, 2, 111.

Parents cannot be coerced into having children, and at first sight such a high proportion of large families might seem unattainable, since to achieve 14% large families a much higher percentage must aim at a large family. But in the next few generations in countries with planned families there will be intense selection for genes favouring genophilia—the desire for, and delight in, children. With few children conceived as the accidental by-product of sexual activity, it will mostly be genophilic impulses that decide family size. Those well-endowed in this respect will contribute an increasing proportion of coming generations; and those who aim at only 2 children for eugenic or other reasons will mostly be doing so unwillingly, with a sense of responsibility, and will need to find other ways to express their genophilic impulses. As some of the environmental causes of diseases are entirely eliminated, and it becomes no longer necessary to maintain selection for freedom from, or resistance, to these diseases, it will be possible to use selection with the much more attractive aim of improving human genetic standards for qualities which are desirable but not directly related to mere survival—for example, general and special types of intelligence, artistic gifts, and, more important still, worth-while qualities of character. To quote BURNET once more: "Whatever we feel about the present social and political impossibility of any programme of practical eugenics, we can be quite certain that decade by decade the importance of action will be progressively more widely realised. Sooner or later action will have to be taken and it is our responsibility to initiate the process of accumulating valid knowledge on which eventual action can be soundly based. I repeat that this is the most important task of medical research today."

Prognosis in Asthma

THE prognosis of asthma, like that of many other recurrent conditions, is still largely a mystery. Long-term follow-up studies are rarely completed, since the disorder waxes and wanes over the years, the patient tries one doctor or hospital after another, and, perhaps from delicacy, he may not answer the follow-up letter.

WILLIAMS[4] observes that in the twenty years between 1930 and 1949 the death-rate from asthma in England and Wales was 7·07 per 100,000 of the population, compared with 1·65 in the United States. In England and Wales during the years 1938–49 deaths from asthma amounted to 0·6% of all deaths, accounting for roughly 3000 deaths per annum; approximately 96% of those dying from this cause were over 30 years of age. WILLIAMS cites 110 reported cases of death from asthma in patients over 30 years of age. Of these patients 51 (46%) had had asthma for less than 5 years, and in this latter group 44 (87%) died within 2 years of the onset. The remaining 59 (53%) had had asthma for more than 5 years—including 36 (33%) for more than 10 years, and 16 (18%) for more than 20 years. WILLIAMS also shows that deaths from asthma have a seasonal distribution corresponding closely with the incidence of respiratory infections and bronchitis. BULLEN[5] studied a group of 176 asthmatics who died in hospital in a town in the United States. Of these patients 94 died during attacks of asthma. Of the total of 176 more than half died within 10 years of the onset, and one-fifth within 5 years. Of 13 patients in whom asthma started before the age of 5 years, 6 died within 1 year and 4 within 7–11 years. Nearly half the patients survived beyond the age of 60, but those whose asthma began when they were over 40 years of age had a much worse prognosis than those who first had symptoms before the age of 25. In a series of 500 asthmatics seen in private practice only 9% first had symptoms after 40 years, compared with 22% of the 176 patients who died in hospital. Thus hospital statistics, as might be expected, probably give an unduly grave impression of the proportion of all asthmatics who die of the disease.

RACKEMANN and EDWARDS[6] give some basic facts on prognosis in a twenty-year follow-up of 688 asthmatic children, most of whom were seen in private practice. All but 29 were traced by letter or interview, so that over 95% are included. 449 were first seen before the age of 13, while the remaining 239, though they became asthmatic before that age, were first seen later. Of the 449 children 4 (less than 1%) had died of asthma by the late 20s, whereas of the 239 older patients 6 (about 2·5%) had died after 20 years—1 at the age of 28, and the other 5 at ages between 40 and 50. Among the 449 children seen before the age of 13, boys outnumbered girls by about 2 to 1. In treatment the most important factor seemed to be withdrawal of feathers, animal dander, "inhalants," and certain foods, rather than specific desensitisation. Some 31% lost their asthma entirely during their 'teens, though not necessarily at puberty. Another 19% remained free of symptoms so long as they avoided the specific allergen to which they were still sensitive; and 21% were free of asthma but had developed another allergic condition, hay-fever being by far the most common. Thus about 70% of the children more or less lost their asthma during their 'teens. About 26% of the patients still had asthma, but only 10% had severe symptoms. One-fifth of the children had negative skin tests, and their attacks were associated with respiratory infections; whereas in the remaining four-fifths the disorder was ascribed to allergy. In the group of 239 patients who were first seen after the age of 13, the results were not so good. After 20 years about 22% were symptom-free, 26% were still sensitive but remained well when avoiding allergens, and 8% were free of asthma but had developed other allergies; about 10% were left with mild, and 25% with severe, asthma. Of 12 patients in whom polypoid sinusitis developed, 4 had died of asthma; so gross nasal disease is a bad prognostic sign.

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[3] Osborn, F. Preface to Eugenics. New York, 1940; p. 248, table 51.

[4] Williams, D. A. Proceedings of the first International Congress of Allergy. 1952.

[5] Bullen, S. S. *J. Allergy*, 1952, 23, 193.

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The 688 cases are placed in five ætiological groups, depending on the clinical features and results of skin tests. Animal allergens account for 190 cases (roughly 29%), and foods for 48 cases (7%) mostly in young children with associated eczema. Pollen sensitivity was regarded as the important factor in 42 cases (5%), and mixed or unidentified allergens in 296 cases (42%). Skin tests were negative in 112 cases (16%), in most of which bacterial infection was thought to be the important cause. Of 86 children who had hay-fever, only 2 were free of symptoms by adult age. In 42 the hay-fever was mild; but in 28 (about a third) it was severe, and of these 13 developed pollen asthma and 7 asthma at any season. In 4 cases eczema recurred in adult life.

This important investigation shows that one child in four treated by a very experienced physician has continued to have asthma after 20 years of age, and about 2% actually died in asthmatic attacks. The proportion of failures is undoubtedly higher in children treated by palliative drugs alone. The prognosis is much graver in patients developing asthma when past 30 years of age; for then infection of the respiratory tract is common and may persist. This study should prompt us to discard the complacent belief that palliative treatment usually suffices. The asthmatic child or adult should be carefully investigated *at the onset* of symptoms and a rational régime instituted forthwith. This should include a serious effort to free the bedroom of dust and inhalant allergens, and to train the patient in remedial breathing exercises under the supervision of a physiotherapist.

Of Mice and Men

THE mills of virus research grind slowly, yet they grind exceeding small. Recent research on smallpox is a most instructive example of the tortuous, winding path that sometimes leads to practical progress. The story is a fascinating one, beginning with the discovery by HIRST [1] and MCLELLAND and HARE [2] that influenza virus agglutinates red cells from a number of animal species. It was soon found that vaccinia,[3] smallpox,[4] and other pox viruses also had this unusual property. The pox viruses have the distinctive property of agglutinating red cells from only 20–50% of fowls; and in 1946 BURNET and BOAKE [5] found that ectromelia virus also had this property and in other ways, too, resembled the pox viruses; and they proposed that ectromelia should be renamed mousepox virus. The next step can be readily pictured. Smallpox could not be studied easily in the laboratory, but mousepox might provide an excellent model of the behaviour of smallpox virus. FENNER was quick to seize the opportunity of learning about the epidemiology of mousepox, and the result was a series of painstaking and brilliant studies.[6] Before long practical applications [7 8] justified this roundabout road to progress.

When GLEDHILL and ANDREWES [9] described a virus which caused hepatitis in mice, it was at once apparent that this might be another instance of the way in which the study of a disease in mice may throw light on some of the difficult problems of epidemiology in man. Mouse hepatitis is an odd disease. The virus is apparently carried in the blood of one breed of mice (P.) which remain symptomless, but it can be transmitted to another breed (V.S.) which contract fatal hepatitis. The viruses of mouse hepatitis and of serum hepatitis in man have somewhat different properties, but superficially the analogy between the two diseases is striking. On an earlier page Dr. GLEDHILL, Dr. DICK, and Dr. ANDREWES describe further researches on mouse-hepatitis virus and reach the rather surprising conclusion that mouse hepatitis is caused by the combined action of two agents, which singly are non-pathogenic but cause fatal hepatitis when present together in the correct proportions. They were led to this conclusion by the results of experiments on the curative effect of terramycin on mouse hepatitis. From mice which had been inoculated with mouse-hepatitis virus and terramycin, a transmissible filterable agent was recovered which was non-pathogenic but immunised against mouse hepatitis; this agent was called S. (for stable). A second agent, called L. (for labile), was recovered by growing mouse-hepatitis virus at high dilution. L. and S. are both transmissible filterable agents which separately are non-pathogenic but together cause fatal hepatitis. We shall have to wait for further information on the lesions produced by these agents and any serological reactions that they evoke, and also for a final decision as to whether they are relations or just friends. Meanwhile the concept of viruses hunting in pairs should arouse great interest. There have been many well-substantiated reports of the simultaneous isolation of poliomyelitis and Coxsackie viruses from patients with poliomyelitis; and the interpretation by MELNICK et al.[10] that the Coxsackie virus may tip the balance towards paralysis accords with the known facts and with the findings in mouse hepatitis.

Experimental work with the viruses of hepatitis in man has also made big strides. Progress in this field still depends on that most unreliable laboratory animal, the human volunteer; and assessment of the results is always more difficult than with mice, which have learnt to say "yes" and "no" but not "maybe." Recently, however, DRAKE and his co-workers [11] have reported that a skin-testing antigen prepared from infective-hepatitis virus apparently protects people during an epidemic of infective hepatitis. In another paper these workers describe [12] results which lead them to believe that they have propagated the serum-hepatitis virus in eggs. Then again γ-globulin has been used successfully for protection against infective hepatitis. It seems, therefore, that the efforts of mice and men are not vain.

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Annotations

TROPICAL FATIGUE

In the past the danger of tropical diseases was sufficient reason for Europeans to be advised to avoid long periods in the tropics. The gradual conquest of these diseases has largely removed this danger, but there is still a widespread belief that life in the tropics can lead to physical deterioration. The term "tropical fatigue" has been introduced to describe a decline in efficiency attributable to environmental conditions. The nature of this failure has often been discussed, but there has been little systematic study. During the war, however, tropical fatigue assumed considerable importance, especially in the Pacific area, and an investigation was carried out in the Australian and New Zealand Armed Forces; Lee and Macpherson have given a detailed account of this work.[1, 2] The first question that needed answering was: Does tropical fatigue exist? And the second: If it does, is it essentially physiological or psychological?

The investigations were carried out in the field in New Guinea and the adjacent islands. Some 1800 men, whose stay in the tropics averaged six months, were examined. Simple methods had of necessity to be used; weight changes, blood-pressure, pulse-rate, cardiovascular response to tilting, and Harvard pack test[3] scores were recorded. A man's efficiency was also assessed by getting his own opinion of how tropical service affected him, and by comparing his views with those of others in a position to judge his work—e.g., his medical officer, commanding officer, and N.C.O. The physical measurements showed no significant changes when compared with those of a control group; but the Harvard pack test score declined steadily with length of service in the tropics. The test consists in stepping on and off a stool every two seconds for five minutes, wearing a pack of one-third the body-weight. Scoring is based on changes in the heart-rate after stopping the exercise. The fall in the scores was slight, but it was correlated significantly with the duration of tropical service. Quite apart from this finding, Macpherson concluded from the subjective and objective assessments of personal efficiency that deterioration was general. Those in the tropical areas agreed, almost universally, that they were less efficient and that they felt less fit. As the physiological measurements showed no changes to explain this decline, it was thought to be largely due to psychological factors.

Ellis, who has published several studies on the effect of environment in the Royal Navy,[4] describes on another page of this issue his work on tropical fatigue in the Navy. His findings are very similar to those of Macpherson, for 80% of those serving in ships in tropical waters considered that they were less efficient than in temperate climates.

The position is still obscure: tropical fatigue may be entirely "subjective," but there can be little doubt of the belief in its existence. It is important to know more about the condition because it affects the whole way of life of the white man in the tropics. Macpherson, for example, attacks the siesta: "One of the cardinal rules for successful tropical living can be summed up in the sentence: keep off your back during daylight hours!" Moreover the social significance of the long-term effects of tropical climates is great, for these have a bearing on emigration policy and on the development of primitive tropical zones. It would be interesting to know whether the native population suffers from tropical fatigue. Ladell[5] has shown that there is no clear difference in acclimatisation to heat between Europeans and Africans in Nigeria; this confirms observations by Weiner[6] on Bantu mine-workers. On the other hand, Robinson et al. found that, among share-croppers in the Southern United States, the Negro workers were mechanically the most efficient; they concluded that the Negroes had a better temperature-regulating mechanism.[7, 8]

One of the main difficulties of the subject is the lack of adequate methods of measuring fatigue. Forbes,[9] in his summary of the work of the Harvard Fatigue Laboratory, emphasised this obstacle. When many observers agree that an effect is to be found, it probably exists. Failure to demonstrate the effect quantitatively usually means that the right parameter has not been measured.

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CORTISONE VERSUS SALICYLATES

The striking biological effects of cortisone and A.C.T.H. are echoed, somewhat faintly, by the action of salicylates in heavy doses. In the clinical field the most obvious similarity is the antirheumatic action; and the reported development of Cushing's syndrome in a patient with rheumatic fever receiving 5 g. of aspirin a day[10] stimulated Hetzel and Hine[11] to investigate the effect of salicylates on the pituitary and adrenal glands of rats, using ascorbic-acid depletion as a measure of adrenal cortical response. They showed that sodium salicylate, in doses giving plasma-levels of 15–30 mg. per 100 ml., depleted the adrenal ascorbic acid to an extent related in linear manner to the dose, and that this effect was abolished by hypophysectomy; they also adduced evidence that the salicylate ion acted specifically in this respect, and they concluded that the therapeutic action of salicylates is mediated through the pituitary and adrenal glands. This view is supported by the inhibition of experimental serum arteritis by both cortisone[12 13] and salicylates,[14 15] and by the action of salicylates in increasing urinary output of 17-ketosteroids,[16] in increasing uric acid excretion[17] and in modifying the reversed passive Arthus reaction.[18]

Investigations of the effects of salicylates on the circulating eosinophils, however, have given conflicting results; for while Kelemen et al.[19] and Roskam et al.[20] found eosinopenia after administration of salicylate, Meade and Smith[21] demonstrated no such effect. These workers, moreover, have confirmed[22] Ingle's[23] finding that aspirin causes reduction of glycosuria in diabetic rats, whereas cortisone exacerbates the diabetes; and they challenge the general conclusion of Hetzel and Hine. Lately, Smith[24] has shown that while administration of cortisone to rats on a high carbohydrate diet leads to hyperglycæmia and glycosuria, this effect is much reduced

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by simultaneous administration of sodium salicylate. In adrenalectomised rats cortisone produced a significant deposition of liver glycogen, but salicylates given in the presence of cortisone caused a contrary and significant depletion. There is, therefore, considerable evidence that the mimicry by salicylates of hormone effects is only partial, and that in experimental conditions salicylates may antagonise cortisone.

In claiming that the therapeutic action of salicylates is mediated through the pituitary, Hetzel and Hine point out that, according to Sayers,[25] a lowered blood-level of cortical hormone stimulates the pituitary to restore homœostasis, and they tentatively suggest that salicylates stimulate the pituitary in this way by increasing the utilisation of cortical hormone in the tissues. In support of this they report experimental evidence that preliminary treatment with cortisone abolishes the ascorbic-acid-depleting effect of salicylates on the adrenals. Conceivably, however, this is a further example of the antagonism between cortisone and salicylates.

THERMOMETERS

DOCTORS learn early that the clinical thermometer is a chancy little tool. If it is to register accurately it must be kept in the mouth for at least three, and in some circumstances, six or seven minutes. Indeed, some years ago in a correspondence on this subject initiated by Dr. Douglas McClean[26] one writer assured us that "ten-minute thermometry has long been the custom in the more efficient sanatoria,"[27] and Dr. E. L. Middleton[28] reported that he always replaced the thermometer in the patient's mouth after the first reading, and went on replacing it after successive readings until two consecutive readings were the same. With these precautions in mind doctors can use thermometers successfully as a guide to one aspect of a case. The general public, however, and even the nursing profession, are not so well trained in scepticism.

Thermometers are made with different sizes of bulb, the smallest being described by manufacturers as "½ min.," and larger sizes as "1 min." and "2 min." thermometers. These terms were intended to indicate the time the thermometer required to register the true temperature; but the manufacturers know as well as the doctors that the time taken is very variable, depending not merely on the size of the thermometer but on whether it has been kept in a cool or a warm place before use, whether the patient's temperature is high or subnormal, whether he has kept his mouth shut or has had it open for talking, and whether the thermometer is competently placed inside it. Thus it has long been desirable that descriptions by time of different types of thermometer should be given up. The British Standards Institution are now revising the specifications for clinical thermometers. They have never allowed any "time" designation to be stamped on British Standard clinical thermometers, but unfortunately they are now proposing to perpetuate this misleading usage as a trade term. Their reasons for doing so are exactly the same as those given in our columns, in 1943, by Messrs. G. H. Zeal Ltd.,[29] manufacturers of thermometers.

> "Unfortunately," this firm wrote then, "long-standing trade usage and the fact that clinical thermometers have always been sold to the medical profession and the general public as 2 min., 1 min., or ½ min. patterns stand in the way of any change; and while this system of marking is admittedly misleading it has served to differentiate between slow, medium and rapid registering varieties. . . ."

The British Standards Institution, though also admitting that time designations can be (in their own words) "extremely misleading," are nevertheless proposing in their draft that the terms "½ min. pattern" and "1 min. pattern" should be retained, the inverted commas and the word "pattern" being added, they say, "to show that these designations are, so to speak, trade terms, and are not to be taken as specifying the time required for the thermometer to register correctly." But the housewife, offered the choice of the two "patterns" by a chemist, will have no chance of seeing the inverted commas, and no means of knowing that she is hearing a trade term. She will take a "½ min. pattern" in good faith, believing she need only keep it in her child's mouth for half a minute to get a reliable reading. The public should not be misled merely because the manufacturers have contracted a bad habit and are unwilling to give it up.

The Association of Scientific Workers, in a comment on the British Standards Institution draft, suggest that the terms "rapid," "medium," and "slow" should be substituted for the misleading terms "½ min.," "1 min.," and "2 min."; but there are obvious trade objections to marketing a thermometer described as "slow." Moreover, the B.S.I. draft specifies only the "½ min. pattern," the "1 min. pattern," and the "stubby-bulb pattern"; which suggests that the "2 min. pattern" is no longer on the market. Perhaps appropriate names for the two remaining types would be "long-bulb rapid" and "long-bulb medium" (to distinguish them from the "stubby-bulb pattern"). The A.S.W. make an alternative suggestion—that there should be only one standard clinical thermometer, and that it should have a minimum reading-time of 3 min. stamped on it, with a recommendation that this time should, if possible, be exceeded. Perhaps the device "3 min. +" would suffice. Certainly the public have been trained so consistently to believe that an accurate reading can be taken in half a minute that this piece of re-education is thoroughly necessary.

NEW RELAXANTS

RELAXANTS are nowadays an essential part of anæsthesia. There are a very large number of drugs that interfere with neuromuscular transmission; indeed, pharmacological chemists would probably have little difficulty in synthesising many more of them, for a great deal is known of the relation between chemical structure and relaxant action. The difficulty is to select compounds that will be useful in clinical practice and to assess their value. Studies on animals help greatly; but, because of species difference and the very considerable environmental differences between the pharmacological laboratory and the operating-theatre, the ultimate test must be on patients undergoing an operation.

So far, relaxants seem to be of two main groups. Those in the first group resemble in action the alkaloid *d*-tubocurarine, interfering with the depolarising action of acetylcholine. The others, acting like hexamethonium, cause persistent depolarisation, inhibiting the activity of the neuromuscular junction.

With regard to *d*-tubocurarine, the original relaxant in anæsthesia, there seems to be little real cause for dissatisfaction, though it is generally believed to cause increased oozing owing either to its histaminic effect or to ganglionic block. Its main action persists for about half an hour; this may sometimes be too long, but neostigmine will cut the time short. Of the curare-like relaxants, only gallamine has so far proved a satisfactory substitute for the natural alkaloid. Gallamine is cheaply made and presumably will always be readily obtainable—which tubocurarine may not be. To its discredit it quite often gives rise to tachycardia owing to a vagolytic action.

Of the depolarising group, hexamethonium had a brief period of popularity. It is potent and has a fairly short-lived action, and it was said to be antagonised by pentamethonium. Unfortunately, however, in clinical practice this antagonism cannot be relied on. Nearly a year ago a newcomer to this group, succinylcholine, was introduced. It was reputed to be the safest of all relaxants because of its very short action and rapid disintegration, and the absence of after-effects. Here again early hopes have not been completely fulfilled; for lately there have been many reports of unexpectedly long-continued effects from this "short-acting" relaxant. The criticism that such untoward effects were largely due to overdosage has not wholly stilled uneasiness about the safety of this drug. The latest synthetic relaxant to be tested, known as Compound 20 or 'Laudolissin,' is described in this issue by Dr. Bodman and his colleagues, who report that it acts in a true curare-like manner, is antagonised by neostigmine, lasts a little longer than the natural alkaloid, and apparently has no side-effects. This objective and encouraging report will no doubt stimulate other clinical research-workers to study this drug further.

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[25] Sayers, G. *Physiol. Rev.* 1950, 30, 241.
[26] *Lancet*, 1943, i, 446.
[27] *Ibid*, p. 539.
[28] *Ibid*, p. 725.
[29] *Ibid*, p. 510.

There is perhaps a danger that successful preliminary tests such as these, made by skilled workers, will be taken by anæsthetists in general as evidence that the drug investigated is the best. That this is not necessarily so is suggested by the story of other relaxants. The somewhat disastrous effect of pentamethonium given to "neutralise" hexamethonium, the unexpected and alarming complications from the use of mephenesin, and the sometimes far from short action of succinylcholine, suggest a need for caution and an open mind.

THE SHAPE OF THE CHEST

COMMUNICATION between humans might be much improved by a collective inward eye. A mental image of a face, a scene, or a patient's physical signs can be so vivid that we itch to pass it on entire. But since visual memories are as subject as other memories to erasions, distortions, and decorations, it is perhaps as well that we rely, for scientific purposes, on less subjective records. The trouble is that some visual images are curiously awkward to record; and among these the shape of the chest ranks high. Dr. H. R. E. Wallis,[1] who has had trouble with it, points out that a photograph does not readily lend itself to accurate measurement; and though funnel chests are fairly easily shown by the camera, Harrison's grooves, to be demonstrated successfully, need a highly skilled photographer. When the subject is a child aged three or four he may also have to be a combination of naturalist, psychologist, and acrobat. Radiography, of course, will show localised deformities of the ribs or spine, and the inclination and spacing of ribs in emphysema and collapse; and lateral views show pigeon and funnel chests. Casts of the chest are useful for following the development of abnormal shapes, such as the bulges associated with congenital heart-disease; but casts are expensive to make and difficult to store, and young children are frightened by the long process of their construction. Even the old-fashioned tape-measure is defeated by this oddly shaped part of the body, this "irregular frustum which ceaselessly expands and contracts in several directions."

Callipers will measure diameters of the chest, and the amount of anteroposterior and lateral respiratory expansion; but since, in children, the expansion is small and the errors in reading apt to be large, the measurements are not of great value. The depth of Harrison's grooves or of a funnel-shaped depression can be measured by a small sliding ruler, attached at right angles to a bar; the bar is laid across the groove, and the ruler pushed in until it touches the bottom of the crater. This measurement, however, tells nothing about the width or slope of the groove: to record these a cyrtometer is needed.

Cyrtometers measure curves, and there are several kinds of them. Strips of soft lead are commonly used, which can be moulded round the chest wall and then removed to a sheet of paper, on which the curves can be traced with a pencil. The two sides of the chest may then be easily compared by superimposing the drawings; and tracings can also be made of the vertical contours of depressions and prominences. Lead, however, is rather stiff, and the physician may find the ribs of a pliable young child fitting themselves to the lead rather than the other way about. Moreover the method is tedious and dirty, and exposes the operator, Dr. Wallis suspects, to a new occupational hazard—chest-physician's colic. He has therefore devised a multiple-rod cyrtometer, composed with great ingenuity from two ebonite plates, 14 in. long and 3 in. wide, and 13 dozen aluminium rods, 9 in. long and $^1/_{16}$ in. in diameter, obtained from the manufacturers of a well-known children's building-set. The lower plate is grooved transversely, and the rods lie side by side in the grooves, projecting on either side of the plate. On top of them is a strip of 'Sorbo' rubber, and then the upper plate; and the plates are held together by two nuts and bolts which allow the rods to be made loose or firm. In practice the rods are loosened, and their free ends are pushed gently against the front of the chest just below the nipple line; they adapt themselves to the shape of the chest wall, forming a line shaped to its contours. The plates are then screwed together, and the outline of the chest wall is traced on paper by running a pencil along the tips of the rods. This little instrument, Dr. Wallis remarks, is easy and quick to use, does not seem to frighten children, and comes in handy when cutting linoleum to fit against moulded corners.

Even an outline of the chest wall, however, does not call up a very lively mental picture of a child's chest. The posture-recorder, used as an aid to physical training in schools, contributes something more.

This consists of a movable lens, a mirror, and a ground-glass screen contained in a box with a flap which acts as a screen against the light. The child stands against a white background, and an image of him in profile is thrown on the glass screen, as in a reflex camera; the outline of this image is traced off on tracing-paper. The method gives a very clear idea of habitual stance, and if the child is shown the tracings they often encourage him to stand better. But small children find it hard to keep still long enough to be drawn, and defective draughtsmanship can influence the result.

Pursuing his ideal of the perfect record, Dr. Wallis has also made use of the optical contour apparatus, designed to facilitate the carving of portrait heads in wood.

It consists of two lamps, each containing two 'Photoflood' bulbs and a parabolic reflector. The lamps are placed opposite each other a foot or so apart, and the light from each of them passes through a screen of plywood strips, $^1/_4$ in. wide and $^1/_{32}$ in. apart. There are 48 strips and 47 spaces; and when anyone stands between the two lighted lamps he is striped with light and dark bands like a zebra. The stripes, of course, follow the contours of his body, and demonstrate very strikingly not only its curves and hollows but any asymmetry between the two sides.

Photographs of children illuminated in this way record accurately the shape of the chest and its movement with respiration; and Dr. Wallis suggests that the apparatus could also be used to record the movements of individual ribs in health and disease.

THE European Congress of Cardiology, which is meeting in London this week, held its first session on Sept. 10. After Sir JOHN PARKINSON, the chairman, had welcomed the delegates, Prof. CHARLES LAUBRY (Paris), the honorary president, delivered his inaugural address. Prof. GUSTAV NYLIN (Stockholm), the president, also spoke.

THE INDEX and title-page to Vol I, 1952, which was completed with THE LANCET of June 28, is now in preparation. A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now.

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1. *Brit. J. Tuberc.* 1952, 46, 136.

Special Articles

HOT-CLIMATE FATIGUE IN THE ROYAL NAVY

A REVIEW OF LAY OPINION

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Opinions vary concerning the relative importance of the climate as a cause of the increased mental inertia and reduced mental stability which affect some persons who come to the tropics from more temperate zones. When mental breakdown occurs, psychiatrists often find that the hot climate is a less important factor than family separations, failure to readjust to new domestic and social circumstances, economic worries, and over-indulgence in alcohol; but they derive this information from the histories of persons who have already succumbed to the circumstances of their tropical environment—the less robust personalities, the overworked, the convalescent, the unhappily married, and the misfits.

The only way to discover how healthy people react is to ask them, and it is desirable to choose persons who are able to relate their tropical experience to previous experience in a temperate climate. Naval officers and men are appropriate subjects for such an investigation. They are usually selected at random to come to the tropics from a temperate zone. Apart from the difference in climate the other environmental stresses of life in a ship are not very different from those experienced in the Home Fleet and are common to all. Moreover, as the thermal environment between decks is considerably warmer than in residences or offices on shore, the effects of different levels of warmth can also be studied.

Naval opinion on these matters was obtained by means of a voluntary questionnaire distributed in March, 1950, to officers and senior ratings in an aircraft-repair ship who had been serving in tropical waters for six months. The replies were sufficiently interesting to justify the distribution of the same questionnaire to men in a cruiser who had been serving on the East Indies Station for twenty months. It was then circulated to those officers and senior ratings on the staffs of the Commander-in-Chief of the Far East Station, of the Flag Officer of the Malayan Area, and of the Royal Naval Barracks, Singapore, who had been living on shore in the tropics for more than six months.

METHOD

The questionnaire used in each of these investigations is shown in table I. The design enabled those questioned to say whether, in their opinion, they were more or less efficient or more or less healthy in the tropics than in a temperate climate, and to indicate the character of any deterioration they recognised. Leading questions, such as "Have you lost or gained weight?" were avoided. The aim was to identify the features which were most prominent in the mind of the healthy layman without professional prompting. The descriptions of ill health, or of the ways in which efficiency deteriorated, were not necessarily those to which a clinician would attach most emphasis after a careful interview, but they were the features which were most obvious to the men who reported them.

Because of the many differences between naval life on shore and afloat, it was undesirable to compare experiences at sea in the tropics with shore life in a temperate climate. Questions 1 and 4 were designed so that the effects of climate experienced on shore in the tropics could be related to earlier experiences on shore in England, and so that the effects of climate afloat in the tropics could be compared with the effects experienced by the same persons afloat in home waters or in the Mediterranean.

The replies to questions 3 and 5 were sorted together to avoid reduplication when loss of efficiency and loss of health were attributed to the same symptom. The factors to which tropical deterioration was attributed were divisible into those which contributed directly, and others which contributed indirectly, to loss of efficiency. The latter were subdivided into adverse effects associated with excessive sweating and adverse effects not obviously associated with excessive sweating.

RESULTS

About 70 voluntary replies were obtained from each of the ships and from the Singapore establishments. Half of the replies from the aircraft-repair ship and two-thirds from Singapore were from officers, and the rest were from senior ratings. The replies from the cruiser were mostly from ratings (93%), including some junior ratings. In this respect the groups are not strictly comparable.

Reduced Efficiency

Of the men who replied from the ships, 88% thought they were less efficient in the tropics than when serving afloat in a temperate climate (table II); and two-thirds of those who were living on shore held the same opinion. The views of officers and ratings, and of men in different age-groups, were in good agreement.

Impaired Health

In the two ships 72% of the men thought they were less healthy than thay had been when serving in the Home Fleet or the Mediterranean (table III). Several considered

TABLE I—THE QUESTIONNAIRE

CLIMATE AND EFFICIENCY QUESTIONNAIRE

1. Do you consider you are more efficient or less efficient serving afloat on the Far East Station ("afloat on the East Indies Station," "on shore in Singapore") than you were when serving afloat
   (*a*) * in the Home Fleet ?________ (*b*) in the Mediterranean ? ________ or (*c*) when living on shore in England ?________
2. If you consider you are less efficient in the tropics, do you consider this to be mainly due to the effects of the climate and temperature conditions between decks (climate), or do you consider it to be due to other domestic, economic, or related factors with which this questionnaire is not concerned (other factors) ?**________
3. If you consider that your efficiency is impaired on this station because of the effects of climate, can you give 3 examples of the ways in which you consider the prevailing climatic conditions affect your efficiency adversely ?
   (*a*)
   (*b*)
   (*c*)
4. Do you consider you are more healthy or less healthy serving afloat on the Far East Station ("afloat on the East Indies Station," "on shore in Singapore") than you were when serving afloat
   (*a*) in the Home Fleet ?________ (*b*) in the Mediterranean ? ________ or (*c*) when living on shore in England ?________
5. If you consider you are less healthy on the Far East Station ("East Indies Station," "in Singapore") than you were previously, will you indicate in broad terms the general nature of your decline in health :
6. What is your age ?________
7. Are you married ?________
8. How long have you been in H.M.S.________ (stationed in the tropics this commission) ?
9. Remarks (please enter on back of form).

Signed :

* Insert "more efficient" or "less efficient," or N.A. (not applicable) if you have served on only one or neither of these stations as appropriate.

** Insert "climate" or "other factors" as appropriate.

TABLE II—NUMBERS WHO CONSIDERED THEY WERE LESS EFFICIENT IN THE TROPICS THAN IN A COOLER CLIMATE

Age-group (yr.)	Cruiser (20 mos. in tropics)			Repair ship (6 mos. in tropics)			Shore bases in Singapore (more than 6 mos. in tropics)		
	Officers	Ratings	Total	Officers	Ratings	Total	Officers	Ratings	Total
20–29 30–39 40–49 50–59	2/2 (*100%*) 2/3 (*67%*)	30/37 (*81%*) 17/21 (*81%*)	32/39 (*82%*) 19/24 (*79%*)	8/10 (*80%*) 9/9 (*100%*) 8/9 (*89%*) ..	21/21 (*100%*) 11/11 (*100%*) 2/2 (*100%*) ..	29/31 (*94%*) 20/20 (*100%*) 10/11 (*91%*) ..	3/6 (*50%*) 13/21 (*62%*) 9/13 (*69%*) 1/3 (*33%*)	8/11 (*73%*) 11/14 (*79%*) 2/3 (*67%*) ..	11/17 (*65%*) 24/35 (*69%*) 11/16 (*69%*) 1/3 (*33%*)
Total	4/5 (*80%*)	47/58 (*81%*)	51/63 (*81%*)	25/28 (*89%*)	34/34 (*100%*)	59/62 (*95%*)	26/43 (*60%*)	21/28 (*75%*)	47/71 (*66%*)
No reply	..	6	6	4	1	5	2	..	2
Numbers questioned	5	64	69	32	35	67	45	28	73

TABLE III—NUMBERS WHO CONSIDERED THEY WERE LESS HEALTHY IN THE TROPICS THAN IN A COOLER CLIMATE

Age-group (yr.)	Cruiser Officers	Cruiser Ratings	Cruiser Total	Repair ship Officers	Repair ship Ratings	Repair ship Total	Shore bases Officers	Shore bases Ratings	Shore bases Total
20–29 30–39 40–49 50–59	1/2 (*50%*) 2/3 (*67%*)	28/38 (*74%*) 17/21 (*81%*)	29/40 (*73%*) 19/24 (*79%*)	5/10 (*50%*) 6/9 (*67%*) 5/9 (*56%*) ..	15/21 (*71%*) 10/11 (*91%*) 2/2 (*100%*) ..	20/31 (*65%*) 16/20 (*80%*) 7/11 (*64%*) ..	3/6 (*50%*) 5/20 (*25%*) 5/13 (*38%*) 0/3	6/11 (*55%*) 5/12 (*42%*) 1/3 (*33%*) ..	9/17 (*53%*) 10/32 (*31%*) 6/16 (*38%*) 0/3
Total	3/5 (*60%*)	45/59 (*76%*)	48/64 (*75%*)	16/28 (*57%*)	27/34 (*79%*)	43/62 (*69%*)	13/42 (*31%*)	12/26 (*46%*)	25/68 (*37%*)
No reply	..	5	5	4	1	5	3	2	5
Numbers questioned	5	64	69	32	35	67	45	28	73

that they were more healthy but less efficient in the tropics. On the other hand 63% of those who were living and working on shore thought that their health was as good as, or better than, it had been in a temperate climate.

Direct Causes of Loss of Efficiency

The subjects' descriptions of the ways in which climate affected efficiency are classified in table IV according to the main symptom groups which they suggest.

The frequency with which these features were reported in the two ships and by the shore-based subjects is shown in table V. The outstanding complaint was lethargy or tiredness in some form or other. In the cruiser 51 out of 63 (81%) reported reduced efficiency (table II), and lethargic symptoms were referred to. Memory defects were reported by 78% of those who were questioned (table V). The office workers on shore were more aware of memory defects, and also of slowing of their mental processes, than those in ships, although fewer of them reported lethargic symptoms. Officers and ratings replied in very similar terms, with only a few differences worthy of mention. Whereas five times as many officers as men in the repair ship commented on a lowered sense of responsibility, five times as many ratings as officers reported symptoms indicating retardation. These changes in emphasis were largely due to differences in relative responsibilities and occupations. Responsibilities of the officers were greater than those of the ratings. The ratings included many skilled technicians and mechanics who were more likely to observe retarding effects in their work.

Indirect Causes of Loss of Efficiency

The reported complaints which were probably associated with excessive sweating are summarised in table VI. The men who were living on shore had few complaints other than mild skin disease. In clear contrast about half the replies from ships referred to discomfort, unsatisfactory sleep, and skin diseases, caused or aggravated by unevaporated sweat on the skin or in the clothing or the bedding.

Discomfort was reported in nearly 60% of the replies from the ships but in only 10% of replies from men living on shore. It was referred to in various ways: "excessive perspiration"; "skin irritation due to sweating"; "physical discomfort off duty"; "physical discomfort reduces will to work"; "heat increases the unpleasant effects of overcrowding"; "unable to relax"; "sweat runs in the eyes"; "perspiration interferes with bench work"; "paper work gets covered with sweat"; "perspiration interferes with the playing of string and wind instruments."

Disturbed or inadequate sleep was mentioned by 44% of the men in the ships but by only 4% of those on shore. Typical observations were: "sleep is interrupted"; "too hot to sleep well"; "continuous feeling of lack of sleep"; "more sleep is required"; "wake up feeling tired."

The complaints not obviously associated with sweating are summarised in table VII. The volunteers living on shore had few complaints. After six months in the tropics, however, a proportion of men in the repair ship reported loss of appetite and weight. These features were referred to in nearly 25% of the replies from the cruiser after

TABLE IV—SUBJECTS' DESCRIPTIONS OF WAYS IN WHICH THEIR EFFICIENCY WAS REDUCED

SYMPTOM	SUBJECTS' DESCRIPTION
Lethargy	Lassitude. Lack of energy. Listlessness. Fatigue easily. Less staying-power. Tire quickly. Less stamina. Easily exhausted. Lack of vitality. Lack of alertness. Physical and mental fatigue. Capacity for long hours less. Hard to stay awake, especially in afternoons.
Reduced concentration	Cannot concentrate. Hard to concentrate on intricate jobs. Hard to think profoundly. "Grasshopper mind." Reduced concentration in the afternoons.
Retardation	More effort is required. Think more slowly. Manual work is more difficult. Reactions are slower. Work takes longer. Output of work is less. Inclination to go slower. More difficult to learn new subjects. New problems must be tackled more slowly. Slowing of mental and physical activities. Capacity for work is less.
Lowered responsibility	Tendency to leave or rush work in hot spells. Neglect of detail. Less incentive to explore responsibilities in hot situations. Procrastination. "Couldn't care less" attitude. Less drive. Accept reports without scrutinising them. Too hot to "jump to it" and "dash around." Tendency to avoid physical effort. Tendency to avoid office work. Make hasty decisions. Lack of interest. Lazy mentally. Harder to maintain discipline. Less keen to get out of the office and see for oneself. Inclined to take the path of least resistance. "Slap-dash" methods.
Personality change	Short-tempered. Irritable. Impatient. Depressed. Neurotic. Anxious. Apathetic. Inclined to worry more. Minor troubles are magnified out of all proportion to their real importance.
Memory defects	Forgetfulness. Forget simple things. Absent-minded. More effort is required to remember.

TABLE V—NUMBERS REPORTING REDUCED EFFICIENCY

—	Cruiser (20 mos. in tropics)	Repair ship (6 mos. in tropics)	Shore bases in Singapore (more than 6 mos. in tropics)
hargy	54 (*78%*)	44 (*66%*)	31 (*42%*)
luced concentration ..	14 (*20%*)	21 (*31%*)	22 (*30%*)
ardation	6 (*9%*)	14 (*21%*)	18 (*25%*)
rered sense of responsibility	16 (*23%*)	23 (*34%*)	10 (*14%*)
sonality changes	13 (*19%*)	22 (*33%*)	13 (*18%*)
nory defects	3 (*4%*)	5 (*7%*)	13 (*18%*)
questioned	69	67	73

LE VI—NUMBERS REPORTING ADVERSE EFFECTS PROBABLY ASSOCIATED WITH EXCESSIVE SWEATING

—	Cruiser (20 mos. in tropics)	Repair ship (6 mos. in tropics)	Shore bases in Singapore (more than 6 mos. in tropics)
comfort	38 (*55%*)	39 (*58%*)	7 (*10%*)
orders of sleep	31 (*45%*)	29 (*43%*)	3 (*4%*)
eases of the epidermis : ..	34 (*49%*)	32 (*48%*)	16 (*22%*)
rickly heat	14 (*20%*)	25 (*37%*)	5 (*7%*)
ungus infections	12 (*17%*)	4 (*6%*)	2 (*3%*)
uts go septic or take longer to heal	3 (*4%*)	8 (*12%*)	5 (*7%*)
calp affections	2 (*3%*)	0	0
ar affections	3 (*4%*)	1 (*1·5%*)	0
oils	3 (*4%*)	1 (*1·5%*)	3 (*4%*)
questioned..	69	67	73

LE VII—NUMBERS REPORTING ADVERSE EFFECTS F TROPICAL SERVICE NOT OBVIOUSLY ATTRIBUTABLE TO XCESSIVE SWEATING

—	Cruiser (20 mos. in tropics)	Repair ship (6 mos. in tropics)	Shore bases in Singapore (more than 6 mos. in tropics)
of appetite	17 (*25%*)	9 (*13%*)	1 (*1·4%*)
of weight	16 (*23%*)	4 (*6%*)	2 (*2·7%*)
ro-intestinal disorders, digestion, constipation ..	5 (*7%*)	9 (*13%*)	4 (*5·5%*)
mon cold, respiratory fections	8 (*12%*)	3 (*4%*)	4 (*5·5%*)
dache	12 (*17%*)	4 (*6%*)	2 (*2·7%*)
eral debility	6 (*9%*)	2 (*3%*)	1 (*1·4%*)
questioned..	69	67	73

nty months' service on the East Indies Station, and % complained of headaches.

he reported loss of weight in the cruiser was supported a review at random of the weights of 35 members of ship's company obtained during their PULHEEMS minations after about six months and eighteen iths in the tropics. There was an average weight loss ·7 lb. for the group, which was statistically significant. s did not include any initial losses on arrival in the pics, and was due mainly to losses by those who were ve average weight, for 17 men above the average ght of 145 lb. lost 2·8 lb. on the average, which was also ificant; whereas the average loss by 18 men below rage weight was only 0·66 lb., which was not significant. nly 2 men referred to dizziness, and only 2 to swollen and swollen legs; 7 men (2 in the cruiser, 2 in the ir ship, and 3 on shore) commented on the unpleasant ts of sun glare on the eyes.

portance of Climate

he great majority (over 80%) of those who thought were less efficient in the tropics, either on shore or at, considered that loss of efficiency was due mainly limatic factors (table VIII). Only 4 out of 157 men %) considered that domestic, economic, or related ors were more important than the tropical climate. remainder thought that climate and other factors implicated equally.

DISCUSSION

It is of value to see how far these statements of opinion are supported by accounts of war-time experience. The resemblance is close between the picture of "hot-climate" fatigue in these ships and that described as "tropical fatigue" by Macpherson (1949) in the New Guinea area in 1944. The term "hot-climate" fatigue is used here because symptoms attributed directly to the effects of excessive warmth were so prominent, and also because the climate in the tropics is very pleasant for much of the time, particularly at the higher altitudes, and because unpleasantly warm climates are encountered outside the tropics.

Macpherson obtained his information by the examination and systematic interrogation of "fit men" in their units. The majority had only been in the tropics about six months. The characteristic complaints were sleepiness, headaches, vague abdominal pain, loss of appetite, pains in the back, loss of weight, and dizziness on standing up. He devoted special attention to dizziness, and found that this symptom was in fact less common (33/1257, or 2·6%) than the reported incidence of "blackouts" suggested. The incidence of dizziness in the present naval replies was even smaller (2/209, about 1%), probably because the subjects were not questioned directly on this point and because the psychological stresses of war were removed. Macpherson's objective observations, including tests for circulatory instability, reduced ability to carry out a set physical task, and periodic weighing, did not suggest a serious degree of physical deterioration. He concluded that tropical fatigue was partly physical, because ill health, particularly skin disease, was more prominent than in a control series of men not serving in the tropics, but that it was psychological to a very much greater extent. The climatic factor was important in its causation, although isolation, boredom, conditions of service, and the moral fibre of the men had to be considered as well.

In an account of naval psychiatric cases observed at Bombay and Trincomalee, Cameron (1945) gave the clinician's viewpoint. He described first the vague symptoms encountered commonly outside the consulting-room:

> "Lassitude, tiredness and awareness of the temperature . . . a somewhat lowered tempo of performance and the need to accept slightly lowered standards in oneself and others. The effects on work and interests, at first, are not markedly significant, and a good performance and healthy outlook are maintained with two exceptions, immediate memory and capacity for concentration are impaired. . . . A serious consequence of impaired attention and anxiety . . . is irritability."

So far the comparison with the present replies is again close. In a contemporary account Critchley (1945) considered that to a newcomer to the tropics the syndrome of undue irritability, alcoholic indulgence, mild hypochondriacal preoccupation, and a tendency towards paranoid feelings of resentment was suggestive of a mild dementia with personality deterioration—but for the clear insight of those affected and the fact that the condition was cured after leave at home.

LE VIII—MEN WHO REPORTED LOSS OF EFFICIENCY TO BE DUE TO CLIMATIC FACTORS, NON-CLIMATIC FACTORS, OR A COMBINATION OF BOTH

—	Cruiser (20 mos. in tropics)			Repair ship (6 mos. in tropics)			Shore bases in Singapore (more than 6 mos. in tropics)		
	Officers	Ratings	Total	Officers	Ratings	Total	Officers	Ratings	Total
atic factors	2 (*50%*)	39 (*83%*)	41 (*80%*)	20 (*80%*)	28 (*85%*)	48 (*83%*)	22 (*85%*)	16 (*76%*)	38 (*81%*)
-climatic factors	..	..	..	1 (*4%*)	1 (*3%*)	2 (*3%*)	1 (*4%*)	1 (*5%*)	2 (*4%*)
.. .. ..	2 (*50%*)	8 (*17%*)	10 (*20%*)	4 (*16%*)	4 (*12%*)	8 (*14%*)	3 (*11%*)	4 (*19%*)	7 (*15%*)
eply to question 2 ..	..	..	..	..	1	1	—	—	—
Total	4	47	51	25	34	59	26	21	47

Cameron then described a "prepsychotic tropical syndrome" which emerged occasionally from this broad backcloth. This was typified by dullness, apathy, unwillingness to confide, tremulousness, conscious anxiety, and paranoid outlook, but not by failure of the intellectual faculties, disorientation, or hallucinosis. Established psychoses (conditions certifiable by British law) were responsible for 1 in 7 of the total number of patients he interviewed. Nearly all the patients seen at Trincomalee came from ships, and nearly half of them showed physical evidence of an adverse reaction to heat, such as prickly heat or some other form of skin disease, in contrast with only 10% at Bombay, where the majority were based on shore. The history was not usually that of an unstable person. The usual progress was towards recovery though the patient remained in the tropics. The peak incidence occurred among those who had been less than six months or more than eighteen months on the station. An unduly high proportion were men aged more than 40. Marital unhappiness was a factor in 25% of the cases. Cameron probably saw a more severe state of affairs than he would have encountered in peace-time, because of the more strenuous climatic and operational conditions of the war afloat, and the larger numbers of older and conscripted men exposed to these stresses.

The emphasis laid by Cameron (1945) and Critchley (1945) on the importance of psychological deterioration in the tropics was not supported by the monthly returns of sickness from the Eastern and British Pacific Fleets between February, 1944, and August, 1945, when the average monthly incidence of fresh patients reporting for treatment who were diagnosed to be suffering primarily from a psychoneurotic disorder never exceeded 0·1% of those at risk (Ellis 1948). On the other hand, skin diseases, excluding uncomplicated prickly heat, caused 10% of ships' companies to report for treatment each month. It has been suggested that, if you eliminate the psychiatrist, psychiatric illness will not figure largely in routine sickness returns; and psychiatrists were in short supply in the Eastern Fleet. This is not to say that psychiatric complaints ceased to exist but that greater prominence was probably given by those living in ships to coincidental physical complaints.

The incidence of the more common causes of ill health was nearly twice as great in ships as in shore establishments. The time lost by air-crew in a fleet aircraft-carrier because of sickness was three times as great in the tropics during the third quarter of 1944 as in the second quarter of that year when the ship was operating off the Norwegian coast (Rogerson 1945). The average working time lost through sickness in a cruiser and a battle-cruiser during five and eight months respectively in the Eastern Fleet in the same year was nearly thrice that lost in the previous period when these ships were in the Mediterranean (Ellis 1946). In the first year after the war the weekly sickness returns from all ships revealed that total sickness was more than doubled in tropical as contrasted with northern temperate waters, and diseases of the skin were increased by three or four times (Fraser Roberts 1948).

There was little doubt that efficiency was also reduced because of the warmth of the environment between decks, although it was not easy to prove this. Men decoding signals in cypher offices, accountants, store officers, and others engaged in sedentary mental work described how, after short periods in their hot offices, they were unable to think and either felt drowsy, made unreasonable mistakes, or failed to concentrate altogether. Others remarked how mistakes were made often without the knowledge of the person making the mistake. Officers in charge of gunnery-control positions noticed that the crews of transmitting stations and calculating positions made more individual errors and their team-work was not so good as it was in home waters. Engineer officers reported that the work of skilled technicians was of a poorer quality than the work turned out in a cooler climate, and the winding of electrical armatures in electrical repair shops took longer, although more men were occupied on this work. Heavier work, such as "bombing-up" a wing of 24 aircraft in a carrier, took half as long again in the tropics.

Experimental evidence also supports the view that efficiency was reduced. The average effective temperature (Bedford 1946) on the mess-decks in the Eastern Fleet was 84°F, and much warmer conditions were encountered in most places where the crews worked between decks (Ellis 1948). Mackworth (1951), in a series of experiments carried out under controlled climatic conditions at Cambridge, showed that the level of performance of men carrying out tasks simulating those of wireless telegraphy, radar, and gunnery ratings deteriorated when the effective temperature of the climate in which they were working was raised from 81° to 86°F.* Observations made at Singapore by Pepler (1951) on naval ratings acclimatised to the tropics also confirm Mackworth's assumption that the performance of certain tasks will deteriorate with increasing warmth at these climatic levels, although he found rather more variability than Mackworth in the levels of warmth at which these effects were observed.

Hot-climate fatigue, though less obvious, was probably just as common as prickly heat in the Eastern Fleet during the war, and when the latter was rife in a ship's company it was a useful indicator of the presence of the former. Under operational conditions it was the rule rather than the exception in many ships, but it did not lead to serious breakdown very often, as it might have done in a less stable community. A man affected by hot-climate fatigue does not necessarily feel ill; indeed his attitude is at times euphoric rather than gloomy. He is unlikely to call on the doctor because he feels more lethargic, less responsible, more forgetful, or more irritable than he is accustomed to be; nor will he seek in the sick-bay a cure for incessant sweating, for these are accepted as unavoidable concomitants of life in an excessively warm climate. When practically everybody is affected to some extent, such features of abnormality are often accepted as normal within the community, although they may appear strikingly abnormal to a trained observer fresh from a temperate climate (Critchley 1945). These men were fatigued by chronic discomfort from continuous sweating, chronic skin diseases, lack of sleep, salt deficiency in some cases, and the body's never-ending struggle to maintain itself in thermal equilibrium with its environment, added to the cumulative effect of four or five years' vigorous naval warfare. When they obtained relief from their hot living and working conditions they usually recovered quickly. When the occasion demanded it, either in action or for the captain's rounds or other inspections, the very great majority would "snap out of it" for the time being, although between times a relaxation of standards, general appearances, and responsibilities, which could not be conducive to full efficiency, might be accepted without comment. The truth probably lay somewhere between the sorry story told by the few psychiatrists in their overcrowded clinics and the more optimistic statements of executive officers who were impressed by what they saw at inspections or by efficiency in action when men were keyed up to give their best performance.

The thermal environment between decks is much warmer than in offices and barracks on shore. In the tropics the average temperature of the air in the living-spaces, which are the cooler parts of a ship, is about 7°F higher than that of the outside air. At these levels of warmth this makes all the difference between a climate which is tolerable and one which is too warm for comfort (Ellis 1952). Adequate methods for controlling the climate within warships are available today; but the necessary modifications in design must be compatible with the other requirements of a fighting ship, and acceptable in other climates.

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* The actual environments used by Mackworth were dry-bulb and wet-bulb temperatures of 90/80°F and 95/85°F when the average air movement was about 100 ft./min. and the men were stripped to the waist.

SUMMARY

Naval officers and ratings serving afloat and on shore in the tropics answered a questionnaire about the effect of climate on their efficiency and health.

The great majority of those serving in the ships thought that they were less efficient in the tropics than when serving afloat in more temperate waters, and two-thirds of those living on shore thought that they were less efficient than when serving on shore in England. Climatic factors were regarded as the main cause of this loss of efficiency by over 80% of 157 men who thought they were less efficient, and only 4 men (2·5%) considered domestic, economic, or related factors to be more important than climate. The views expressed by officers and men were in close agreement.

Whereas over 70% of those in the ships thought that they were less healthy in the tropics, nearly two-thirds of those living on Singapore Island thought that they were equally healthy or more healthy in the tropics than in a temperate climate.

When healthy men serve for a long time in an unduly warm climate, some of them will suffer from hot-climate fatigue, typified by lethargy, mental retardation, reduced powers of concentration and sense of responsibility, irritability, and mild changes in personality and forgetfulness, which are associated often with excessive sweating, unsatisfactory sleep, skin diseases, loss of weight, loss of appetite, and ill-defined digestive disorders. This syndrome develops when men live and work at levels of warmth which result in the presence of unevaporated sweat on the skin and in the clothing or bedding. The majority of men exposed to these conditions will suffer in one way or another after a time, but in a healthy community serious breakdown will not be encountered very often, and there will be little reference to the condition in routine sickness returns. Most of these effects can be surmounted temporarily when it is necessary to make a special effort, and are relieved by resumption of life in a cooler climate.

The evidence available suggests that hot-climate fatigue does not raise many serious problems among the male naval community in Singapore Island but becomes increasingly prominent with long service afloat in a tropical climate.

This account is published by permission of the Admiralty and the Medical Research Council's Royal Naval Personnel Research Committee. I am indebted to the Commander-in-Chief, Far East Station, and the Flag Officer, Malayan Area, for permission to circulate the questionnaire; to Surgeon Commander T. Barlow, R.N., who arranged for its distribution and collection in the cruiser; to the officers and men who provided the answers; and to Sir Frederic Bartlett, Dr. R. K. Macpherson, Dr. J. O. Irwin, and Dr. K. Cameron for helpful advice.

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THE HEALTH OF THE ARMY

In the complexities, stresses, and strains of modern warfare, health has become increasingly important to the fighting Services; and the switch of emphasis from the prevention of disease to the attainment and maintenance of health is shown by the change of title of the Directorate of Hygiene to that of Army Health. This tendency can also be seen in the recently published Report on the Health of the Army in the years 1946–48, which covers the period of demobilisation and run-down from the war-time peak.*

HEALTH EDUCATION

An accurate definition of "health" and a satisfactory method of assessing it are essential; and the chapter on recruiting and medical classification is important. The introduction in 1948 of the PULHEEMS system of medical classification into the three Services improved the assessment of physical and mental health; and the Interdepartmental Standing Committee on Medical Classification, set up in the same year, was given the responsibility, among others, of keeping the PULHEEMS system up to date. The lead given by the Services in medical classification and in personnel selection might with advantage be followed in civilian life to a greater extent than at present.

During these post-war years physical training was modified in accordance with the Army's changing requirements. Coöperation between physical-training staffs and the medical services became closer; and medical supervision of the recruit and the trained man in their basic and battle training, and tests, was intensified. The remedial aspect of physical training for the sick and wounded and for the substandard recruit was also developed, especially at the three physical-development centres, where the physique of substandard recruits was built up. In 1946 these three centres were amalgamated in one centre at Chester, accommodating 1800 recruits. In 1948 man-power shortage led, unfortunately, to its closure. Presumably mobilisation plans provide for these centres to be reopened. But it might be worth considering whether these substandard recruits should not be detected long before call-up, and given physical-development courses under civilian auspices before they leave school.

The Army tackled health education vigorously. All cadets and recruits, and all officers, N.C.O.s, and trained men received essential instruction, planned according to their needs, from medical officers, and instructors trained at the Army School of Health. At the school and in centres abroad, courses were held for unit sanitary and water-duty personnel. Instruction on service in the tropics and subtropics was given on all troopships proceeding to the Middle and Far East. All possible use was made of films, filmstrips, models, pamphlets, books, and the like. The difficulty was to ensure that, in the welter of training and instruction which the soldier received, sufficient time was set aside for education in health. In this the support of the military training authorities was invaluable.

ENVIRONMENTAL RESEARCH

During the late war personnel research was carried out under the ægis of the Military Personnel Research Committee, which lapsed in 1945. In 1948, in view of the increasing complexity of modern equipment and of the wide range of environments in which the soldier of today has to serve, a new committee was formed, under the chairmanship of Sir Charles Lovatt-Evans, F.R.S., to consider applied physiological and psychological research. The members include civilian physiologists and psychologists as well as representatives of the three Services and of the Ministry of Supply. Four subcommittees deal with special aspects of the work, such as clothing and equipment, fighting vehicles, and steel helmets and body armour. Some progress has been made, but the personnel and resources for the large amount of applied research required seem inadequate. Fundamental research remains the responsibility of the Medical Research Council through its Interservices Personnel Research Committee.

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* This report is not on sale, but copies have been sent to learned societies.

Of recent years soldiers have been increasingly exposed to industrial hazards owing to the formation of large workshops, light-aid detachments, and similar units. It became clear that to combat these hazards the Army needed outside help; and a committee was set up, under the chairmanship of Dr. E. R. A. Merewether, H.M. senior medical inspector of factories, which included representatives of the three Services and of the Ministries of Health, Supply, Labour, and National Service.

PREVENTION OF DISEASE

No striking advances in prevention were made in the period under review, but research was continuously in progress.

In 1948 proguanil was substituted for mepacrine in prophylaxis against *malaria*. Proguanil causes no skin discoloration, and a shorter period of build-up is required.

A sharp increase in *diphtheria* among troops in Germany at the end of 1945 led to an inquiry into the immunisation state of recruits; and in 1946 instructions were issued for the Schick-testing, and immunisation when necessary, of all recruits. This measure is now normal practice; and in Germany, along with other more local measures, it resulted in a drop in diphtheria incidence from 3·06 per 1000 in 1946 to 0·95 in 1948.

In Germany and Austria *acute ulcerative gingivitis* also caused much anxiety. Here the only certain method of prevention was a high standard of oral hygiene and, in treatment, penicillin.

Native food-handlers in kitchens and messes were considered to be responsible for small localised outbreaks of the *enteric group* in the Middle East. It was difficult to trace the carriers owing to the intermittency of the condition. A contributory factor was the relatively low standard of accommodation and sanitation in many parts of the Middle East. Together with fly infestation, this was also responsible for much of the dysentery in the Middle East. In fact, in the years under review the incidence increased from 24·05 per 1000 in 1946 to 33·01 in 1948. The dysentery-rates for the Middle East were higher than those for the Far East. The failure to improve this situation, despite adverse factors, should be investigated further.

In 1947 there was not a single case of *cholera* in British troops or their families, though in Egypt they were living in the closest proximity to the outbreak in the Canal area; all those concerned deserve the highest credit. Reliance was placed mainly on general measures, and on the coöperation of the Forces in these measures. It was at a late stage in the outbreak, when the battle was already almost won, that popular anxiety at home led to inoculation of the troops with cholera vaccine.

Venereal disease in Germany and in the Far East caused concern in 1946. Since then there has been a steady improvement in the Far East and a dramatic drop in Germany. In the Middle East the rates were comparatively low, and in the United Kingdom low.

The introduction of chloramphenicol in 1948 completely changed the outlook for *scrub-typhus*.

Skin diseases remain, as in the past, an important cause of sickness and inefficiency. Apart from scabies, which runs parallel with venereal disease, the type of case varied with the Command. In the Far East fungus infections caused the most trouble, in the Middle East septic conditions. In 1948 a team visited the Far East to study improved methods of prevention of skin diseases. An investigation at Aldershot in the same year showed that in a random sample of 1016 newly joined National Servicemen 3·67% had tinea pedis. Communal showers and swimming-pools were thought to be more important causes than hyperhidrosis.

The average incidence of *tuberculosis* in overseas theatres was less than 1 per 1000 per annum. In the United Kingdom it was about 3 per 1000 owing to the inclusion of recruits found by mass miniature radiography to be infected on entry. Mass miniature radiography was carried out mainly by 10 mobile Army teams, but the Ministry of Labour and National Service has now agreed to this work being done at the initial medical board. Owing to shortages of staff, apparatus, and accommodation, the take-over by the Ministry is gradual, and it will be some time before the transfer is complete.

The war-time emergency vaccine laboratory at Everleigh has been transformed into an independent unit, with the title of Army Vaccine Laboratory. It has a mixed military and civilian staff divided into a bacteriological department for the preparation of immunising vaccines and diagnostic sera and suspensions, and a transfusion department for the preparation of crystalloids and the servicing of transfusion-sets. In 1948, 960 litres of T.A.B. vaccine were produced, and 198 litres of other kinds of vaccine.

PROBLEMS OF INTAKE

Psychiatric disorders accounted for 9 discharges per 1000 of the strength each year—far in excess of any other cause. Every effort was therefore made to screen thoroughly the recruits at intake centres. Personnel selection officers interview each recruit and refer to a military psychiatrist all who are so dull as to be unlikely to absorb military training or who appear to be of doubtful stability for a Service life. The rise in the percentage of intake referred from 10% in 1946 to 17% in 1948 was due rather to an increasing awareness of the value of the psychiatric screen than to deterioration in quality of the intake.

The problem of the employment of men of low intelligence remained as difficult as ever, as also the special problems of the S.G.5 group—i.e., the lowest group in terms of ability to learn—into which approximately 13% of the Army's recruit intake fell. About 5% of the Army's recruits were unable to assimilate normal training and had to be allocated to the Royal Pioneer Corps for simple labouring duties.

HOSPITAL PROBLEMS

On the surgical side in 1946–48 there was a steady decline from a first-class and fully staffed specialist service in the Royal Army Medical Corps to an overstretched service of doctors with minimum specialist cover. Furthermore, there was the general difficulty of recruiting doctors for the R.A.M.C., on account of unsatisfactory pay and conditions of service. At the same time overseas responsibilities increased greatly; for in certain commands British civilian members of the Control Commission became entitled to treatment, and the number of military families increased greatly. A high standard of surgery was, however, maintained, and a policy adopted of evacuating early from overseas long-term cases and those needing highly specialised forms of treatment.

The hospital admission-rates per annum among British troops in the four large commands over the three years were as follows (per 1000 strength):

	1946	*1947*	*1948*
U.K.	432	360	311
Germany	499	586	456
Middle East	479	390	473
Far East	685	571	551

CONCLUSION

The progressive attitude of the Army medical authorities shown in this report can reassure us all that the soldier is in excellent hands. The National Serviceman should return to civilian life physically and mentally improved, and the cumulative effect of this on the nation as a whole must be considerable. Inter-Service coöperation and liaison with the civilian medical world, which was such a profitable feature of the war years, has continued and indeed increased. Moreover, the opportunities for research in the controlled community of the Army are clearly not being lost.

In England Now

A Running Commentary by Peripatetic Correspondents

WE are daily assailed by warnings that the population is ageing, and that in 40 years a handful of wage-earners will be attempting to support a ponderous agglomeration of unproductive and senile citizens. A colleague recently pointed out to us that attention has not been adequately drawn to the increase in the rate of advance of old age, and adduces as evidence the fact that for him the millennium is here and now. Though a man of only some 48 winters, his ulcer is already well established, and his asthma and his rheumatism trouble him at night. His discs do not prolapse in a well-conducted way, but moulder away quietly, and already he has reached a stage of forgetfulness which would do credit to a stage professor. The crowning blow came the other day, when he went to his dentist for a regular check-up and was told that his teeth were being attacked by a disease of old age.

Unfortunately the potential wage-earners in his family are not yet of an age at which he can hand on the torch to them, being 6 and 2 respectively, so he is battling on despite his manifestly outworn mental and physical equipment—a man in advance of his time.

* * *

Last week I had a kind of busman's holiday attending the British Pharmaceutical Conference at Nottingham, and I found that the buses our pharmacist brethren drive are pretty complex affairs. Early in the proceedings a paper on the structural requirements for antibiotic activity in the chloramphenicol series showed me how little I know of modern pharmacological chemistry; after which the coup de grâce was administered by a discussion on polarographic determination of riboflavine. I gathered from the cognoscenti that the standard of the more esoteric papers was as high as the standard of those I could understand. In a symposium on the pharmacy of antibiotics there were some interesting remarks on what the pharmacist can teach the doctor; and, though some dissentients thought that physicians resented any such attempt, I for my part am willing to learn about all new drugs from any informed person—as indeed most of us are.

One speaker quoted Sir A. V. Hill's recent praise at the British Association for the scientific attitude of industry in this country, and claimed that the section which most deserved approbation was the pharmaceutical. There might have been a little of the "Here's tae us, wha's like us!" spirit in this, but nevertheless the conference was itself good evidence in support of the claim.

* * *

I have always prided myself on an ear for accents. I used to boast that I could spot a patient's origin and upbringing after about three sentences. But never again. After that young woman who has just left I've finished with country and class spotting for good.

"Aim a little worried about meh haht," she said. (Ah, English public school of course—Roedean, Wycombe, Cheltenham. One of those.) But the lady had not been registered before. How was that? "Well, as a metter of fect, Aim not English."

"No, no, of course not. Your name is, let me see, ah yes. Miss Pumpernickel. You will be German then?"

"Er ner, Aim not German."

"No? What are you then? You ought to be English by your accent."

"Ai expect Ai picked up meh accent from the English girls in Geneva. As a metter of fect Aim an American, and Ai wanted to awsk you if meh haht——"

* * *

The trial of suramin in cases of ocular onchocerciasis in the Gold Coast has been encouraging, but the treatment often has unpleasant side-effects—œdema of the feet and hands, severe pruritus, and sometimes loss of taste. Here is one patient's story, in his own words.

"I get four injections it begin me small. I feel from the foot it come for my hand it come for the body the skin no good at all it be tight. I get five injections it get me down I no fit get up. My tongue he bigger but no sore. I am feeling cold. If you chop something you never savvy he be good or no good. You savvy pepper. Sweet thing you never know him at all. You no fit bend your hand at all. Skin be like alligator. You feel scratch—too much, he no be small thing. All my foot make sore sore.

"That time you never inject me I never see fine. I fit shoot to here (*10 yards*). Now I fit shoot guineafowl as far as the school (*100 yards*). My eye get strong proper. Long time I never fit do this before."

This patient has at least recovered the full use of his limbs. He recently returned, on foot, from a visit forty miles away, and has been fined for beating his wife. I have no evidence on his savvying or not savvying sweet things; his wife might perhaps hold decided views.

* * *

I have to report two serious cases of hat-addiction. The first is that of a harbourmaster aged 75 who is convinced that to be bareheaded except when indoors is for him synonymous with death. Two years ago he and his son Daniel spent many anxious hours of darkness in a dinghy picking up craft of various kinds which had broken from their moorings during a heavy storm, and towing them to places of comparative safety. In the middle of one of these trying and dangerous manœuvres the harbourmaster's hat blew off. He clapped his hand in despair to his bare, bald head. "'Tis all over," he cried, "I'm gorn." Acting with prompt devotion Daniel snatched off his own hat and crammed it on to the old man's head. "No, father," he shouted, "you'm all right!" The old man is certain that his life was thereby saved.

The second case is that of a stonewaller aged 82 whose just pride it is that the walls he builds never fall down. He also works with his son, a promising kid of about 45 who should, according to his father, make a good stonewaller one day. The son states that only once has he seen his father without his hat, a battered bowler worn indoors and out, and even in bed. Five years ago the old man had to have a prostatectomy, from which he made an uneventful recovery. While he was in hospital his son visited him and walked straight past his bed. "Diddn reckernise 'im, y'see," he explained. "'E addn got 'is 'at on."

* * *

Which is the better reformer—the reasoner or the agitator? Most of us, I suppose, would say the reasoner, but when it's a matter of getting something done quickly, I fear the agitator has it. Our son, aged two and five months (2·416 yr.) obviously thinks so. My wife had dragged him into the local fish-shop, though he wanted to be at the level-crossing; and she was expecting crescendo screams of "want to see trains." But with the distractibility of children he soon noticed the flies hovering over the fish, and since he is scared of flies he informed the queue that they wouldn't hurt. Passing from the pragmatic to the more purely conceptual aspects of the fly-cloud, he said "Look at the nasty flies! What a lot of nasty flies! One, two, six, eight" (his scale of numbers has got some missing rungs). He thought this was a good word-collection, and kept on using it loudly and clearly. Most of the queue laughed, but some looked embarrassed, and others began to mutter "There *are* a lot of flies." The fishmonger himself made no comment, but he had an electric fan put in the next day. Another triumph of agitation?

* * *

The window-cleaner poked his head in. "Better now, sir?" "Much better, thank you, Tom." "What exactly is the matter, sir?" I began my prepared statement in monosyllables. "You know the bones in the back? Well, between them there are bits of . . ." "Oh, it's a disc, is it?" "So they say, Tom." "I know just what it's like: a cold wind goes right through you like a knife. It strikes the kidneys, no matter what you wrap up in. It proper doubles you up. It's quite the fashion these days, though I never heard tell of it before. It could be these artificial fertilisers they put everywhere, don't you think so? Myself, I think it's rheumatics. Well, so long sir, take it easy." He disappeared down his ladder.

Letters to the Editor

SELECTION OF MEDICAL STUDENTS

SIR,—In the interesting discussions on this subject in your issue of Aug. 30 little or no attention was given to the *size* of the problem.

About 2700 medical students are accepted annually; no-one seems to know what is the total number of applicants. At University College it seems that 600 students apply for 60 places; at less well favoured schools the ratio of applicants to places is apparently 7, 6, or 5 to 1. But it is well known that students generally apply to many schools, sometimes to all, in the hope of being admitted somewhere. The total number of university undergraduate students in all faculties is about 84,000—or, say, about 25,000 in each year of study. Is it to be supposed that all or even a substantial proportion of the students in the faculties other than medicine wanted to do medicine but failed to find a place? One occasionally meets a student who failed to be accepted anywhere, but there is no evidence that such cases are numerous; there is, for instance, no association of indignant rejected applicants. The matter could easily be settled if all candidates were required to fill in their application forms in duplicate, and one of the copies was sent to a central registry which collated the information. I gratuitously suggest that such a registry might be set up by the General Medical Council, the Royal Colleges, the ever helpful Nuffield Trust, or one of the universities. I hazard a guess that such an inquiry would show that the majority, perhaps the great majority, of those wanting to do medicine find places, although not necessarily in the school of their first choice.

I think we are too ambitious in our attempts at student selection: we aim at choosing the best; we should be satisfied to exclude the worst. We, of course, all know the ideal student: tall, handsome, of great personal integrity, beautifully mannered, cultured, highly intelligent, a tireless worker, original, good with his hands, skilful in exposition, a good mixer, athletic, devoting his spare time to extramural activities, with a good family background, and so on and so forth. But, of course, such students do not exist. The qualities required for success in the many occupations which a doctor can take up are so varied that I imagine that no group of selection tests, however elaborate, can be reliable. How is one to select, say, the future editor of THE LANCET, the medical officer of a Polar expedition, or an able academic research-worker? What, however, we can and must do is to exclude the student who is unlikely to display a certain minimum standard of intellect and industry; I suggest that this minimum might be the ability to get a pass or a near-pass at the 2nd M.B. at the first attempt and to get through without undue effort at the second attempt (should that be necessary). As some of your correspondents have pointed out, a candidate's school record and an honest report from the school authorities are a fair guide; the standard of performance at the 1st M.B. or the higher school certificate is even more helpful. But one should always allow for a margin of error of, say, 10–15%; and some deans, in deciding the number to be admitted, assume that a small proportion of their students will fall by the wayside for one reason or another.

The statistical inquiry that I have suggested will probably show that more students of the minimum standard set out above apply than there are places for. I doubt whether it is worth trying to sift them too thoroughly. Any method used will reject candidates who are as good as those who are selected. By allowing deans or selection committees scope for their individual whims and fancies we shall probably get students with the wide range of valuable supplementary qualities that the community needs.

Department of Physiology,
Middlesex Hospital Medical School,
London, W.1.

SAMSON WRIGHT.

HÆMOPOIESIS IN THE FŒTUS

SIR,—When I first became interested in hæmatology some thirty years ago, it was customary to describe megaloblastic blood formation as seen in cases of pernicious anæmia as a reversion to an embryonic or fœtal type of hæmopoiesis. Presumably this conception was largely based on the original description by Ehrlich, who gave the name of "megaloblast" to certain primitive nucleated red cells in the embryo. The modern view is that megaloblastic blood formation results from a deficiency of certain hæmopoietic factors (vitamin B_{12}, folic acid, &c.). Since there is no reason why the fœtus should be deficient in these factors, it seemed to me difficult to understand why fœtal hæmopoiesis should be megaloblastic.

Accordingly, I decided to examine films made from the bone-marrow and from the juice expressed from the cut surface of the liver of embryos of different ages. The films were stained with Leishman's stain. Dr. Agnes [illegible] was able to provide me with [illegible] liver-juice films from one fœtus of 16 weeks, one of 20 weeks, two of 22 weeks, two of 26 weeks, and one of 34 weeks. In every instance blood formation was normoblastic in type, and most of the nucleated red cells were late normoblasts with late pyknotic nuclei.

Department of Medicine,
University of Edinburgh.

L. S. P. DAVIDSON.

A.C.T.H. AND ASCORBIC ACID

SIR,—Since the preliminary communication by Lewin and Wassén[1] there have been many reports concerning the action of ascorbic acid on rheumatoid and formalin arthritis. On the basis of our observations on the potentiation of the thymolytic effect of A.C.T.H. by ascorbic acid (unpublished data), we performed the following experiment.

In normal male albino rats, weighing 130–150 g., formalin arthritis was produced by injecting 0·1 ml. of 2·5% solution of formalin beneath the plantar aponeurosis of the right hind-leg. The inflammation of the joints was assessed by measuring daily the volume of the extremity by Bacchus's method.[2]

In the first part of the experiment 25 animals with formalin arthritis were divided into five groups and treated daily with A.C.T.H. (Armour) subcutaneously and ascorbic acid (A.A.) intraperitoneally. The data are briefly presented in table I.

TABLE I—EFFECT OF A.C.T.H. AND ASCORBIC ACID IN ARTHRITIC RATS

Group	Daily treatment	Swelling of the leg (c.cm.)*
1	1 mg. A.C.T.H. in 0·5 ml. 1 ml. 0·9% NaCl	0·314 ±0·024
2	0·1 mg. A.C.T.H. in 0·5 ml. 1 ml. 0·9% NaCl	0·356 ±0·039
3	50 mg. A.A. in 1 ml.	0·343 ±0·016
4	1 mg. A.C.T.H. in 0·5 ml. 50 mg. A.A. in 1 ml.	0·125 ±0·014
5	0·1 mg. A.C.T.H. in 0·5 ml. 50 mg. A.A. in 1 ml.	0·209 ±0·025

* Mean value of all measurements over a period of 6 days and standard error of the mean.

There was a significant difference between the animals treated with 1 mg. A.C.T.H. daily, and the group that received the same dose of A.C.T.H. combined with ascorbic acid ($p<0·001$). In the same way the addition of ascorbic acid

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1. Lewin, E., Wassén, E. *Lancet*, 1949, ii, 993.
2. Bacchus, H. *Endocrinology*, 1951, 49, 789.

TABLE II—EFFECT OF CORTISONE AND ASCORBIC ACID IN ADRENALECTOMISED ARTHRITIC RATS

Group	Daily treatment	Swelling of the leg (c.cm.)
1	1 mg. cortisone in 0·5 ml. 50 mg. A.A. in 1 ml.	0·440 ±0·013
2	1 mg. cortisone in 0·5 ml. 1 ml 0·9 %-NaCl	0·420 ±0·013

increased the effect of a dose of 0·1 mg. A.C.T.H. ($p<0{\cdot}01$). Finally, there was a significant difference in the presence of ascorbic acid between 1 mg. and 0·1 mg. A.C.T.H. ($p<0{\cdot}01$), whereas without ascorbic acid there was no statistically significant difference between these doses ($p>0{\cdot}05$). Ascorbic acid alone did not modify the formalin arthritis more than A.C.T.H. alone.

In the second part of the experiment we tried to exclude a peripheral synergism of cortisone (Merck) and ascorbic acid. 10 adrenalectomised animals with formalin arthritis were given cortisone subcutaneously and ascorbic acid intraperitoneally. The results are given in table II.

This table shows that the activity of cortisone applied in these doses cannot be potentiated by ascorbic acid ($p<0{\cdot}05$). This experiment indicates that there is neither a peripheral synergism of corticoids and ascorbic acid, nor a peripheral sensitisation of the tissues by ascorbic acid to the action of corticoids.

These experiments accord with the well-known, but not generally accepted, assumption that ascorbic acid acts at the level of the adrenal gland on the synthesis of corticoids.[3] There is, however, still another possibility—that A.C.T.H. is inactivated at a slower rate in the presence of large quantities of ascorbic acid.

These experiments were carried out at the Institute for Industrial Hygiene, Yugoslav Academy of Science, Zagreb.

Medical Faculty,
University of Zagreb, Yugoslavia.

LJ. BOŽOVIĆ.
S. MILKOVIĆ.

OBSERVATION ON WHOOPING-COUGH

SIR,—I should like to record a personal clinical observation.

At the end of August, 1951, I had the misfortune to develop whooping-cough, having caught it from my 3-year-old daughter, who in turn had caught it from her 5-year-old cousin. During the 2nd week of my attack, I developed an area of hyperæsthesia in the posterior part of each external auditory meatus, and any stimulus (such as the introduction of an aural speculum) to this area induced a typical attack of paroxysmal coughing. After about 6 weeks this phenomenon ceased, and stimulation of this area did not produce any cough at all.

I suggest that this observation adds, although slightly, to the evidence in favour of the paroxysmal stage of whooping-cough being due to a toxin produced by *Hæmophilus pertussis,* rather than to the accumulation of secretions following damage to the cilia[4] or to enlargement of the tracheobronchial glands. Damage to the cilia and enlarged tracheobronchial glands occur in many other conditions, but the typical paroxysmal cough terminating in vomiting is rare except in whooping-cough.

That *H. pertussis* produces an endotoxin has been known since the original papers of Bordet and Gengou (1906). More recently Evans and Maitland[5] have studied the characteristics of a thermolabile toxin, and Flosdorf and Kimball[6] have described a thermostable toxin. Thompson[7] prepared an endotoxin which he used therapeutically. He noticed that a few hours after subcutaneous injection there was exacerbation of coughing paroxysms. Many physicians believe that convulsions and encephalitis may sometimes be due to the toxin[8]; and Laurent[9] and Dolgopol[10] hold that on rare occasions a secondary encephalitis reaction may be observed in addition to the circulatory lesions. There is, therefore, evidence for the production of a neurotoxin, and some workers[8] consider that this toxin sensitises nerve-endings in the respiratory mucosa to external stimuli. In consequence of the observation recorded above, I would suggest that the toxin acts on the vagus nerve, after the fashion of tetanus toxin, the (?) toxin of eclampsia, and strychnine, all of which sensitise the nervous system so that it reacts violently to trivial stimuli.

Further circumstantial evidence to the hypothesis that the catarrhal stage of whooping-cough is due to local infection with *H. pertussis* whilst the paroxysmal stage is due to a neurotoxin is found in the reports on treatment of whooping-cough with the modern antibiotics. Most workers agree that the best results are obtained if chloramphenicol is given within the first 2 weeks of the disease, the treatment having little effect once the paroxysmal stage is really established.[11] This observation is analogous to the neuritic complications of diphtheria, in that by the time the paralyses develop in diphtheria the local bacterial infection has usually ceased to be significant. The action of the pertussis neurotoxin, however, would appear to be excitatory rather than depressant.

London, W.5. M. D. WARREN.

BOXING CONTESTS

SIR,—I would be interested to know if Dr. Blonstein could justify his statement last week that boxing fosters a high physical and moral standard in the nation's youth.

Physically the muscular development produced by training will raise the performer's ability for muscular work, but much of this is temporarily or even permanently offset by injuries. I do not know of any evidence that muscular development protects an individual against disease. During my Service life in the R.A.F. I looked after a physical-training school, where the sickness-rate was as high as among other airmen and the accident-rate much higher.

As regards moral betterment I feel that Dr. Blonstein has a much weaker case. The training of individuals to dominate each other by physical force is surely a poor training in social adaptation and peace.

The educational effect of watching such contests is about as high as that of reading the baser comics.

Middlewood Hospital,
Sheffield.

G. I. TEWFIK.

HICCUP DURING ANÆSTHESIA

SIR,—Most of the letters on this subject have referred to hiccup during upper abdominal operations. I should like to describe a case where it occurred during an appendicectomy.

A healthy male European, aged 32 and weighing 12 st. 8 lb., was admitted with lower abdominal pain and vomiting of 2½ hours' duration.

At operation he was given sodium thiopentone (1·5 g.) and 'Flaxedil' (80 mg. followed by 60 mg.). The operation lasted 40 min. He started to hiccup when the appendix was pulled upon, and he stopped when the appendix was severed.

The second dose of flaxedil was given during the period of hiccup; nitrous oxide was given to dilute the oxygen, but had no effect.

I can offer no explanation of this case, but I think it is worth recording.

Jokai Central Hospital, Assam. D. A. H. MCNAUGHT.

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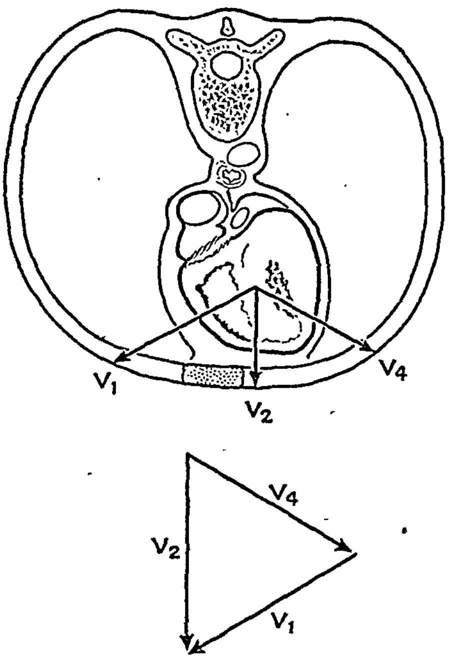
3. Lowenstein, B. E., Zwemer, R. L. *Ibid,* 1946, 39, 63.
4. Pullen, R. L. Communicable Diseases. London, 1950.
5. Evans, D. G., Maitland, H. B. *J. Path. Bact.* 1937, 45, 715.
6. Flosdorf, E. W., Kimball, A. C. *J. Immunol.* 1940, 39, 475.
7. Thompson, A. R. *Lancet,* 1937, ii, 733.
8. Harries, E. H. R., Mitman, M. Clinical Practice in Infectious Diseases. Edinburgh, 1951.
9. Laurent, L. J. M. *In* Modern Practice in Infectious Fevers. Ed. H. S. Banks. London, 1951.
10. Dolgopol, V. B. *Arch. Neurol. Psychiat.* 1941, 46, 477.
11. Swift, P. N. *Lancet,* 1948, i, 133. Gray, J. D. *Ibid,* 1950, ii, 800. Lassen, H. C. A., Grandjean, L. C. *Ibid,* 1951, i, 763. Bogdan, A. *Ibid,* ii, 1204.

LEADS IN ELECTROCARDIOGRAPHY

SIR,—We would like to make some comments on your leading article on this subject (May 31).

The different leads used in electrocardiography can be set out usefully and clearly by a geometrical method. The classical Einthoven's triangle is an example of how to represent the three standard leads. But any lead can be defined by a segment of a straight line orientated in space [1]: we call this line the axis of the lead. The axis of a unipolar lead lies on the straight line connecting the centre of the heart with the exploring electrode. The axis of a bipolar lead does not always lie on the line connecting the two electrodes, but can be found in a simple geometrical way.

What we record in any lead is the projection of the electrical vectors upon the axis of the lead. The axes of the standard leads are situated in the frontal plane, and therefore they record the electrical activity of the heart, projected on the frontal plane. The axes of the precordial leads are situated in the horizontal plane, and therefore one would expect them to record the same phenomenon as the standard leads, projected on the horizontal plane. But a different conception has been widely accepted: these leads have been thought to record almost exclusively the activity of the myocardium immediately beneath the exploring electrode. This conception may seem justified by the fact that the precordial leads are unipolar and the exploring electrode is near the heart. In fact such a fundamental distinction between bipolar and unipolar leads is not justified. What defines any lead, either unipolar or bipolar, is its axis.



It has been shown experimentally, for instance, that a unipolar and a bipolar lead record the same tracing when their axes are parallel.[2] Actually the similarity usually seen between I (bipolar and limb lead) and V6 (unipolar and precordial lead) is due to the similar orientation of their axes.

We submit that the proximity of the exploring electrode to the heart is quite relative, and does not allow any great "selectivity" in differentiating the various parts of the heart.

It has been shown [3] that, as a rule, the precordial leads record the activity of the heart in toto, and not of a single part of it. Moreover it is well known from physics that to put an electrode very near to an electrical source of energy is not always the best method of recording a higher potential; if the electrode is, for instance, on the perpendicular to the vector representing the electrical source—i.e., equidistant from its negative and positive sides—there will be no potential recorded, however near to the electrical source the electrode may be. Other objections have been raised to the so-called "local effect" theory.[4–6]

We think it is unjustifiable to consider the precordial leads to be so different from the limb leads as to need the interpretation that has been given them in English-speaking countries. Both the standard and the precordial leads obey the law of the projection of the electrical vectors upon the axes of the leads, and they record the same phenomenon; only the plane of the projection is different.

In other words, the same relationship exists between standard and precordial leads as, for instance, between anteroposterior and lateral or oblique views of the thorax in radiology. The analogy between standard and precordial leads is such that it is possible to find a system of three precordial leads which form, with their axes, a horizontal equilateral triangle, similar to the frontal one of Einthoven.[7]

The accompanying figure shows the axes of these three leads, and the equilateral triangle formed by them.

With the "local effect" theory one must always accept the possibility that a part of the heart may have escaped exploration, however numerous the precordial leads; but we feel that the examination can be satisfactorily carried out with these three leads alone. We think therefore that the precordial leads should be interpreted in the same general way as the standard leads.

ALDO SELVINI
AUGUSTO PILOTTI
FRANCO LANZA.

Medical Clinic of the University,
Milan.

COMPLICATIONS OF CONTROLLED HYPERTENSION

SIR,—In your leading article of July 5 you refer to a report of mine [8] on the effect of intravenous hexamethonium bromide on kidney function.

I should like to correct the impression conveyed by your article that the dose used each time was 100 mg. In fact, this very large dose was used in only one patient, who had already become habituated to the drug. In the remainder the dose varied from 15 to 50 mg.

E. GARTH MCQUEEN.

Department of Medicine,
University of Queensland,
Brisbane, Australia.

NICOTINIC ACID AND BURNING FEET

SIR,—A 31-year-old man with lupus vulgaris of the face was treated with isonicotinic acid hydrazide 150 mg. daily by mouth. After one week's treatment he developed a severe burning sensation of the soles of the feet—"as if there was a fire under my feet." This sensation continued for 2 days after the tablets were discontinued. He then, of his own accord, took a reduced dose of 50 mg. daily for 3 weeks without ill effect. The patient has always had hyperhidrosis of the feet, and on one occasion he developed a mild burning sensation in the feet while taking medicine of unknown nature.

The symptoms in this case recall the "burning feet" syndrome described in India and in Japanese prisoner-of-war camps. This syndrome is characterised by severe burning or freezing sensations in the feet, accentuation of the reflexes, and hyperhidrosis of the feet. While accentuation of the reflexes is a well-recognised effect of isonicotinic acid hydrazide, burning feet has not been reported before, as far as I am aware, as a toxic effect of the drug. The hyperhidrosis was present already in this case and so cannot be ascribed to the action of the drug. Gopalan [9] has ascribed the "burning feet" syndrome to deficiency of pantothenic acid, but the findings in the case described here suggest that nicotinic-acid deficiency may play a part in the ætiology of this condition, since isonicotinic acid hydrazide may conceivably block the action of nicotinic acid by competitive inhibition.

J. S. PEGUM.

London, S.W.1.

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5. Holzmann, M. *Ibid*, 1951, 40, 577.
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7. Selvini, A. Communication to the 13th Congress of Italian Cardiology: Naples, 1951 (in the press).
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9. Gopalan, C. *Ind. med. Gaz.* 1946, 81, 22.

CHLORAMPHENICOL IN ERYSIPELOID OF ROSENBACH

SIR,—I have found that chloramphenicol inhibits in vitro the growth of *Erysipelothrix rhusiopathiæ*, and I recently gave the drug to 4 patients with erysipeloid of Rosenbach, 2 of whom had not responded to treatment with penicillin.

Doses of 2 g. per day produced rapid resolution in 3 cases; in fact, after the first day of treatment, pain, œdema, and erythema quickly subsided, and after the third day only pigmentation and desquamation remained.

The 4th case was more resistant, and vivid-red erythematous areas persisted at the circumference of the lesion. But healing was complete after five days' treatment. Supplementary local treatment with 2% chloramphenicol in a base of 'Carbowax' produced no local or general intolerance.

This is insufficient evidence for a definite conclusion, but it justifies further study of the drug in erysipeloid.

Dermatology Clinic,
University of Bologna,
Italy.

PAOLO MORONI.

MALARIA

SIR,—I feel humble and appreciative in respect of your review (Aug. 30) of my book on *Malaria*. One point, however, disturbs me. I want to make it clear that I have the highest respect for, and I accept, the work of Shortt and Garnham and their colleagues on the pre- and exo-erythrocytic stages of malaria plasmodia. My term "in the shadows," referring to these early forms of the parasite, seemed fair when I wrote it because the earliest development following the sporozoite had not been described by any observer. Even today, although further progress has been made, there remain points that are not clear. It was not my intention to reflect on the fundamental studies mentioned, to which in fact I gave full credit in the short historical chapter of the book.

Division of Medicine and Public Health,
Rockefeller Foundation,
European Office, Paris.

PAUL F. RUSSELL.

SORE THROAT AND RHEUMATIC FEVER

SIR,—In his letter (Aug. 16) Dr. Collis asserts that "Schlesinger's contribution was his observation of the silent period between the initial throat infection and the subsequent rheumatic-fever attack, or relapse, and the effect on the subsequent attack of salicylate if given during the silent period."

Schlesinger, as far as I know, has never claimed that he first observed the silent period, although he was an ardent advocate of salicylate therapy, as he made clear in his Milroy lectures of 1938.[1] I suggest that the chief credit for observing the silent period goes to C. Haig-Brown, who in *Tonsillitis in Adolescents* (1886) wrote:

> "An attack of acute rheumatism is very frequently preceded by one of acute tonsillitis, it may be by as long a time as five or six weeks, but more usually ten days or a fortnight; while, as has been already stated, the two may be coincident in time. In fact, it is rare to meet with a case of rheumatic fever which has not been recently preceded by a sore throat; and though I am not prepared to say that tonsillitis is the fore-runner or the companion of every case of rheumatic fever, the last eleven cases of the latter which I have had to treat have, within six weeks of the onset of the joint-pains and fever, been under my hands with sore throats."

This was probably not the original description, for Haig-Brown modestly says:

> "As has been observed by others than myself, it is very frequently found that the subject of articular rheumatism has had a 'sore throat' perhaps a month, but more commonly ten days or so, before he felt pain in his joints, or that simultaneously with the joint-affection, there is tonsillitis."

Rugby.

R. E. SMITH.

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[1] Schlesinger, B. *Lancet*, 1938, i, 593, 649.

MEPACRINE AND RHEUMATOID ARTHRITIS

SIR,—We have read with interest the preliminary communication by Dr. Freedman and Dr. Bach (Aug. 16). Since Page's[1] report appeared, we have used mepacrine on a limited scale in selected cases.

A young woman with acute lupus erythematosus was dangerously ill when treatment with A.C.T.H. was started. She improved rapidly, but on account of side-effects of A.C.T.H. we tried mepacrine with apparently good results. The withdrawal of mepacrine was followed by deterioration.

We have given mepacrine to 11 patients with rheumatoid arthritis. The longest period of observation is five months and the shortest six weeks. All of the patients declared that their pain gradually eased, and in 5 there is already definite objective improvement. Treatment with mepacrine is not followed by eosinopenia or increased excretion of 17-ketosteroids; nor is the erythrocyte-sedimentation rate or temperature influenced in our experience.

During the last two years, 2 patients with bronchial asthma have been admitted to our hospital repeatedly on account of status asthmaticus. Several times we have had to use A.C.T.H. for short periods. Six months ago we started giving these 2 patients mepacrine. Follow-up examinations have shown that both are entirely free of symptoms and signs of bronchial asthma.

We agree with Freedman and Bach regarding dosage and length of treatment. The variable course of rheumatoid arthritis and bronchial asthma makes it very difficult to differentiate between a spontaneous remission and an effect of administering mepacrine. We hope that extended trials of mepacrine will soon solve this problem.

Medical Department,
Rogaland County Hospital,
Stavanger, Norway.

ARNFINN ENGESET.

AVERSION TO ALCOHOL

SIR,—The chance observation by Dr. Walker and Dr. Boyd (Sept. 6) that a heavy beer drinker exposed to tetraethyl lead (T.E.L.) abruptly stopped drinking (and also developed a voracious appetite) a few weeks before being admitted to hospital for T.E.L. poisoning, is of great interest to those engaged in the study and prevention of alcoholism. The same voracious appetite and distaste for alcohol was observed in 1938 in a number of workmen exposed in a clay pit to hydrogen sulphide.[2] The advent of 'Antabuse' (not 'Antabus' as recently adopted by THE LANCET) has stimulated interest in substances—of which there are quite a number[3]—causing aversion to or distaste for alcohol, which are not the same things.

In the case of antabuse it is an aversion, for one avoids contact with alcohol because of the unpleasant symptoms which then supervene. A similar aversion appears to exist in the initial stages of Hodgkin's disease, where pain, cough, and itching become intensified on taking even small amounts of alcohol.[4] On the other hand, hydrogen sulphide appears to produce a distaste, no other symptoms except the voracious appetite being reported.

Chance observations such as these may help us eventually to find a means of readjusting physiological imbalance as the cause of alcoholism. This society is anxious to collect further observations of the kind, especially on substances producing distaste or disinclination for alcohol.

H. PULLAR-STRECKER
Hon. Secretary,
Society for the Study of Addiction.

Wyke House, Isleworth,
Middlesex.

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[1] Page, F. *Lancet*, 1951, ii, 755.
[2] *Brit. J. Addict.* 1949, 46, 47.
[3] See *Ibid*, 1951, 48, 72.
[4] Verbeeten, B. *Med. Tijdschr. Geneesk.* 1952, 96, 12.

ANTITHYROID ACTION OF P.A.S.

SIR,—Clausen and Kjerulf-Jensen[1] have described three cases of thyroid enlargement with myxœdema during *p*-aminosalicylic acid (P.A.S.) therapy, and Komrower[2] has reported another. I should like to add a further case.

An unmarried woman, aged 23, was admitted to hospital on July 3, 1951, with pulmonary tuberculosis of two years' duration, clinically affecting the right lower lobe. A chest radiograph showed, in addition to the disease at the right base, some apparently new lesions at the left base. In view of this, chemotherapy was decided upon. Thiosemicarbazone ('Ethizone') (starting dose 50 mg., then 150 mg. daily) and sodium P.A.S. (3 g. four-hourly) were given.

On Sept. 17 (eleven weeks later) she complained of a swelling in the neck, and a soft diffuse, non-pulsatile, slightly tender swelling of the thyroid gland was felt. The pulse-rate was normal and the blood-pressure was 100/70 mm. Hg. There was no exophthalmos or sweating. Both drugs were stopped immediately; a total of 1170 g. of P.A.S. and 7·75 g. of ethizone had been given. She was watched for further signs of disturbed thyroid function, but none developed.

Five weeks later (Oct. 23) the swelling had subsided. The chest radiograph was unchanged. Further progress was uneventful; the left basal signs subsided, leaving the right side unchanged.

On June 18, 1952 (about eleven months later), the thyroid gland was just palpable. Her weight had remained steady at 7st. 7½ lb.

The patient has an immature and hysterical personality. She has had an unhappy home life with life-long episodes indicative of instability and insecurity. She is prone to temper-tantrums and on Jan. 1, 1952, had a prolonged episode of this sort. A psychiatrist advised certification if she proved difficult to manage, but she has since been quiet and coöperative.

Investigations.—Sept. 22, 1951: Sputum contained scanty atypical acid-fast bacilli; barium swallow normal; laryngoscopy, no gross tracheal compression; erythrocyte-sedimentation rate 4 mm. in first hr. (Westergren) at room-temperature; white blood-cell count 4400 per c.mm. (polymorphs 61%, lymphocytes 20%, monocytes 4%, eosinophils 14·5%, basophils 1%); blood-cholesterol 270 mg. per 100 ml.; basal metabolic-rate −22 (a further test was refused); weight 7 st. 9 lb.

Dec. 18: Hb 87%; blood-cholesterol 100 mg. per 100 ml.; weight 7 st. 13 lb.

It was natural to speculate whether either of the two drugs had caused the thyroid depression.

Bergqvist and de Mare[3] described a patient who died of hypothyroid goitre and cerebral œdema after treatment with 'Conteben,' and another who had definite hypothyroid symptoms after prolonged treatment with P.A.S., dihydrostreptomycin, and conteben. Domagk[4] however had never heard of an instance during conteben therapy. Mertens and Bung[5] did not mention thyroid enlargement in a review of conteben toxicity, neither did the report of the pilot trial of the British Tuberculosis Association[6] or Nagley's review of thiosemicarbazones.[7] A full account of anti-thyroid drugs by Suter[8] also made no reference to it. For these reasons, ethizone was discounted.

That P.A.S. could be responsible is borne out by Komrower's case[2] and the 3 Norwegian cases.[1] In the case described here, apart from the thyroid swelling, lowered B.M.R., and high normal blood-cholesterol, there were no overt signs of hypothyroidism, unlike the other reported cases. Unfortunately the patient refused a further B.M.R. test, and return to normal had to be judged clinically. The high eosinophil-count is interesting and may be evidence of drug allergy.

Kjerulf-Jensen and Wolffbrandt[9] have shown that rats fed with P.A.S. and *m*-aminophenol developed moderate cellular hyperplasia of the thyroid gland. Using radioactive iodine, Hanngren[10] found that uptake of iodine in the thyroid gland during P.A.S. therapy was inhibited in 3 patients. He thought that enlargement of the thyroid was compensatory, and caused by increased formation of pituitary thyrotropic hormone. He considered that when P.A.S. is given therapeutically a certain blood concentration will inhibit thyroxine synthesis just as thiouracil does. Doses in excess of the patient's thyroid sensitivity may cause myxœdema.

As in the other cases, the therapeutic effect of P.A.S., if any, did not appear to be antagonised by its antithyroid effect, which may even be beneficial in itself. The metabolic-rate is usually normal in active tuberculosis,[11] but whether a decreased rate is an advantage is debatable.

Nash[12] however gave thiouracil to 3 patients in 1947, with unexpected spread of the tuberculous lesions as a result. I remember a girl, aged 16, with thyrotoxicosis and pulmonary tuberculosis who was treated with thiouracil in 1945, and the tuberculosis became worse. *It is interesting to note that* Madigan et al.[13] suggested that the B.M.R. might rise during P.A.S. therapy, though whether a rise precedes a fall is speculative in the absence of serial tests.

The effect of myxœdema on tuberculosis is of interest. Pagel[14] merely stated that affections of the thyroid are reputed to be associated rarely with tuberculosis—i.e., they are antagonistic to its development. Other authorities[15-17] are more pessimistic, and say that untreated cases of myxœdema may die of intercurrent infections such as tuberculosis—i.e., their resistance to the disease must be lowered.

In the case reported here gross swelling of the thyroid subsided within five weeks of stopping the drugs, though it was still palpable after one year. Obviously the longer administration is continued after the thyroid swelling has appeared, the greater is the risk of myxœdematous change. Komrower's case developed after nine months' treatment. The short period of three months in this case perhaps explains the minimal thyroid changes. Whether irreversible damage can occur is speculative.

Alternatively the thyroid swelling could be ascribed to an unstable endocrine system associated with mental *instability, but the lowered B.M.R. is against this.* Nash[12] wondered whether the antithyroid effect of P.A.S. could exist *without clinically obvious hypothyroidism.* This case suggests that it can.

I should like to thank Dr. J. Spencer and Mr. J. Mallard, A.I.M.L.T., for the metabolic investigations, Mr. L. Whittaker, A.I.M.L.T., for the other investigations, and Dr. G. L. Brown for his help.

Ilford Isolation Hospital,
Chadwell Heath, Essex.

I. M. LIBRACH.

AMŒBIC ABSCESS OF BONE

SIR,—Amœbic abscesses have now been described in many tissues of the body. In this part of West Africa, where amœbiasis is heavily endemic, it has to be considered in the differential diagnosis of many clinical conditions.

I have recently had under my care an African man of the Mende tribe who complained of a hard painful lump in the middle of his thigh. Two years ago he was treated at this hospital for amœbic dysentery with a course of 6 injections of gr. 1 of emetine. There was no recurrence of dysenteric or other symptoms until the onset of fever, malaise, and pain in the left thigh one month before I saw him.

The patient was emaciated and looked ill; on the middle third of the left femur there was a tender mass about 8 cm. long; it was fixed to the bone, and though firm it was not bony hard; there was no detectable fluctuation, although the mass was clearly palpable through the wasted muscles. X-ray

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1. Clausen, A. K. H., Kjerulf-Jensen, K. *Nord. Med.* 1951, 45, 475.
2. Komrower, G. M. *Brit. med. J.* 1951, ii, 1193.
3. Bergqvist, N., de Mare, O. *Nord. Med.* 1951, 45, 474.
4. Domagk, G. *Irish J. med. Sci.* 1951, p. 474.
5. Mertens, A., Bung, R. *Amer. Rev. Tuberc.* 1950, 61, 62.
6. British Tuberculosis Association. *Tubercle*, 1951, p. 217.
7. Nagley, M. M. *Practitioner*, 1952, 168, 523.
8. Suter, C. M. *In* Medicinal Chemistry. New York and London, 1951; vol. I, p. 105.
9. Kjerulf-Jensen, K., Wolffbrandt, G. *Acta. Pharmacol. scand.* 1951, 7, 376.
10. Hanngren, A. *Lancet*, 1952, ii, 117.
11. Kayne, G. G. *In* Pulmonary Tuberculosis by G. G. Kayne, W. Pagel, and L. O'Shaughnessy. London, 1939; p. 306.
12. Nash, F. A. *Lancet*, Aug. 2, 1952, p. 245.
13. Madigan, D. G., Griffiths, L. L., Lynch, M. J. G., Bruce, R. A., Kay, S., Brownlee, G. *Ibid*, 1950, i, 239.
14. Pagel, W. *In* Pulmonary Tuberculosis. London, 1939.
15. Fishberg, M. Pulmonary Tuberculosis. Philadelphia, 1932.
16. Tidy, H. L. Synopsis of Medicine. London, 1939; p. 874.
17 Rich, A. R. Pathogenesis of Tuberculosis. Springfield, Illinois 1946.

examination was not available; the fæces contained mature cysts of *Entamœba histolytica.*

After several days' rest in bed with hot fomentations to the thigh, the mass began to soften and was explored with a needle. 3 ml. of a thick, dirty white pus was aspirated, and this contained many active *E. histolytica*; no other organisms were found in stained smears.

Six daily injections of gr. 1 of emetine were given, after which the mass had subsided, leaving no apparent thickening of the bone nor any tenderness. The patient was seen one month later when he was in much better health and gaining weight. The thigh appeared normal and had given him no trouble.

This is a case of metastatic amœbic abscess occurring, presumably, deep to the periosteum of the femur. There was no history of trauma to explain the site of the lesion; and although it had been there at least one month there can have been little, if any, new bone formation around it. The rapid and apparently complete cure also implies the absence of bone destruction on any large scale. In view of the extensive destruction of other tissues exposed to the cytolytic powers of this amœba, it would be interesting to know its action on bone in the absence of secondary infection. This case again raises the question of the mode of spread of the organism within the body. It also indicates that it is not, perhaps, so effective in its attack on bone as on, say, the liver.

Methodist Hospital, Segbwema,
Sierra Leone.
J. R. ROSE.

PROLONGED APNŒA

SIR,—There have been several reports of prolonged apnœa following "balanced" anæsthesia with thiopentone together with succinylcholine.

After carefully reading these reports I cannot see that a clear case against succinylcholine has been established in any one case. In my experience of administering thiopentone with a relaxant there have been a few instances of prolonged apnœa; and in each such case the mode of recovery, and the signs accompanying it, have clearly pointed to thiopentone as the cause.

In my experience the response to, and the recovery-time from, a given dose of a relaxant drug varies very little with either the age or the physical condition of the patient. Indeed I have repeatedly been surprised at the tolerance to these drugs of aged and very sick patients, including some aged over 70 and desperately ill with intestinal obstruction. It has been my impression that these patients require relatively more relaxant than the fit younger patients. My experience with thiopentone is quite the reverse of this; not only is there a progressive decrease in the tolerance of patients for this drug with advancing years and deteriorated physical condition (either from shock or toxæmia), but there is also a disconcerting variation in the tolerance of individual patients in the same age-groups irrespective of their physical condition. For these reasons, if my observations are correct, prolonged apnœa after administration of thiopentone together with a relaxant is many times more likely to have been caused by the thiopentone than by the relaxant.

In no case in my experience, nor in the cases reported, has consciousness returned before the restoration of breathing —a state for which I have many times been profoundly grateful. We know from experimental evidence that even massive doses of relaxant drugs have no effect on consciousness, provided that artificial respiration is adequate; and the same is true of suspended respiration due to the action of local analgesics or of the virus of anterior poliomyelitis on the motor nerves. Thus when unconsciousness accompanies and outlasts suspended respiration after the administration of a relaxant and a hypnotic, which is also a powerful respiratory depressant, the cause must surely be the hypnotic.

Once active respiration is suspended and controlled respiration has been instituted, other factors tend to prolong apnœa. Manually controlled respiration by compression of a reservoir bag usually tends to maintain a tidal volume much in excess of the normal. If this controlled respiration is carried out with an absorbing canister in circuit, as it should be, the overventilation causes such hyperoxygenation, carbon dioxide depletion, and exhaustion of the Hering-Breuer reflex that it may prolong apnœa indefinitely. Many a seemingly interminable apnœa can be ended by discontinuing controlled respiration for a few minutes. I think that apnœa produced by overventilation may have played a not inconsiderable part in prolonging apnœa initiated by either the relaxant or the thiopentone. It should be remembered that it is more easy to produce apnœa by overventilation in the presence of central respiratory depression than to abolish the peripheral neuromuscular mechanism by the same means.

I have observed two signs which determine whether the apnœa is primarily due to central or to peripheral respiratory depression.

The first sign of restoration of the neuromuscular mechanism following full curarisation is rhythmical tone in the muscles of respiration. This muscle-tone appears some time before active muscular contractions take place; its presence is indicated by the feeling of resistance when the reservoir bag is compressed out of phase with the returning respiratory rhythm. This resistance to inflation may be mistaken for evidence of the return of abdominal-muscle tone and lead to the administration of a further dose of relaxant: or, if the bag compressions are completely out of phase, the resistance to inflation, in the presence of a relaxed abdomen, may lead to a diagnosis of bronchial spasm.

I have found this sign both useful and reassuring. It fails to appear only when there is simultaneous and complete central respiratory depression.

Emergence from respiratory arrest due to central respiratory depression is first indicated by another sign.

Gentle handling of the bag will elicit a point at which the very lightest compression initiates a slow but full diaphragmatic contraction followed again by respiratory inactivity until another gentle touch on the bag again causes a further diaphragmatic contraction. After a few repetitions of this manœuvre spontaneous respiration returns. The feeling in eliciting this response is of toppling over a very finely balanced mass by the lightest touch; and I have named this sign the "trigger response" because the lightest touch sets it off. I have elicited it during emergence from the depression caused by both thiopentone and pethidine. For some reason, for which I am unable to account, it is more readily and constantly elicited in the emergence from depression due to thiopentone.

If this response is caused, as it would seem to be, by stimulation of the stretch receptors in the lungs, it would appear to be a reversal of the Hering-Breuer reflex by which stimulation of the stretch receptors terminates the act of inspiration and initiates expiration. Furthermore, since the separate central respiratory centres are depressed in the reverse order of their evolution, and recover in the order of their evolution, may it not be that this "trigger response" represents the most primitive of the respiratory reflexes; and, if this is so, may not the stimulus of the atmospheric pressure acting, through the open mouth, on the stretch receptors of the infant's lungs play an important part in initiating respiration in the newborn?

To modern methods of anæsthesia have been sacrificed one by one the cherished signs of anæsthesia, by which we used to teach the art and upon which we relied to pilot our patients through rough waters to safety. To the onlooker the plight of the patient, completely paralysed and apnœic, with pulse-rate disrupted by gallamine and the blood-pressure "controlled" at some near-catastrophic level, must seem extreme. Electroencephalography will perhaps come to be our Radar; but meanwhile these two signs may prove useful. By their help I have been able to determine the nature of respiratory arrest; and with unduly prolonged arrest the final emergence of the "trigger response" has almost invariably pointed to thiopentone as the causative agent.

Bournemouth.
S. F. DURRANS.

CURE OF TOBACCO-SMOKING

SIR,—I suggest that the gist of Dr. Lennox Johnston's article last week can be expressed in a few words:

> Smoking is a modern social habit; it is expensive, and not obviously detrimental to health. The habit can quite easily be broken by the exercise of a small amount of self-control, provided that there is a real desire to stop smoking.

I have yet to find the smoker who is an addict in the sense that a drug-taker is an addict, or the smoker who has been adversely affected in bodily or mental health when through force of circumstances tobacco has been denied to him.

I would suggest that smokers who fail to give up the habit after they have been advised to do so, or have expressed some intention of so doing, invariably have no real intention of abstaining. In my experience the provident man or woman who finds smoking too expensive a luxury, and definitely decides to stop the habit, always succeeds without great difficulty.

Louth, Lincolnshire. E. C. CORDEAUX.

SIR,—Dr. Johnston has given one account of the effects of giving up smoking. Let me, from a much shorter experience of abstinence, give another.

For thirty years I smoked heavily. The threat of lung carcinoma affected me not at all; I would willingly risk that possibility to continue to have the pleasure and comfort of smoking. But about six weeks ago I decided, for financial reasons, to stop smoking.

Instead of a "sustained uplift of spirits and of general interest" I have been morose, irritable, and unable to concentrate. Time hangs heavily on my hands, I have lost interest in my work and my hobbies, and I have nothing to look forward to. I have acquired an enormous appetite which is impossible to satisfy, and a great increase in flatulence and flatus. I have become lazy and depressed, and only my sexual potency, of which I had no complaints, remains unaffected.

Until I read your contributor's article I was well content not to touch my many comforting pipes. Since reading it my resolve has weakened, and I can see no reasonable future without tobacco.

TEMPORARY NON-SMOKER.

PS.—My colleagues disagree with this and say that at work I am much better tempered.

SIR,—Dr. Lennox Johnston, in his erudite paper, has told us everything about tobacco-smoking, except the cure.

Vague psychotherapy, in which the physician has to be patient (and the poor victim more so), reinforced by the induction of a cancerphobia, is, in my opinion, unlikely to overcome the habit. Dr. Johnston has, however, illustrated the suggestive element of smoking, and this, I believe, provides the answer. About 50% of people can be cured of the smoke habit by simple suggestion, used rapidly, under varying degrees of hypnosis, and the figures are higher if hypnotherapy and re-education are used.

Prince of Wales's General Hospital,
London, N.15. GORDON AMBROSE.

SIR,—I found Dr. Lennox Johnston's article more interesting as an account of the development and perpetuation of the tobacco habit than helpful to those desirous of emancipating themselves. He touches on all the relevant points under "how to stop smoking," but in my view does not sufficiently emphasise auto-suggestion.

Before going to sleep one should think of smoking as an unnecessary, expensive, somewhat offensive, and physically deleterious habit. One should concentrate on the obvious disadvantages of smoking—such as irritation to the respiratory passages, eyes, and tongue, interference with appetite, staining of teeth and fingers, risk of damage to the eyes from hot particles of ash while driving, the destruction caused to paintwork and carpets by careless guests, the pollution of the consulting-room atmosphere by nervous patients and colleagues who chain smoke, and so on.

Some effects of smoking are more resented than others; so the patient is advised to concentrate on those aspects of the habit which particularly annoy or repel him, and these should constitute his main auto-suggestive theme. After a few sessions of counter-suggestion the smoker finds his cigarettes less enjoyable, and within a matter of days will be smoking less and more frequently refusing the offer of cigarettes from others.

He does not require to be adamant about giving up smoking but should just set about altering his attitude towards the habit. He should continue to carry cigarettes but should endeavour to remember to ask himself if he really wants one before actually lighting up.

The object is to develop an awareness of the desire to smoke and then to elect to have a cigarette or not. Even if one fails to achieve this awareness, the distaste for cigarettes, which is inevitable after a period of counter-suggestion to smoking, may enable one to bring the habit well into consciousness. At that point the decision to continue the cigarette or not can be made.

I do not agree with Dr. Johnston that "it is necessary to do much more than merely decide to give up smoking." One can start to toy with the idea of giving it up. One need not forswear smoking. The greater the determination to abandon the habit the more the desire for a smoke is made conscious and the law of reverse effort operates—i.e., the harder one tries the less one succeeds. Why try so hard? The habit should not be given so much importance. *If one decides to give it up* one should proceed with the ritual of auto-suggestion which will bring the habit into consciousness. It is a habit which is much more readily abandoned than is commonly appreciated. I entirely agree with Dr. Johnston that smoking is harmful. "Is smoking bad for one?" should always be answered with an unequivocal "yes."

London, W.1. ELLIS STUNGO.

WHAT OF GENERAL PRACTICE?

SIR,—Your leading article of Sept. 6 states:

> "The medical student, trained in scientific method, naturally measures the general practitioner's opportunities by the precise yardstick of science—and shakes his head. What may escape him is that the good family doctor laces science's cold portion with the warmer stuff of humanism. Some of this humanism is being formalised in the doctrine of social medicine, which is finding its way into curricula; but, even so, the general practitioner's twofold technique remains essentially empirical, . . . Dons, especially those who pursue scientific disciplines, are not remarkable for their tolerance of the empirical."

This seems to imply that science and empiricism are antitheses and that science must be inhuman. According to the *Concise Oxford Dictionary* empiric means "based, acting, on observation and experiment, not on theory." Excellent examples of empirical studies are, therefore, provided by those numerous *controlled experiments* which demonstrate the value, or lack of value, of drugs, and which are such a feature of modern medicine. The antithesis of empiricism is doctrine based on theory alone, and much medical treatment of the past, and even of the present, rested on such a basis. Our forefathers performed phlebotomy to get rid of the phlegms which could be seen when the patient's blood was allowed to stand; they starved the feverish patient to prevent the fires of his fever burning more fiercely; and they purged people to rid them of noxious matters. We refrain from giving lettuce to the subjects of peptic ulcer, because lettuce leaves will erode the ulcer; we make dropsical patients thirsty because we deduce that if we allow them to drink freely their dropsy will increase; and we still give freely—or at least are advised to do so *in the very latest articles—brisk purges* to the subjects of innumerable conditions, from boils to acute tonsillitis, to minimise their toxæmia. And witchdoctors mutter imprecations and go through elaborate ceremonial to get rid of the evil spirits which are responsible for the patient's illness. Is it then to be supposed that these remedies are scientific, and that giving penicillin (the belief in the value of which is based on innumerable observations on mankind) is not scientific ? No-one, of course, adopts such a view, and all would agree that controlled experiments to illustrate the value of drugs are scientific. But it is still commonly believed that the use of remedies depending solely on theory is scientific; in fact such remedies should always be suspect.

So far from his technique being "essentially empirical," the general practitioner is at a disadvantage by comparison with those who work in hospitals because it is difficult for him to make sound empirical observations. The general practitioner who says he is convinced that a tonic has benefited a patient is making unjustified deductions from his observations; all he should deduce legitimately is that the patient has apparently improved over the period in which he has taken the tonic. To assess the value of the tonic requires a large series of similar cases, half of whom are given the tonic and the other half an inert but similar-looking preparation, and all of whom are questioned closely and consistently. The general practitioner can hardly perform an investigation of this kind, and he has to depend on the empirical observations of others.

The view in your leading article that science is inevitably inhuman suggests that a doctor is being scientific when he looks at a patient with numerous persistent complaints and profound personal problems from a purely organic angle—as a conglomeration of organs, disease of which must either be identified or excluded by means of a large number of investigations with expensive apparatus. And if in the end disease is excluded, he concludes that the patient must have "nothing the matter." But why should such a performance be called scientific ? It is certainly folly, and it is strange that folly should be given the name of science.

Farnham, Surrey. JOHN W. TODD.

PARACOLON BACILLUS SEPTICÆMIA

SIR,—Dr. Kernohan's[1] account of this disorder reminds me of a similar case I saw earlier this year.

A man, aged 52, was admitted to hospital on Feb. 25 after moderate hæmatemesis that morning. He gave a history of two previous hæmatemeses, the last one, in 1947, being definitely preceded by ingestion of aspirin tablets for lumbago. On this occasion, he had had "gastric influenza," with anorexia, malaise, nausea, and retching for the previous 10 days; and the day before admission he had taken some brandy and aspirins. He had had no dyspepsia.

He was moderately febrile (100°F) but there were no signs of recent severe blood-loss (blood-pressure 110/70 mm. Hg, Hb 110%). There were no abnormal physical findings except for a very furred tongue and moderate abdominal distension. Expectant treatment was adopted.

Next morning his temperature had risen to 102°F, and it remained at this level until next day (Feb. 27) when the pulse-rate fell to 66 per min (Faget's sign). Enteric fever was now seriously considered, and was suggested further by absolute constipation for 5 days past, tympanites, and increased lethargy with absence of physical signs in the chest or elsewhere. There was no splenomegaly, but there were several faint dusky "rose red" spots on the trunk.

On Feb. 28 the white blood-cell count was 4300 per c.m. (polymorphs 36%, lymphocytes 61%) and next day 4600 (polymorphs 40%, lymphocytes 40%, monocytes 18%, eosinophils 2%); erythrocyte-sedimentation rate 3 mm. in 1st hr. (Westergren). Blood-culture was sterile after 3 days, but confirmatory evidence of a septicæmia was obtained from the urine and stools, which yielded a non-lactose-fermenting gram-negative bacillus, identified provisionally as *Salmonella paratyphi B* by agglutination, but by the Salmonella Reference Laboratory as a paracolon bacillus.

With treatment by chloramphenicol the patient's temperature fell and his general condition improved dramatically. He was discharged fit on March 17.

It was thought that this patient's hæmatemesis had resulted from gastric irritation produced by aspirin, together with increased gastric vascularity associated with gastritis due to infection with paracolon bacillus.

I should like to thank Dr. R. B. Niven for permission to publish this case.

Winchester. P. G. CRONK.

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[1] Kernohan, R. J. *Lancet*, 1952, i, 1090.

EMPLOYMENT OF REGISTRARS

SIR,—At a meeting of the consultants and specialists of the Bromley group, held on July 31, the proposals for the employment of senior registrars (including the exchange scheme) and registrars as agreed between the regional hospital board and the teaching hospitals were considered.

The meeting was very concerned to learn that it had been laid down that all candidates for the position of senior registrar must have held the post of registrar in a teaching hospital for 2 years. If this was correct it seemed clear that registrarships in non-teaching hospitals would be "dead-end" jobs, that there might very soon be difficulty in filling such posts at all, and that candidates for such posts would be of a poorer type than formerly, with the inevitable result that the health service would suffer.

The following resolution was therefore unanimously passed:

(*a*) That a strong protest should be made against the decision that candidates for the post of senior registrar must previously have held the post of registrar in a teaching hospital for 2 years.

(*b*) That the present proposal that of senior registrars should be selected entirely from the registrars of teaching hospitals would mean that doctors applying for registrarships in non-teaching hospitals would be of a poorer type than formerly, and that the health service would inevitably suffer as a consequence.

(*c*) That senior registrarships and registrarships should both be interchangeable between teaching and non-teaching hospitals.

RUFUS C. THOMAS
Acting Chairman.
A. C. GLENDINNING
D. P. VAN MEURS
Acting Secretaries.

SALT-LOSING NEPHRITIS

SIR,—Recently attention has been drawn to a phase or type of nephritis in which loss of salt in the urine is a prominent feature. In your issue of Sept. 6 Dr. Joiner and Dr. Thorne describe 3 cases in which this diagnosis was made. A second possibility present in 2 of their cases is that the salt loss was related to the presence of pulmonary tuberculosis.

Westwater et. al.[1] found the serum-sodium to be less than 137 m.eq. per litre in 55 out of 169 cases of pulmonary tuberculosis admitted to a sanatorium. 21 of these cases came to autopsy, and, apart from amyloid disease in 1 instance, no renal disorder was discovered. These patients had weakness, skin pigmentation, hypotension, diarrhœa, and vomiting, many of which symptoms occurred in the cases described by Dr. Joiner and Dr. Thorne.

Furthermore we cannot agree that their second case showed chloride depletion, whether the levels are taken in milligrammes per 100 ml. or in milli-equivalents per litre (the values given do not appear to correspond). The diagnosis in their third case would appear to be based solely upon a single serum-sodium level of 131 m.eq. per litre, which was obtained after a period of eight days in which added salt was excluded from the diet. In a patient with chronic nephritis some fall in the serum-sodium level might be expected to occur.

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[1] Westwater, J. O. Stiven. D. Garry, R. C. *Clin. Sci.* 4, 73.

Evidence of long-standing pyelonephritis is a not infrequent finding at autopsy; and in our view the presence of active pulmonary tuberculosis is more likely to account for the salt loss in cases one and two. In case three the evidence of salt loss submitted seems insufficient for it to be included in the group with excessive loss of salt in the urine.

University College Hospital,
London, W.C.1.

M. ATKINSON
T. A. J. PRANKERD.

MALARIAL FEVER THERAPY

SIR,—The article by Mr. Shute (Aug. 16) draws attention to an undesirable practice. This states that malarial infection by intramuscular inoculation of whole blood is an alternative to the technique of using parasites.

As one who has witnessed the tragedies of hæmolytic disease of the newborn, and transfusion morbidity, from untimely disregard for the known facts of Rh sensitisation, I would ask the Malaria Reference Laboratory to bear in mind the inadvisability of using this method to infect girls and also women of the child-bearing years. If the method is to be retained, then due regard should be paid to the possibility of such sensitisation.

Uxbridge, Middlesex.

JOHN PRICE.

DEFORMING FACTORS IN POLIOMYELITIS

SIR,—I have read with great interest Mr. Mitchell's analysis last week of "muscle spasm" and allied disorders and also the treatment he advised in his earlier communication.[1]

In this connection I feel that we should report some recent experiences in the treatment of acute poliomyelitis at Stoke Mandeville Hospital isolation block, where, during the present outbreak of the disease, we have had the benefit of the services of a nurse trained at St. Thomas's Hospital who has recently studied poliomyelitis in the U.S.A.

This experience has led us to institute very frequent passive movements with gentle stretching of tight muscles, and frequent changes of position in bed, from the first day of the disease. The physiotherapist treats the patient once a day, but on at least five other occasions in each 24 hours passive movements are carried out by the nurse, who is trained to do them. In addition the posture of the patient in bed is changed on about ten occasions during the 24 hours, the supine, lateral, semi-prone, and prone positions all being used. This plan gets rid of most muscle tightness within 2–3 weeks, and seems to be entirely satisfactory in practice. The nursing methods used could be demonstrated to a limited number on application to the Matron, Stoke Mandeville Hospital, Aylesbury, Buckinghamshire.

Department of Neurology
Radcliffe Infirmary, Oxford.

W. RITCHIE RUSSELL.

Diary of the Week

SEPT. 14 TO 20

Wednesday, 17th

ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5.30 P.M. Mr. Howard Reed: Keratome and Scissors for Cataract Incision.

Friday, 19th

RENAL ASSOCIATION
1.30 P.M. (41, Portland Place, W.1). Prof. J. G. G. Borst [illegible] Electrolyte and Water Balance with [illegible] duey.
[illegible] Glasgow). Scientific papers (opening of two-day meeting).

Saturday, 20th

INSTITUTE OF LARYNGOLOGY, 330, Gray's Inn Road, W.C.1
11 A.M. Dr. Stacey R. Guild (Baltimore): Recent Research in Otology.

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[1] Brit. med. J. 1952, i, 619.

Public Health

Neglecting the Countryman?

IN his report for 1951, Dr. D. P. Lambert, divisional medical officer for the North Craven division of the West Riding of Yorkshire, says:

> "Country folk are becoming increasingly conscious that most of the benefits of the Welfare State are concentrated in the cities, and . . . it is felt that some things could and should be better shared. Medical services are especially wished for; and the demand for mobile clinics and for mobile consultation facilities increases each year. For major surgery and for prolonged medical investigation patients will always have to go to the big hospital centres; but there is a great deal of diagnostic work . . . that could be as well done in a mobile clinic as in a hospital outpatient department."

Infectious Diseases in England and Wales

Disease	Week ended August				
	2	9	16	23	30*
Diphtheria	19	19	17	23	22
Dysentery	93	119	125	119	90
Encephalitis:					
Infective	7	2	9	2	7
Postinfectious	1	2	2	1	1
[illegible]	164	150	146	190	139
[illegible]la	7310	7012	6099	5256	3649
[illegible]	20	18	35	29	28
[illegible]	34	19	34	39	25
[illegible]	130	63	40	58	44
Pneumonia, primary or influenzal	229	239	247	207	220
Poliomyelitis:					
Paralytic	139	167	170	153	152
Non-paralytic	91	83	88	68	65
Puerperal pyrexia and fever	228	242	242	244	216
Scarlet fever	999	722	643	559	557
Smallpox	—	—	—	—	—
Typhoid fever	5	4	4	13	4
Whooping-cough	2045	1766	1872	1806	1861

* Not including late returns.

Appointments

CONNOLLY, M. R., L.R.C.P.E.: first asst., anæsthetic department, Royal Free Hospital, London.
SALMON, L. F. W., M.B.E., M.S. Lond., F.R.C.S.: consultant ear, nose, and throat surgeon, Guy's/Evelina Hospitals, London.
STEPHENS, J. P., M.B. Camb., F.R.C.S.: senior surgical registrar, Norfolk and Norwich Hospital.
SUMMERS, H. A. H., M.B. Belf., D.P.H.: asst. county M.O.H. and district M.O.H., borough of Daventry and the rural districts of Daventry and Brixworth.

Colonial Service:

BIRD, A., M.D.: M.O., Windward Islands.
BURY, E. J., M.R.C.S., D.P.H.: D.D.M.S., western region, Nigeria.
CHARLES, E. D. B., M.D. McGill, M.P.H.: M.O.H., Jamaica.
COHEN, R. I., M.B. Lpool, F.R.C.S.: M.O., South Pacific Health Service.
DIDSBURY, BRIAN, M.B. Manc.: M.O., Malaya.
GOULDING, M. D., M.B.: M.O., Federation of Malaya.
HARRIES, J. R., M.B. Lond., M.R.C.P., D.C.H.: M.O. (special grade), Kenya.
HARRIS, B. P., M.A., M.D. Camb., D.T.M.&H.: senior M.O., Kenya.
HODGES, W. A. A., B.A., M.B. Camb., F.R.C.S.: M.O. (special grade), Tanganyika.
PARK, ROBERT, M.R.C.S.: senior M.O., Nyasaland.
PASQUAL, R. S. H., M.B. Edin.: M.O., Kenya.
REID, H. A., M.B. Edin., M.R.C.P.E., D.T.M.&H.: specialist physician, Malaya.
SEXTON, J. P., M.B. Edin., D.P.H.: regional senior health officer, northern region of Nigeria.
SINCLAIR-HALL, A. H., M.D. Manc., F.R.C.S.: senior specialist, Nigeria.
VERLEY, DORIS, M.B. Edin., D.A.: medical specialist (anæsthetist), Jamaica.
WATERS, I. R., M.R.C.S.: M.O., Nyasaland.
WELLS, R. H. C., M.B. Lond.: M.O., Federation of Malaya.

Manchester Regional Hospital Board:

CALDER, A. G. S., M.B. Edin., F.R.C.S.E.: consultant E.N.T. surgeon, Wigan and Leigh Hospitals.
DARK, J. F., M.B. Manc., F.R.C.S.: consultant thoracic surgeon, Baguley and Park Hospital, Manchester.
JACK, G. D., M.B. Edin., F.R.C.S.: consultant thoracic surgeon, Baguley and Park Hospital, Manchester.
PARKER, R. P., M.B. St. And.: asst. anæsthetist, Burnley and district hospitals.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

ROYAL MEDICAL BENEVOLENT FUND

DURING 1951 the Royal Medical Benevolent Fund helped 8 new applicants, and the number of its beneficiaries is now over 600. Reporting on the year, Dr. R. Cove-Smith, the hon. secretary, says that during the year £41,467 was disbursed, including £21,865 in grants, £10,609 in annuities, £2028 as Christmas gifts, and £2020 as New Year gifts. Working expenses amounted to 6·6%. Investment income was £13,794 and subscription income £24,410; income-tax recovered under covenants totalled £5810. In addition, £18,114 was received in legacies and credited, as usual, to capital account. Dr. Cove-Smith observes that, with income-tax at 9*s.* 6*d.* in the pound, each guinea of covenant subscriptions represents an income of £2 to the Fund; and he asks all supporters to consider this method of subscription. The headquarters of the Fund are at 1, Balliol House, Manor Fields, Putney, London, S.W.15.

A NEW KIND OF CECIL HOUSE

WOMEN wandering about the streets of London in search of a cheap lodging are fortunately no longer as common as they were in 1925, when Mrs. Cecil Chesterton set out, with nothing in her pockets, to see what it felt like to be one of them. But there are still more than enough of them to disturb our peace of mind if we stop to think about it. The Cecil Houses, which she founded, still fill themselves every night, and the numbers turned away do not diminish. Those who get there in time can still get a clean and comfortable bed, a hot bath, and *facilities for* washing clothes, *for* a sum which has risen, with the change in the value of money, from 1*s.* to 2*s.* 3*d.*; a cot for a baby costs an additional 3*d.* They are asked no questions; they want, and are paying for, a night's lodging, and their private lives are respected. The only stipulation made is that they shall be sober.

Over the course of the years six Cecil Lodging Houses have been opened; some were closed for a time by bombing, and have since reopened—all but one, which is let temporarily for light industry until it can be rebuilt. In 1938 a new kind of Cecil House was opened—a residential club, in Gower Street, for 72 working girls who pay £2 a week, and must not be earning more than £5. This building was let during the war to the Canadian Legion but has been fulfilling its original purpose since 1947. Next year another new venture is to be launched—a residential club for 72 old ladies. The building is up, in Medlake Street, North Kensington; and it is delightful, from the roof garden and verandahs, and the nineteen dormitories, to the comfortable common-rooms, the convenient kitchen, and the central-heating installation in the basement.

Once launched, the Cecil Houses pay their way, and the new residential home will be no exception; but it has cost £65,000 to buy the site and build on it, and not all of this sum has been collected yet. Those who wish to contribute should send their subscriptions to the Hon. Treasurer, Cecil Houses (Inc.), 193, Gower Street, London, N.W.1.

A VOICE FROM THE PAST

Daniel Drake was born in New Jersey in 1785. At the age of 2 he took part in the migration to the western parts of the United States. In the turmoil of those pioneer days a boy's education was apt to be neglected, but Daniel was soon able to take the matter in his own hands; for, as he later wrote, "I could read and examine a dictionary for the meaning of words and here is the starting point of all improvement." And improvement thus started led to his apprenticeship at 15 with a doctor in Cincinnati, and carried him on to a place of distinction in the history of American medicine. He became a physician, teacher, and writer whose reputation spread far beyond the Ohio Valley where he spent most of his life.

Biographical facts, however impressive, give a poor picture of the man, but his written words do much to fill in the details—and Dr. Drake was a vigorous and prolific writer. His essays on medical education and the medical profession, first published in 1832, have now been reprinted.[1] Many of his pungent criticisms must have been unpopular at the time, and indeed some of them may touch a sore spot here and there even now. "The profession abounds in students and practitioners who are radically defective in spelling, grammar, etymology, descriptive geography, arithmetic, . . . and book-keeping." He also demanded "a competent knowledge of the elements of physical geography, general history, the art of composition, algebra, geometry, and mechanics." How his students must have quailed! He deals as devastatingly with the failings that he detected in the medical schools of the time; and his ideas on a proper medical training laid the foundations of modern American teaching methods. He wrote so entertainingly that he should be read again even if his lessons had all been learnt, which is by no means the case.

THE WORKS OF SIR ALMROTH WRIGHT

Dr. Leonard Colebrook, F.R.S., loving disciple of an unusual man, has prepared a bibliography of all the published works of Sir Almroth Wright,[1] and has appended to each title a short account of the contents. Most of these deal with immunisation, Wright's major interest, and it is impressive to see the vast field he ranged and the notable contributions he made to this subject. Two works on which Dr. Colebrook evidently sets a high value are *Prolegomena to the Logic which searches for the Truth*, and *Alethetropic Logic* (still unpublished) to which the *Prolegomena* was written as a foreword. The main work began to take shape, Dr. Colebrook says, in the 'nineties, when Wright had become interested in the physiological processes associated with emotional disturbances. This led him to reflect on the nature of belief, and the intellectual operations usually included in the word "logic." "It seemed to him that the modern development of psychology and physiology called for a new system of logic—one which was not concerned only with Reasoning, but took account also of all the processes by which we arrive at our Beliefs." Three contributions, whose shocking illiberality nowadays raises a smile, are concerned with the case against woman suffrage; perhaps it would have been kinder to leave them out.

SAFETY FOOTWEAR

IN industry injuries to the feet are a common cause of disablement. The Ministry of National Insurance found that in 1949 and 1950 such injuries accounted for about 4% of all successful claims for injury benefit. The British Standards Institution, in coöperation with other organisations, has issued a standard for men's safety boots and shoes (B.S. 1870/1952, price 2*s.* 6*d.*). Shoes made by this standard, which were demonstrated in London this week, have an external or internal steel toecap, weighing 2 oz. and designed to withstand a shock test of 150 foot-lb. or a dead weight of 3 tons.

Royal Medico-Psychological Association

Dr. W. Rees Thomas will deliver the Maudsley lecture to this association on Thursday, Nov. 6, at 2.15 P.M., at 1, Wimpole Street, London, W.1. He is to speak on The Unwilling Patient.

London Hospital

On Thursday, Oct. 9, at 4.15 P.M., at the Medical College, Prof. S. P. Bedson, F.R.S., will deliver the Schorstein lecture on Twenty-five Years' Progress in Virus Research.

Royal Free Hospital

Sir Henry Dale, O.M., F.R.S., will deliver the opening address of the 1952–53 session to the medical school on Friday, Oct. 3, at the Senate House, University of London, W.C.1, at 3 P.M.

Guy's Hospital

The biennial dinner for past medical and dental students will be held in the Connaught Rooms, Great Queen Street, London, W.C.2, on Friday, Oct. 3, at 7.30 p.m. Tickets (25*s.* exclusive of wines) are obtainable from Mr. O. Gayer Morgan, hon. secretary of the dinner, Medical School, Guy's Hospital, London, S.E.1.

Westminster Medical School

On Monday, Oct. 6, at 3.45 P.M. at Church House, Great Smith Street, S.W.1, Sir Raymond Evershed, P.C., the Master of the Rolls, will give the inaugural address.

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[1] Practical Essays on Medical Education and the Medical Profession in the United States. By DANIEL DRAKE, M.D. Baltimore: Johns Hopkins Press. London: Oxford University Press. 1952. Pp. 103. 20*s.*

[1] Bibliography of the Published Writings of Sir Almroth Wright, M.D., F.R.S. London: Heinemann. 1952. Pp. 32. 6*s.*

Society of Chemical Industry

On Monday, Oct. 20, at 5.30 P.M., at the rooms of the Chemical Society, Burlington House, London, W.1, at a meeting of the crop protection panel of the agriculture group, Dr. J. M. Barnes will speak on Health Hazards in Crop Protection.

Rubber Products for Hospital Use

With the collaboration of the professional and industrial interests concerned, the British Standards Institution is preparing a series of standards for rubber products used in surgical and hospital practice, and the following have now been published:

B.S.1803—Surgical rubber gloves (price 1s. 6d.) deals with gloves made by dipping in rubber solution (both cold and hot vulcanised), or by dipping in latex. Recommendations are given for storing and sterilisation.

B.S.1883—Rubber ward-dressing gloves and porters' gloves (2s.) covers three types of gloves—namely, rubber-solution dipped, rubber-latex dipped, and those built up from sheet rubber. Methods of marking to show date of manufacture are laid down.

B.S.1884—Rubber post-mortem gloves (2s.) is similar in scope to B.S.1883.

B.S.1882—Rubber tubing for hospital use (2s.) includes specifications for pressure, drainage, stethoscope, and Paul's tubing. Transfusion tubing is still under consideration, and will be dealt with by an amendment slip to the present standard as soon as the work is completed. Exact methods o [illegible] ensions and tolerances, are specified, and [illegible] ical tests to ensure that the quality of rul [illegible] for each purpose.

Copies of these standards may be had from the sales branch of the Institution, 24, Victoria Street, London, S.W.1.

British Legion Homes

This year the British Legion has completed its post-war plan to provide 8 special homes. The 4 country homes for the aged at Westgate, Cromer, Ripon, and Bwlch, near Brecon, accommodate 220 men and women, 130 of whom are disabled. Every year more than 3000 men and women spend a fortnight at the convalescent homes at Southport, Weston-super-Mare, Sevenoaks, and Helen's Bay in Northern Ireland.

Institute of Child Health, London

Ten postgraduate lectures on Disease in the Young Animal and the Child are to be given at the Hospital for Sick Children, Great Ormond Street. The lectures will be held on Mondays, at 5.30 P.M., beginning on Oct. 13. Further particulars may be had from the secretary of the institute, Great Ormond Street, W.C.1.

Wessex Rahere Club

The autumn dinner of this club will take place at the Grand Spa Hotel, Clifton, Bristol, on Saturday, Oct. 25. Membership of the club is open to all Barts men practising in the West Country. Further details may be had from Mr. A. Daunt Bateman, the hon. secretary, 3, The Circus, Bath.

Vellore Christian Medical College, South India

Friends of Vellore are to hold their annual reunion on Wednesday, Oct. 8, at Caxton Hall, Westminster, S.W.1, at 3.30 P.M. The speakers will include: Dr. Margaret Brand, Mr. Paul Brand, Dr. Gwenda Lewis, and Dr. P. Koshy.

Association of Clinical Pathologists

The annual general meeting of this association will be held at the Westminster Hospital Medical School, London, S.W.1, from Oct. 2 to 4.

Hunterian Society

The annual party of this society is to be held at 41, Portland Place, London, W.1, on Thursday, Oct. 2, at 6 P.M., when recent additions to the museum will be shown.

Rations for Patients with Cœliac Disease

A new category of extra rations has been introduced for children with cœliac disease. In future children who are being treated on a wheat- or gluten-free diet may be allowed one extra ration of fats (butter, margarine, and cooking-fat), one extra meat ration, and one priority allocation of eggs a week. These allowances are alternative to, and not additional to, the extra rations at present granted. Medical certificates, in addition to providing the figures for a stool fat-analysis or fat-absorption test, should state that the patient is on a gluten-free diet. The Ministry of Food's medical advisers are prepared to give consideration to adults suffering from steatorrhœa who have been placed on a similar diet.

International Congress on Rheumatic Diseases

The eighth International Congress on Rheumatic Dis will be held at Geneva from Aug. 24 to 28, 1953. The follo subjects have been chosen for discussion: Connective Tis and Rheumatism; Steroids in the Treatment of Rheumati the End-results of Surgery for the Rheumatic Hip; a Occupational Reablement. Further particulars may be h from Prof. K.-M. Walthard, Institut de Physiatrie, Hôpit Cantonal, Geneva, Switzerland.

St. Thomas's Hospital

The old students' dinner will take place at the Trocade Restaurant, Piccadilly Circus, London, W.1, on Frida Oct. 17, at 7.30 P.M., when Mr. L. E. C. Norbury, will ta the chair. Tickets (29*s*. exclusive of drinks) can be obtain from the hon. secretaries, G. A. MacGregor, R.A.P., and C. E. Savage, R.A.S., St. Thomas's Hospital, S.E.1.

Illuminating Engineering Society

On Jan. 28, Prof. E. D. Adrian, O.M., P.R.S., will deliver th Trotter-Paterson lecture to this society. He will speak on th Nervous Reactions of the Retina. Dr. W. J. Wellwood Ferguson will deliver the presidential address on Oct. 1 Both meetings will be held at the Royal Institution, Albem Street, London, W.1, at 6 P.M.

Newsholme Lectures

Prof. W. M. Frazer, medical officer of health for Liverpool, is to deliver these lectures at the University of London in 195

Mr. A. S. Parkes, D.SC., F.R.S., head of the division of experimenta biology of the National Institute for Medical Research, Mill Hi London, leaves on Sept. 17 for a lecture tour in Latin Americ which has been arranged by the British Council.

The British Standards Institution has issued a draft Britis Standard for clinical maximum thermometers (B.S. CO(LBC) 332 comments on which should be sent before Oct. 9 to the Institutio 24, Victoria Street, London, S.W.1.

The Cambridge Instrument Company Ltd. are issuing to delegate at the European [illegible] monograph on th *Development of the* [illegible] L. Barron, M.I. to which Sir Alan L [illegible] a foreword. So additional copies ar [illegible] without charge t doctors who apply to the company, 13, Grosvenor Place, Londo S.W.1.

Births, Marriages, and Deaths

BIRTHS

ATKINSON.—On Sept. 1, at Bromley, Kent, to Mollie (née Mortl wife of Mr. W. J. Atkinson, M.D., F.R.C.S.—a daughter.

CLARKE.—On Aug. 29, at the Purey Cust Nursing Home, Yo to Catherine (née Waugh), wife of Mr. P. R. R. Clarke, F.R.C —a son.

FELIX-DAVIES.—On Aug. 29, in London, to Joan (née Kellett), wi of Dr. D. Felix-Davies—a son.

HICKS.—On Sept. 3, at Edgware General Hospital, Edgware, to Marie, wife of Dr. Frederick N. Hicks—a daughter.

HIGHTON.—On Aug. 25, to Dr. Roberta Highton (née Baker), wi of Dr. Thomas C. Highton, M.R.C.P., of Rotorua, New Zealan —a son.

LOTHIAN.—On Aug. 31, at Shoreham, Kent, to Joan (née Hamb wife of Dr. William Lothian—a son.

LUCAS.—On Aug. 25, at Princess Elizabeth Hospital, Nairob Kenya, to Dr. Shelagh Lucas (née Fair), wife of Mr. J. M. Lucas, M.R.C.V.S., Box 2141, Nairobi—a daughter.

MUNRO.—On Sept. 6, at Crayford, Kent, to Dr. Olive Munro, wife of Dr. Ian Munro—a daughter

ROBERTSON.—On Sept. 4, to Helen (née Preston), wife of Dr. Jam Robertson, 66, Gloucester Gardens, W.2—a son.

TASKER.—On July 25, at Northampton, to Anita, wife of Dr. J. R. Tasker—a son.

WOHL.—On Aug. 31, at the London Clinic, to Hilda (née Hoffman wife of Dr. M. Wohl—a daughter.

MARRIAGES

DEVITT—BROWNLEE.—On Sept. 6, at Pinner, Herbert P.-S. Devit M.R.C.S., to Carol Brownlee.

DEATHS

ANDREWS.—On Sept. 2, at Gorse, Blatchington, Seaford, He Arthur Andrews, M.R.C.S., formerly of Tonbridge, aged 8

INNES.—On Aug. 24, at Grantown-on-Spey, Inverness-shire, F Riddell Innes, M.B. Edin., formerly of the Christian Medi College, Vellore, S. India, and of Brisbane, Australia.

MCKIBBIN.—On Sept. 5, at his home, Frederick McKibbin, O.B.E. M.B. Belf., colonel, late R.A.M.C.

POLLARD.—On Sept. 3, at Pound Hill, Framfield, Sidney Pec Pollard, M.D. Camb., F.R.C.S.

SMALL.—On Aug. 25, at his residence, Kinghurst, Stoke Gabri Devon, Robert Small, M.R.C.S., D.P.H., D.T.M., formerly M.O. Mombasa.

WARDROP.—On Aug. 30, at his home, 45, Northumberland Roa Leamington Spa, John Glen Wardrop, M.D. Lond., aged 6

MILIARY TUBERCULOSIS IN CHILDREN*

ROBERT DEBRÉ
M.D. Paris
PROFESSOR OF PÆDIATRICS, UNIVERSITY OF PARIS

MILIARY tuberculosis has been much discussed for nany years by clinicians, pathologists, and radiologists. Acute miliary tuberculosis was described by the French nternist Empis (1865) as a clinical entity with high pyrexia, severe dyspnœa, and a fatal outcome. The diagnosis of *granulie* meant to the French physician this acute disease, with its regularly fatal prognosis. Then came, with routine radiography, the description, especially by Burnand and Sayé (1924), of less acute miliary tuberculosis, which could sometimes heal spontaneously—*granulies froides, granulies curables.* Following such observations, the interpretation of the clinical and radiological pictures, and their bearing on the prognosis, became somewhat confused, and it has been my task to make a clear-cut difference between those cases of miliary tuberculosis that can heal spontaneously and those that are as hopeless as tuberculous meningitis. I showed in 1934 that they could be distinguished both clinically and radiologically. I have kept the word *granulie* for the acute fatal form, calling the other one " subacute miliary tuberculosis," and its radiological picture *image granulo-réticulée.*

Streptomycin has changed the character of miliary tuberculosis, but this distinction has remained of value for the prediction of meningitis, which is now the main, almost the only, danger. The creation of centres for treating tuberculous meningitis has allowed a much wider observation of this form of tuberculosis, and I summarise here my experience during the last few years, in coöperation with H. E. Brissaud, Henriette Noufflard, S. Kaplan, and others, of the clinical picture of miliary tuberculosis in children, and of its evolution under streptomycin treatment.

ÆTIOLOGY

In the years 1947–49 and 1950, 170 cases of miliary tuberculosis were admitted to the Clinique Médicale des Enfants in Paris. In almost all these children miliary dissemination appeared very early in the history of the disease, almost simultaneously with primary tuberculosis. In only 8 of these 170 cases could there be found a past history of tuberculosis 1–6 years earlier: conversion of skin test, or bone tuberculosis. And skin tests are now so widely used as a routine in France that it is unlikely that many other cases of postprimary tuberculosis would have been missed in this group.

In almost all the cases there was nothing in the past history of the child suggesting tuberculosis; often there were recent contamination and recent proved conversion of the skin tests; and the symptoms for which the skin test was made were usually those for which the radiograph was made that showed miliary tuberculosis: pyrexia and loss of weight for several weeks or a few months without remission. In some cases there was a remission of a few weeks or months followed by recurrence of the pyrexia and discovery of miliary tuberculosis. If miliary tuberculosis in children appears usually as a severe form of primary or postprimary tuberculosis, the question arises: why does it occur in certain cases and not in the others? Does it occur more readily in certain groups of children or after heavier contamination?

Sex.—Of these 170 children, 69 were boys and 101 girls—a slight but significant difference, occurring only in the older age-group.

Age.—Fig. 1 shows the ages of the patients. Most cases fall in the younger age-group: 22 children were aged less than 1 year, and 61—i.e., more than a third—were aged less than 3 years. This is far from parallel to the tuberculin index even in France, and shows definitely that widespread miliary dissemination occurs more readily in infants and younger children.

Contamination.—Of 154 cases in which the inquiry had been thorough enough the contamination was found, unquestionably or with great probability, in 69. In about half these cases it was a very heavy familial contamination (in 19 cases by the father, 8 by the mother, 1 by both parents, and 4 by grandparents).

SYMPTOMS AND SIGNS

In nearly half my cases meningitis was present on admission, and in about a quarter the history was mainly that of the meningitis, miliary tuberculosis being only discovered by routine radiography of the chest and examination of the optic fundi.

In all the other cases miliary tuberculosis was diagnosed first, and the history was somewhat monotonous, being that of a systemic disease, with pyrexia, fatigue, anorexia, and loss of weight. The temperature is usually very high (102°–104°F) but sometimes moderate (100°–101°F). I have never seen an absolutely normal temperature. And this pyrexia had lasted many weeks, sometimes several months, before the right diagnosis was made. The physician often thinks of typhoid fever before he thinks of tuberculosis, in spite of the latter being much more common. In only a few cases was there severe dyspnœa with cyanosis. Usually nothing calls attention to the chest. On physical examination there are few signs. The spleen is enlarged in about half the cases. In many instances no meningeal signs are found; even though meningitis may be present, as shown by routine lumbar puncture.

In infants the diagnosis is difficult when contamination is unknown, because of the technical difficulties of radiography and of the examination of the optic fundi.

There are a few other circumstances in which miliary tuberculosis has been diagnosed: it may be discovered by routine radiography in a child with bone tuberculosis; and twice I have seen it associated with signs of a

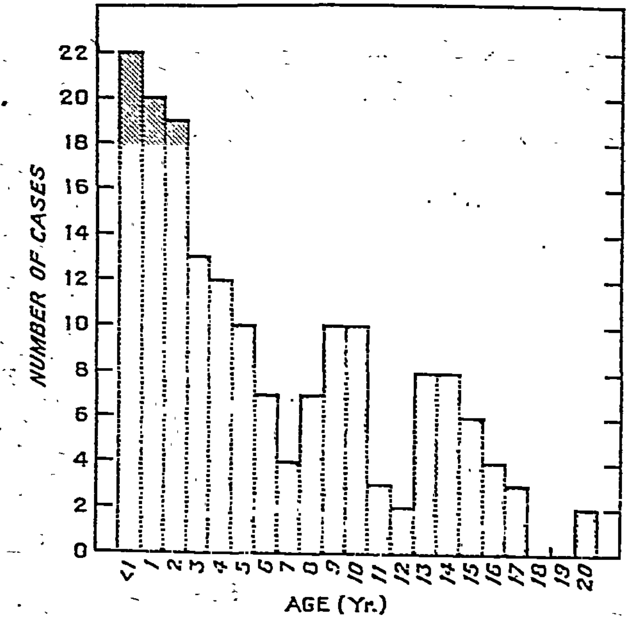

Fig. 1—Age-distribution of miliary tuberculosis.

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* Lecture read at the meeting of the British Pædiatric Association at Windermere on May 1, 1952.

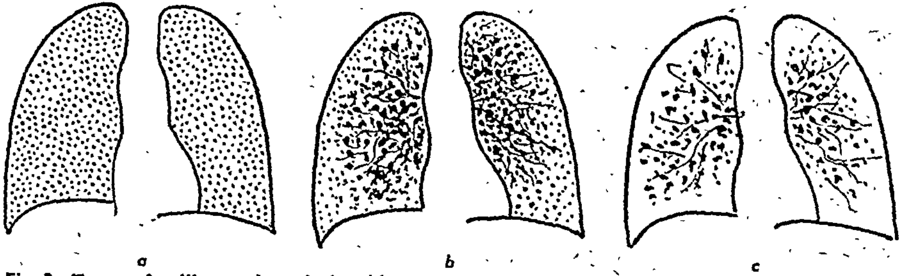

Fig. 2—Types of miliary tuberculosis of lungs: *a*, acute; *b*, subacute very dense; *c*, subacute more discrete.

cerebellar tumour (the tuberculoma was successfully removed in both cases).

The tuberculin test is usually the first to give the right orientation. It is well known that it can be negative in miliary tuberculosis even when the patient is not in too poor a condition. I have found a weak allergy (negative Pirquet and positive Mantoux at a more or less high dilution) in 12 cases, and complete absence of allergy (negative Mantoux at the higher concentrations of tuberculin) in 3 cases. Of these 3 cases 1 became positive after a month; the 2 others, which remained negative throughout the disease, both had positive gastric washing. Misleading as they are, such cases are the exception, and only mean that a negative skin test is not enough to reject the diagnosis of acute tuberculosis if there are good reasons to keep it in mind.

CHEST RADIOGRAPHY

Miliary tuberculosis can be completely missed at fluoroscopy or on a technically imperfect plate. A good plate, made with a rapid exposure from a distance of not more than 1 metre and with rather soft X rays during inspiration, will show either of the following two pictures:

(1) Fig. 2*a* shows the very acute form of miliary tuberculosis, the *granulie d'Empis*, made of innumerable tiny spots so small that no differences of size can be seen between them, and so numerous that they appear to be scattered throughout both lungs, no part of the lungs being clear of them. This type of miliary tuberculosis never heals by itself, and even with streptomycin treatment its evolution differs from that of the other kind.

(2) Figs. 2*b* and *c* show the other type of miliary tuberculosis. Here the spots are larger and unequal. Caseous diffuse pneumonia is excluded from present consideration. Though the borderline between these pictures and caseous diffuse pneumonia is sometimes difficult to trace, these are still very small spots though larger than in the first type. They do not stipple both lungs so uniformly as in the first type: they appear denser near the hilum, where the lung is thicker, and scarcer at the periphery. A kind of network can often be seen between the spots. In fig. 2*b* the spots are still very numerous though unequal in size and distribution, whereas in fig. 2*c* they are much less numerous. This is the picture that is often found in tuberculosis of lymph-nodes or of bones and joints. This is the type that can heal spontaneously and for which the term *granulie curable* has been used.

TUBERCLES OF THE CHOROID

Tubercles of the choroid were described and pictured by Bouchut (1869), chief physician at the Hôpital des Enfants Malades in Paris, shortly after the first ophthalmoscopes had been made. It has since been denied that they are at all common, and they have been somewhat forgotten of late. I have found them of great value both in diagnosis, because they can easily be observed without moving the child from the bed, and in prognosis.

The early lesion looks like a little pink or yellowish clear spot with hazy edges on the red fundus. Sometimes it is brilliantly white in the centre. It is no bigger than a quarter of the optic disc. There can be many such lesions in both eyes—miliary tuberculosis of the choroid. We have seen as many as 26 in one eye, anywhere in the choroid, even far from the centre and difficult to see (fig. 3). When they heal, black pigment appears on them, but some of the smaller tubercles can disappear completely.

In some cases larger tubercles can be found, and then there are only one or two of them. They have a white centre and a yellowish corona, and are surrounded by œdematous tissue. On six occasions I have seen a real tumour—tuberculoma of the choroid.

CORRELATION BETWEEN CHEST RADIOGRAM AND CHOROID

There is a definite correlation between the chest radiogram and the choroid. The accompany table shows that typical acute miliary tuberculosis (fig. 2*a*) is almost always associated with the presence of tubercles of the choroid (in 55 out of 58 cases), and that this tuberculosis of the choroid is then usually of the miliary type (in 41 out of 55 cases).

On the other hand, in subacute miliary tuberculosis the incidence of tubercles of the choroid is very different: in only 18 out of 39 cases in the very dense type (fig. 2*b*), or in 58 out of 106 including the more discrete type (fig. 2*c*).

INCIDENCE OF MENINGITIS

The main importance of the distinction of these types is its bearing on the incidence of meningitis (fig. 4):

Of 61 children with typical acute miliary tuberculosis (fig. 2*a*) 52 developed meningitis. Of the 9 children who did not 4 died very quickly with acute dyspnœa, and 3 developed what I have called a slight meningeal reaction because, in the absence of definite proof, I did not dare to consider it as actual tuberculous meningitis, but it might well have been. Only 2 can really be said to have escaped meningitis, and in 1 of these electro-encephalography showed definite changes in spite of the fact that the cerebrospinal fluid (C.S.F.) appeared normal.

In subacute miliary tuberculosis (figs. 2*b* and *c*), even when the radiogram shows extensive disease, the incidence of meningitis is much less: 51 of these 109 children did not get meningitis at any time.

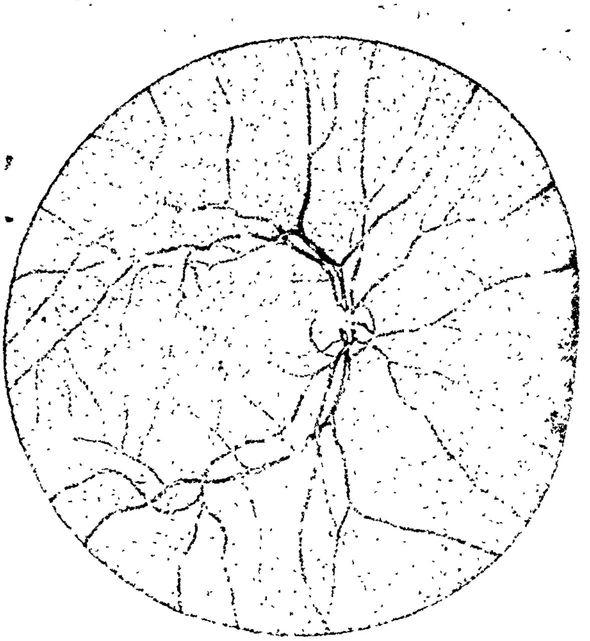

Fig. 3—Tubercles of choroid.

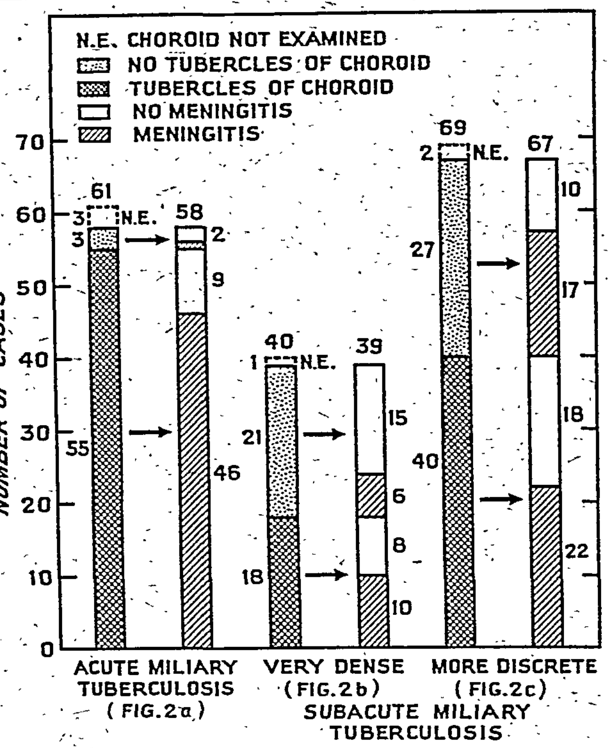

Fig. 4—Correlation of tubercles of choroid with meningitis.

This finding is all the more important because with streptomycin treatment meningitis is the main danger of miliary tuberculosis (see fig. 5):

Of 170 patients 108 either had meningitis on admission or developed it during or after streptomycin treatment. In this group the mortality-rate has been about 60%, much higher than the over-all mortality for tuberculous meningitis, which is 46% in my department.

On the other hand, only 9 patients died of the 62 who did not develop meningitis, making a mortality of about 15%.

This is to say that, on admission as well as throughout the course of the disease, and even after treatment has been discontinued, the main anxiety is about involvement of the meninges.

TUBERCULOUS MENINGITIS

As previously stated, meningitis is already present in nearly half the patients with miliary tuberculosis at the time of admission to hospital. Sometimes the history is that of a tuberculous meningitis, the chief complaint being vomiting and headache. Sometimes, on the other hand, miliary tuberculosis has been diagnosed and it is only on being questioned that the patient tells of a mild headache, or at a careful examination that he is found slightly drowsy and that meningitis is suspected. In many cases it is only by the routine lumbar puncture that the diagnosis can be made. It is therefore imperative not to start the treatment before making sure that the c.s.f. is not abnormal.

CORRELATION BETWEEN CHEST RADIOGRAM AND CHOROID

Type of miliary tuberculosis of lungs	No. of cases	Choroid				
		Not examined	No tubercles present	Tubercles present		
				Miliary*	Isolated†	Total
Typical acute (fig. 2*a*) ..	61	3	3	11	14	55
Subacute :						
Very dense (fig. 2*b*) ..	40	1	21	2	16	18
More discrete (fig. 2*c*) ..	69	2	27	5	35	40

* More than 3 tubercles in each eye.

† Less than 3 tubercles in each eye, or tuberculoma.

If the routine lumbar puncture, before treatment is started, shows a normal c.s.f., this does not mean that the patient will not develop meningitis at any time under treatment, but the chances of his doing so seem to decrease with length of treatment:

In 80 patients meningitis was present on admission.

In 11 patients meningitis was discovered in the first two months of treatment (but in 5 it was not proved that it did not exist on admission).

In 4 patients meningitis was discovered during the fourth month of treatment.

In 1 patient meningitis was discovered during the sixth month of treatment.

In 1 patient meningitis was discovered during the twenty-first month of treatment.

In the remaining 11 patients meningitis was discovered after completion of the treatment.

Therefore once treatment has been started, lumbar punctures are repeated, if not routinely, at least for very slight symptoms, especially in the first two months: the slightest headache or a new rise in temperature or loss of weight, even if it is moderate.

Usually the changes in the c.s.f. are typical enough to make the diagnosis eventually obvious, on repeated lumbar puncture. But in some cases the changes, though definite, are so slight that they are difficult to interpret, and in 3 cases I could neither rule out nor prove the presence of meningitis. Moreover, in 4 children with miliary tuberculosis tubercle bacilli were found on culture of the c.s.f., which was otherwise completely normal. In all 4 children, when the culture was reported as positive from three to six weeks later, a further lumbar puncture, in spite of the absence of any meningeal symptoms, showed typical changes in cells and albumin in the c.s.f. The clinical course of these cases of meningitis was that of any other tuberculous meningitis but on the whole more severe.

In the 17 cases in which meningitis developed during streptomycin treatment tubercle bacilli were found in the c.s.f. at the beginning of the meningitis in 12 cases, and were tested for their sensitivity to streptomycin in 9 cases. They were all sensitive, but in 3 cases a rather resistant strain developed at a later stage. It can be concluded that bacteriological resistance may be one of the factors to account for the bad prognosis of these cases of meningitis.

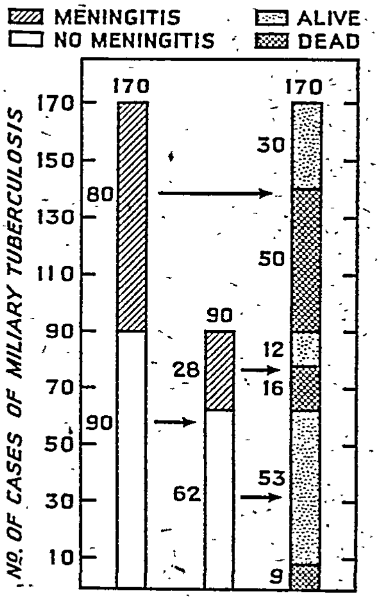

Fig. 5—Onset of meningitis and fate of patients.

CLINICAL COURSE WITHOUT MENINGITIS

In the absence of meningitis the clinical course of miliary tuberculosis treated with streptomycin is usually quite simple. Dyspnœa, if present, usually subsides quickly. The temperature begins to fall quite soon but does not become normal until the second or, more often, the third or fourth month of treatment. The patient

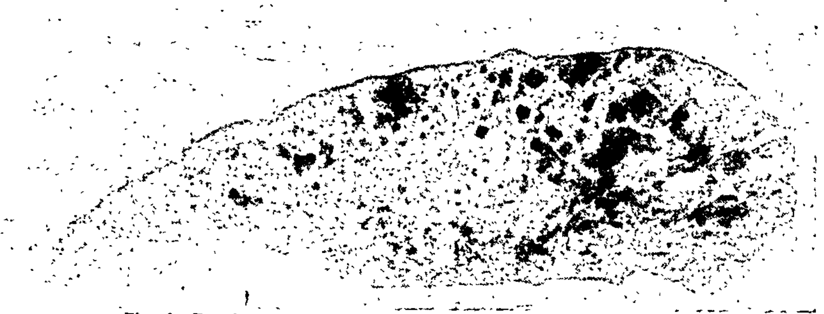

Fig. 6—Emphysematous bullæ of lung due to miliary tuberculosis.

usually starts gaining weight only after the temperature has started to drop. The erythrocyte-sedimentation rate (E.S.R.) returns to normal slowly. At the same time the lesions in the lungs and eyes clear up remarkably. Usually within a month there is already a dramatic improvement in the chest radiogram. The acute *granulie* may have almost disappeared, leaving only a thin reticulum. The larger spots become smaller, resembling for a while the more acute form. The complete clearing up, however, though it can be surprisingly quick (one or two months), usually takes at least three months and sometimes nine. Either it is complete or it leaves a very thin network pattern, which appears unchanged in subsequent radiograms.

Some of the tubercles of the choroid disappear completely; on the bigger ones a black pigmentation can be seen, and they leave a little scar that can be readily recognised. New tubercles, however, have been seen to develop during streptomycin treatment and then to heal on continuation of the same treatment.

COMPLICATIONS

After the chest and eye lesions have completely healed, and the general condition is good after the treatment has been stopped, certain dangers are still to be feared.

Meningitis can still develop. In 11 patients meningitis was discovered only after treatment had been discontinued; but 5 of these were early cases in which no lumbar puncture had been done, and it is likely that meningitis was present much earlier, perhaps from the very beginning, and that what had been taken for the onset of meningitis was only the first manifestation of a relapse. In the 6 other patients lumbar puncture had shown a normal C.S.F. during treatment, and they developed meningitis after treatment had been discontinued for several months in 4 cases, and for a few weeks in 2. It is worth emphasising that 3 were early cases which had been treated for less than three months, another 1 had been treated for three and a half months, another 1 for five months, and another 1 for ten months. With the present treatment lasting more than six months, continued long after the radiogram is back to normal, post-treatment meningitis has become very rare. Indeed, I have seen it only once in such circumstances.

Relapse of miliary tuberculosis is very rare, too. I have seen it twice:

The first case was in a girl, aged 13, admitted in February, 1947, with very acute miliary tuberculosis. After the completion of five and a half months' treatment she went home for two and a half months and then was readmitted with tuberculous meningitis; meanwhile her chest radiogram remained normal, and there were no new tubercles of the choroid. She was treated nearly a year for her meningitis, and then discharged with normal C.S.F. and in good condition; but she was readmitted ten months later with acute miliary tuberculosis both of the lungs and of the choroid, but with no relapse of meningitis. Treatment was resumed and proved as efficient as before. Now she has been off treatment for two years and is doing very well; but she is deaf.

The second case was in a boy, aged 4 years, who had tuberculous cervical lymph-nodes and acute miliary tuberculosis that cleared up very slowly in spite of high dosage of streptomycin and prolonged treatment with combined streptomycin, sulphones, and *p*-aminosalicylic acid (P.A.S.). Treatment was discontinued after more than eighteen months in spite of persistent pyrexia. Five months later the cervical lymph-nodes became enlarged again and, shortly after, miliary dissemination was found again both in the lungs and in the choroids. The child died of a late streptomycin-resistant meningitis.

These are the only 2 cases that I have seen of relapse in 170 cases of miliary tuberculosis.

Other Complications.—In other cases I have seen, after streptomycin treatment, bone-and-joint tuberculosis in 3 patients, tuberculous cervical lymph-nodes in 1, and discrete apical tuberculosis in 1. This, out of the 95 patients who are still alive, means an excellent prognosis as a whole. Of these 95 patients 21 are still being treated or have been off treatment for less than 1 year; 12 have been off treatment for 1–2 years; 35 for 2–3 years; 19 for 3–4 years; and 8 for 4–5 years.

CLINICAL FORMS

Fatal Acute Miliary Tuberculosis.—In the present series of 170 patients 9 died of miliary tuberculosis and not from meningitis. The main cause of death was acute asphyxia. I have seen it in 3 cases due not only to actual miliary lesions but also to rupture of emphysematous alveoli, causing either pneumothorax or acute mediastinal and subcutaneous emphysema (fig. 6). The other patients died of more or less rapidly progressive cachexia.

Miliary Tuberculosis with Localised Tuberculosis.—Tuberculosis of bones and joints or of lymph-nodes is seen with subacute miliary tuberculosis. I have seen 2 tuberculomas of the cerebellum; both were successfully removed under streptomycin treatment.

Late Miliary Dissemination.—In a few cases miliary dissemination took place from some unknown cause several years after the onset of the primary tuberculosis. I have twice seen a child, admitted with meningitis without miliary tuberculosis, have a typical miliary spread at the time of a relapse of the meningitis. One of these children is off treatment and in good condition, and the other is still being treated and doing well. In a third case miliary tuberculosis was found at necropsy in a child who had died of a relapse of tuberculous meningitis due to resistant tubercle bacilli.

TREATMENT

I give 0·02–0·04 g. daily per kg. of body-weight. I give more to small children (0·50 g., for instance), and never more than 1·50 g. to older children. This dose is given in three injections daily, continuously for at least eight months.

I always give P.A.S. too by mouth 0·30–0·50 g. per kg. of body-weight taken in 1–4 fractions a day, continuously until the streptomycin is discontinued.

This treatment has to be continued if the regression of the signs and symptoms (radiological picture, temperature, E.S.R.) takes longer than usual. In some such cases the treatment has lasted thirteen months.

After completion of a course of treatment, it has to be resumed in the following circumstances:

(1) If there is a relapse of miliary tuberculosis.

(2) If there is a secondary *tuberculous focus* (lymph-nodes, bones and joints, &c.).

(3) If meningitis develops. In this case streptomycin 20–4 mg. is immediately given by the intrathecal route, usually lumbar, twice a day for a few days (in addition to two intramuscular injections a day) and then once a day until the C.S.F. has been normal for two months. The intramuscular injections are discontinued at least two months after the intrathecal injections.

The recent introduction of isoniazid in the treatment of tuberculosis adds a new weapon to the struggle against this disease; but by no means does it exclude streptomycin and P.A.S., especially streptomycin, which remains the fundamental antituberculous drug.

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INFECTIOUSNESS OF COMMUNICABLE DISEASES IN THE HOUSEHOLD

(MEASLES, CHICKENPOX, AND MUMPS)*

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MEASLES, chickenpox, and mumps have similarities which link them in a natural group with a number of other diseases. Each is a characteristic communicable illness to which most people are liable, and each usually produces enduring immunity. The causal agent of each is an obligate parasite natural to man which passes direct from sufferer to susceptible, apparently without the need of an intermediate agency. Inapparent infections are rare, at least in measles and chickenpox, infection of a susceptible ordinarily leading to the manifest disease, and the carrier state does not seem to play an important part in distribution.

These properties, with some others, determine the way a disease behaves in a community, and in fact the three diseases resemble one another sufficiently closely in their epidemic and endemic behaviour to justify comparative investigation by similar methods. Nevertheless there are differences. Despite the broad similarity, just as each disease has its peculiar clinical picture, so it has its own epidemiological pattern due to consistent differences of degree in those very attributes which link the diseases together in a natural grouping. Both measles and mumps, for example, tend to attack exposed susceptibles, but measles habitually strikes more readily than mumps, and so it comes about that mumps works its way through a community more slowly than measles, leaving behind more susceptibles to be dealt with at second or third visits. This peculiarity is reflected in the age-distribution of any adequate collection of cases. Communities of various types may vary much in the age at which their members take these diseases, but in a single community over a given period the average age of attack will be somewhat younger for measles than for mumps.

The epidemic pattern depends in part on the natural characters of the parasite, in part on the behaviour of the human host. When investigating a particular property of the parasite it is therefore necessary, so far as possible, to reduce or eliminate any disturbing effects of human behaviour—the human community must be standardised for the purpose. The household has often proved the most suitable community in which to compare and contrast various properties of different human parasites under similar conditions.

Having studied a particular property in one type of community one can repeat the study in other types of human environment, and so, step by step, learn something both of the effect of human behaviour on the biology of the organism, and of those details of the host-parasite relationship with which deliberate human interference may be practicable and desirable. Moreover, the method is fruitful in assessing the results of such interference.

Distinctions between similar diseases may sometimes be qualitative, as when transmission is effected by sputal droplets in one disease and by fæcal contamination in another. More often the differences are quantitative and require numerical assessment and presentation.

TABLE I—EXAMPLES OF METHOD OF RECORDING EPIDEMICS FOR CALCULATION OF THE EXPOSURE ATTACK-RATE IN THE HOME (INFECTIOUSNESS)

Case index no.	Generation														
	I			II			III			IV			V		
	Date	Sex	Age (yr.)	Date	Sex	Age (yr.)	Date	Sex	Age (yr.)	Date	Sex	Age (yr.)	Date	Sex	Age (yr.)
Example I:															
A	Jan. 2	F	7												
B	..	..	..	Jan. 16	M	10	..	..	..	..	..	..	..	..	..
C	..	..	..	„ 16	F	7	..	..	..	..	..	..	..	..	..
D	..	..	..	„ 17	M	9	..	..	..	..	..	..	..	..	..
E	..	..	..	„ 18	M	6/12	..	..	..	..	..	..	..	..	..
Example II:															
A	Jan. 2	F	7												
B	..	..	..	Jan. 16	M	10	..	..	..	..	..	..	..	..	..
C	..	..	..	Esc.	..	..	Jan. 28	F	7	..	..	..	..	..	..
D	..	..	..	Esc.	..	..	„ 29	M	9	..	..	..	..	..	..
E	..	..	..	Esc.	..	..	„ 29	M	6/12	..	..	..	..	..	..
Example III:															
A	Jan. 2	F	7												
B	..	..	..	Jan. 16	M	10	..	..	..	..	..	..	..	..	..
C	..	..	..	Esc.	..	..	Jan. 28	F	7	..	..	..	..	..	..
D	..	..	..	Esc.	..	..	Esc.	..	..	Feb. 12	M	9	..	..	..
E	..	..	..	Esc.	..	..	Esc.	..	..	Esc.	..	..	Esc.	M	6/12
Example IV:															
A	Jan. 2	F	7												
B	..	..	..	Esc.	M	10	..	..	..	..	..	..	..	..	..
C	..	..	..	Esc.	F	7	..	..	..	..	..	..	..	..	..
D	..	..	..	Esc.	M	9	..	..	..	..	..	..	..	..	..
E	..	..	..	Esc.	M	6/12	..	..	..	..	..	..	..	..	..
B	Feb. 5.	M	10												
C	..	..	..	Feb. 13	F	7	..	..	..	..	..	..	..	..	..
D	..	..	..	„ 15	M	9	..	..	..	..	..	..	..	..	..
E	..	..	..	Esc.	..	..	Esc.	M	6/12	..	..	..	..	..	..

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* The word "infectious" is used in some parts of the English-speaking world synonymously with our use of the word "infective"; hence in such places "infectious diseases" would mean all those of microbic agency whether naturally communicable or not. For those which are communicable the word "contagious" is used (Dorland 1938). For transatlantic readers the initial word of the title of this paper should be: "Contagiousness."

TABLE II—INFECTIOUSNESS (EXPOSURE ATTACK-RATE AMONG SUSCEPTIBLES AT RISK IN THE HOME)

Age-group (yr.)	Measles	Varicella	Mumps
0–15 :			
Susceptibles	251	238	218
Exposures	266	282	264
Transmissions	201	172	82
Escapes	65	110	182
Exposure attack-rate (infectiousness)	75·6%	61·0%	31·1%
Over 15 :			
Susceptibles	36	64	96
Exposures	47	100	125
Transmissions	7	12	43
Escapes	40	88	82
Exposure attack-rate ..	14·9%	12·0%	34·4%
Total :			
Susceptibles	287	302	314
Exposures	313	382	389
Transmissions	208	184	125
Escapes	105	198	264
Exposure attack-rate ..	66·5%	48·2%	32·1%

Infectiousness, the ability of a disease to spread in a community, is a measurable characteristic and should be susceptible of being expressed precisely. It is insufficient to recognise that measles is more infectious than mumps. How much more infectious is it? Is it more so than chickenpox? A means of measuring infectiousness not only adds to our knowledge of the biology of this interesting group of parasitic organisms but also provides an approach to the solution of some practical problems. Does infectiousness vary from time to time, and from place to place? What other attributes of a disease are quantitatively associated with its degree of infectiousness? Is change in infectiousness responsible for the waxing and waning of epidemic prevalence?

The present paper describes studies on the infectiousness of measles, chickenpox, and mumps in households in a semi-rural area of Gloucestershire—a town of some 11,000 inhabitants and the surrounding agricultural area to a radius of 6–8 miles containing a slightly larger population. The records for measles and chickenpox cover the four years from June 1, 1947, to May 31, 1951. Those for mumps include also a further seven months until Dec. 31, 1951.

A member of the epidemiological research unit visited all the cases and contacts several times. Much care was taken to ensure accuracy and to indicate which data were fully reliable and which only approximate. Approximately accurate data, though useful for certain purposes, can be most damaging when associated with more accurate data for other purposes. Close association with a general practice, the ready coöperation of the other general practitioners in the area, and long familiarity with the district gave unusually favourable opportunities. For example, the parent of a child with an attack of measles claimed that five years earlier the child had had a previous attack of measles diagnosed as such by the doctor. Reference to the contemporary notes of the doctor showed that the previous attack was one of rubella. In many such instances it was possible to increase the accuracy of the records.

Method of Calculating Infectiousness

PRINCIPLE

Measurement of infectiousness is based on the attack-rate. Attack-rates are assessed in different days, and to secure comparable figures it is important to define which way is being used. In one which has been much used an estimate is made of the proportion of susceptibles who become infected in homes into which the disease has been introduced; this gives a secondary attack-rate. Attractive because of its convenience and simplicity, this reckoning conceals several sources of error and should be reserved for diseases in which it is impossible to determine the details of spread inside the individual households—e.g., whooping-cough. An excellent example of the use of this method is to be found in the report of the Medical Research Council (1951) on the prevention of whooping-cough with vaccine. The results are not precisely comparable with those of the method used here and tend to give a consistently higher rate.

In determining infectiousness the *susceptible-exposure attack-rate*—i.e., the proportion of exposures of susceptibles leading to a transmission—should be used whenever possible. An exposure takes place each time that a susceptible—one giving no past history of the disease—is at risk with one or more infectious cases. Each susceptible in a household in which another occupant is ill with the disease is deemed to have undergone exposure unless he is simultaneously ill with the same disease. The desirability of counting in this way is clear if one considers families of different sizes. A solitary susceptible escaping an exposure in the home has no further opportunity to catch the disease there, whereas when two susceptibles are simultaneously at risk of whom only one takes the disease the other is exposed a second time. The larger the number of susceptibles the greater is the opportunity for several generations inside the family. Each exposure must therefore be recorded to allow those leading to a temporary escape equal value with those leading to a more permanent escape. Four examples are given to make the method clear:

I, A infects B, C, D, and E.

Exposures	4
Transmissions	4

II, A infects B, but C, D, and E escape. Then B infects C, D, and E.

Exposures	7
Transmissions	4

III, A infects B, but C, D, and E escape. B then infects C, but D and E again escape. Then C infects D, but E again escapes. E also escapes the infective stage of D, so escaping finally.

Exposures	10
Transmissions	3

IV, A fails to infect B, C, D, and E. Five weeks later B gets the disease and infects C and D, but E escapes. Here there are two distinct entries of the virus into the household:

(i)	Exposures	4
	Transmissions	0
(ii)	Exposures	4
	Transmissions	2

Table I shows these four examples set out on the epidemic sheet from which the exposure attack-rate in the home is compiled.

EFFECT OF FAULTY MEMORY

A person who mistakenly represents himself to be a susceptible produces a double error by falsifying both the

TABLE III—EXAMINATION OF POSSIBLE MEASURING-POINTS IN MEASLES

Interval (days)	Between			
	Onsets (137 pairs)	Conj. (44 pairs)	R.I. (162 pairs)	R.II. (203 pairs)
	%	%	%	%
6	2·2	..	1·2	2·0
7	14·0	13·6	3·7	3·9
8	5·8	4·5	6·2	6·9
9	8·8	2·3	14·2	15·3
10	12·4	11·4	21·0	14·3
11	8·0	25·0	17·9	20·8
12	14·7	13·6	9·3	12·3
13	8·0	15·9	11·7	7·8
14	9·5	4·6	8·0	7·8
15	5·8	4·5	2·5	4·9
16	3·6	2·3	3·7	2·0
17	3·6	2·3	..	1·0
18	0·7	..	0·6	1·0
19	2·9	..	..	..
20	..	..	..	..
Total	100	100	100	100

Conj., first day of conjunctivitis.
R.I., " " " rash.
R.II., day of maximum rash.

TABLE IV—EXAMINATION OF POSSIBLE MEASURING-POINTS IN VARICELLA

Interval (days)	Between	
	Onsets (67 pairs)	R.I. (184 pairs)
	%	%
6	..	..
7	4·5	3·8
8	7·5	4·3
9	1·5	2·7
10	1·5	4·9
11	3·0	3·8
12	6·0	6·0
13	9·0	12·0
14	20·8	29·9
15	16·4	10·3
16	6·0	5·4
17	9·0	7·6
18	11·8	3·3
19	1·5	3·8
20	1·5	2·2
Total	100	100

R.I., day of first rash.

number of exposed susceptibles in the family and the proportion of escapes. In example III given above, for instance, if E is not susceptible but immune, the number of presumed escapes is raised from 3 to 7, a serious augmentation. The larger the family the greater is the error, because most immunes at risk will always escape, however often exposed. Increasing age brings forgetfulness of childhood ailments, a source of error which becomes considerable in the elderly. Against measles there appears to be no evidence of increasing immunity apart from an attack of the disease. Epidemics in areas unprotected by endemic disease affect the older equally with the younger members of the population, as was shown in the Solomon Islands and in the Faroe Islands (1846). The position is probably the same for varicella.

TABLE V—EXAMINATION OF POSSIBLE MEASURING-POINTS IN MUMPS

Interval (days)	Between	
	Onsets (105 pairs)	S.I. (142 pairs)
	%	%
9	1·0	..
10	3·8	1·4
11	1·0	..
12	1·9	2·8
13	4·8	2·1
14	8·6	14·1
15	6·6	4·9
16	10·5	10·6
17	12·4	9·9
18	7·6	9·2
19	8·6	8·5
20	6·6	7·0
21	6·6	7·0
22	4·8	5·7
23	1·0	0·7
24	1·9	4·2
25	3·8	4·2
26	1·9	2·1
27	1·9	2·1
28	1·0	2·1
29	..	0·7
30	1·9	..
31	..	..
32	..	0·7
..	..	..
35	1·0	..
36	..	..
37	1·0	..
Total	100·2	100

S.I., first day of swelling.

For measuring infectiousness the attack-rate is therefore calculated on susceptibles aged 14 or less. The rate in alleged susceptibles above that age is very different (table II), and one presumes that this disparity is due in large part to the fading memory of childhood illness. It is not unreasonable to suppose that of the 36 persons aged more than 14 representing themselves to be susceptible to measles only about 10 were so. In mumps the position is different; mumps is less infectious and therefore attacks on an average at a later age. The attack-rate among those aged more than 14 claiming to be susceptible does not differ materially from that in the younger group. At present there seems to be no knowledge of the effect of ageing on susceptibility. The figure for the infectiousness of mumps, 31·1%, reckoned on the susceptibles aged less than 14 differs but little from the attack-rate at all ages (32·1%). It is therefore probably unnecessary to make, as we have done, an adjustment of the sort used in measles and varicella to the figures for mumps.

TABLE VI—INFECTIOUSNESS THROUGHOUT THE SEASONS BASED ON SUSCEPTIBLE EXPOSURE-TRANSMISSION RATE UNDER THE AGE OF 15

—	Measles			Varicella			Mumps		
	Exposures	Transmissions	Infectiousness (%) 3 months' moving averages	Exposures	Transmissions	Infectiousness (%) 3 months' moving averages	Exposures	Transmissions	Infectiousness (%) 3 months' moving averages
January	4	3	62·5	10	7	69·3	3	..	37·5
February	..	..	86·4	51	35	65·1	5	1	44·4
March	18	16	77·4	25	14	68·5	10	7	40·0
April	13	8	80·6	16	14	56·6	15	4	36·0
May	31	26	76·9	42	19	58·6	25	7	26·8
June	73	56	74·7	29	18	50·9	31	8	24·5
July	66	46	75·0	37	18	59·3	53	12	27·6
August	33	27	70·6	15	12	52·6	38	14	28·6
September	10	4	75·5	5	..	60·9	13	4	34·9
October	10	9	70·8	3	2	53·3	32	11	31·5
November	4	4	83·3	22	14	67·3	31	9	35·2
December	4	2	75·0	27	19	67·8	8	5	33·3
Mean			75·7			60·9			33·35

(See also fig. 3.)

PRIMARY AND SECONDARY CASES

From what has already been written it is seen to be important to distinguish clearly between primary (infecting) cases and secondary (infected) cases. During an epidemic three or four generations of the disease may occur in a family, the second-generation cases in their turn becoming primary to the tertiary, and the tertiary to the quaternary. A right estimate of the number of exposures and transmissions depends on a knowledge of the span of a generation, a measurement peculiar to each disease.

Point of Measurement

It is necessary to define a point in the course of the disease from which to measure the serial interval from case to case. Most diseases present several features that might be used for the purpose, and the principles on which to choose the most suitable have already been discussed (Hope Simpson 1948). The event on which to base a *measuring-point* must be regularly present, readily recognised, and constant in the time of its appearance in the cycle of the illness. In measles four events have been examined for suitability (table III):

(1) *Onset of symptoms of illness.*—This, though often used, is unsatisfactory because the serial intervals cover a wide range with a shallow mode.

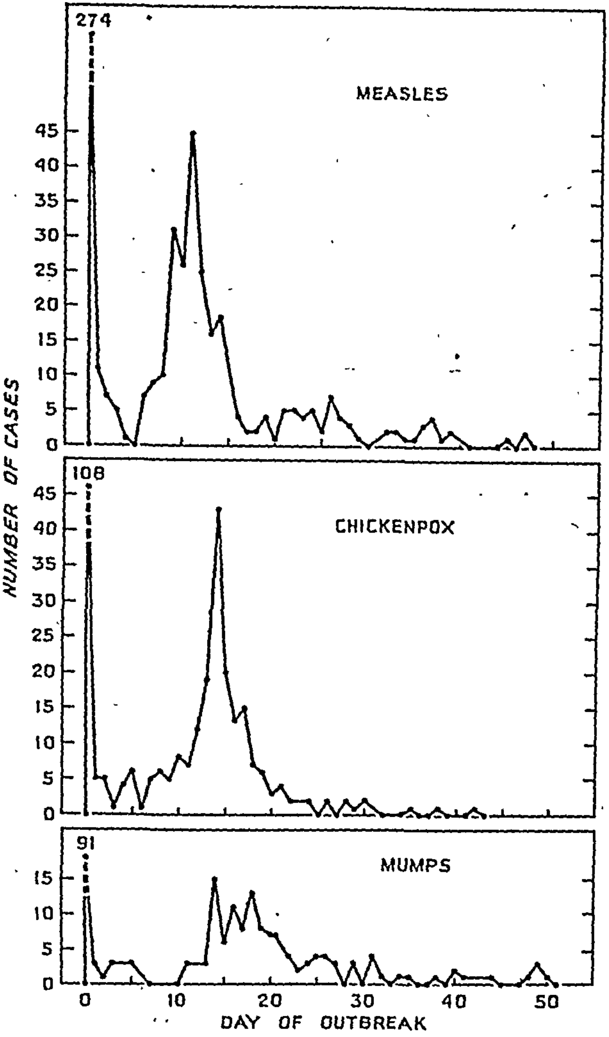

Fig. 1—Primary and secondary cases in outbreaks in households.

(2) *First appearance of conjunctivitis.*—This gives a satisfactory range and mode, but the symptom is often absent or unrecognised, or its day of onset is forgotten.

(3) *First appearance of rash.*

(4) *Day of maximum rash.*

Between these last two there is little to choose. Parents are perhaps less certain of the date of the first appearance. Some parents are more observant than others. We can ourselves confirm the day of fullest development more often than the day of first appearance of the rash. For these reasons we have chosen the day of fullest flowering of the rash. When, as occasionally happens, the rash remains equally florid for more than one day, the first day of maximum rash is used.

Table IV examines the onset and the first day of rash in chickenpox, and table V the onset and the first day of swelling in mumps. The days of measurement used in the present study are as follows:

Measles: maximum rash,
Chickenpox: first appearance of rash,
Mumps: first appearance of swelling.

The point of measurement in each case is midnight after the day of measurement.

First-generation Primaries

It is next necessary to distinguish between those cases in the home which are co-primary with the first case and have been infected outside the household, and second-generation cases infected by the primary case within the household. To do this, the first case in the home is *considered as occurring at the zero point,* and the intervals between the measuring-point in this and subsequent cases are tabulated. The experience of all the households combined shows a steep decline for the first few days owing to the decreasing number of co-primaries, succeeded by a rise towards the mode of the curve of secondary cases (fig. 1). The lowest point, where the decreasing primaries are intersected by the increasing secondaries, is taken as the division between first and second generations, and at this point primaries erroneously included as secondaries most nearly balance secondaries wrongly considered primary. A small error remains because there are inevitably more secondaries than primaries.

TABLE VIII—PERCENTAGE OF SECONDARY CASES ESCAPING TEMPORARILY

Disease	Secondary cases	Percentage escaping temporarily	
		Once	Twice
Measles	201	4·0	0·5
Varicella ...	172	8·1	0·6
Mumps	82	12·2	3·7

Cases which have had two escapes are also included among those which have escaped once.

The following are the intervals during which cases are considered co-primary with the first case in the household:

Measles: 6 days, Varicella: 7 days, Mumps: 10 days.

Second Generation

The second generation must be distinguished not only from the first as described above but also from subsequent

TABLE VII—INFECTIOUSNESS: EXPOSURE TRANSMISSIONS UNDER THE AGE OF 15
(Three months' moving averages against central month and deviation from mean)

—	Measles			Varicella			Mumps		
	Infectiousness	Deviation from mean	% deviation from mean	Infectiousness	Deviation from mean	% deviation from mean	Infectiousness	Deviation from mean	% deviation from mean
January ..	62·5	−13·2	−17·4	69·3	+ 8·4	+13·8	37·5	+ 4·2	[illegible]
February ..	86·4	+10·7	+14·1	65·1	+ 4·2	+ 6·9	44·4	+11·1	[illegible]
March	77·4	+ 1·7	+ 2·4	68·5	+ 7·6	+12·5	40·0	+ 6·7	[illegible]
April	80·6	+ 4·9	+ 6·4	56·6	− 4·3	− 7·1	36·0	+ 2·7	+ 8·1
May	76·9	+ 1·2	+ 1·6	58·6	− 2·3	− 3·8	26·8	− 6·5	−19·5
June	74·7	− 1·0	− 1·3	50·9	−10·0	−16·4	24·5	− 8·8	−26·4
July	75·0	− 0·7	− 0·9	59·3	− 1·6	− 2·6	27·6	− 5·7	−17·1
August ..	70·6	− 5·1	− 6·7	52·6	− 8·3	−13·6	28·6	− 4·7	−14·1
September ..	75·5	− 0·2	− 0·3	60·9	0	0	34·9	+ 1·6	+ 4·8
October ..	70·8	− 4·9	− 6·4	53·3	− 7·3	−12·0	31·5	− 1·8	− 5·4
November ..	83·3	+ 7·6	+10·0	67·3	+ 6·4	+10·5	35·2	+ 1·9	+ 5·9
December ..	75·0	− 0·7	− 0·9	67·8	+ 6·9	+11·3	33·3	0	0
Mean ..	75·7			60·9			33·3		

(See also fig. 3.)

BLE IX—EXPOSURE ATTACK-RATE % AMONG FAMILIES WITH FFERENT NUMBERS OF SUSCEPTIBLES UNDER THE AGE OF 15

isease	No. of susceptibles in family				
	One	Two	Three	Four or more	Total
easles	140 (*77·9*)	68 (*76·0*)	24 (*70·0*)	16 (*70·0*)	248 (*75·6*)
aricella	104 (*75·0*)	80 (*60·0*)	48 (*48·6*)	15 (*45·5*)	247 (*61·0*)
umps	78 (*32·1*)	98 (*38·3*)	81 (*31·1*)	55 (*25·3*)	312 (*31·1*)

Rates are shown in parentheses.

TABLE X—INFECTIOUSNESS AND AGE-DISTRIBUTION

—	Measles	Varicella	Mumps
fectiousness (%)	75·6	61·0	31·1
ean age at which infection takes place (yr.)	5·6	6·7	11·5
andard deviation of age distribution	4·73	5·45	10·50
ge by which 90% of cases have had the disease	8 yr. 4 mos.	10 yr. 8 mos.	29 yr.

enerations. Mistaken inclusion of tertiaries reduces the roportion of escapes, and mistaken inclusion of second-eneration cases among tertiaries reduces the proportion f transmissions. Epidemic studies are of great assistance n solving this problem. Fig. 2 shows accumulated epi-emics with the first case of each recorded at zero point. t is easy to find the mode of generation after generation. rom these figures the following intervals have been hosen:

	First generation (days)	*Second generation (days)*	*Tertiaries (days)*	*Quaternaries (days)*
easles ..	1–6	7–18	19–30	31–42
aricella ..	1–7	8–21	22–35	36–49
umps ..	1–10	11–30	31–50	51–70

(Both days are included in the intervals.)

Certain interesting relationships emerge from this study. It will be seen that the generation-time is twice the interval during which cases are considered to be co-primary with the first case. Further, the generation-time is identical with the mean interval between the modes of successive generations, and indeed this forms the simplest method of estimating it.

Here is a biological measurement of great interest, susceptible of precise estimation, differing consistently from disease to disease in a manner peculiar to each parasite. Domiciled in man for millennia, the causal organism of measles has burst into reproductive activity and sent forth a fresh colony on the average every twelfth day. The figure of twelve days used here for measles is too long, but for present purposes it is impossible to split the day into portions. The reproductive cycle of varicella is almost exactly fourteen days. For mumps the data are as yet insufficient to give a precise figure, and twenty days must be considered as tentative.

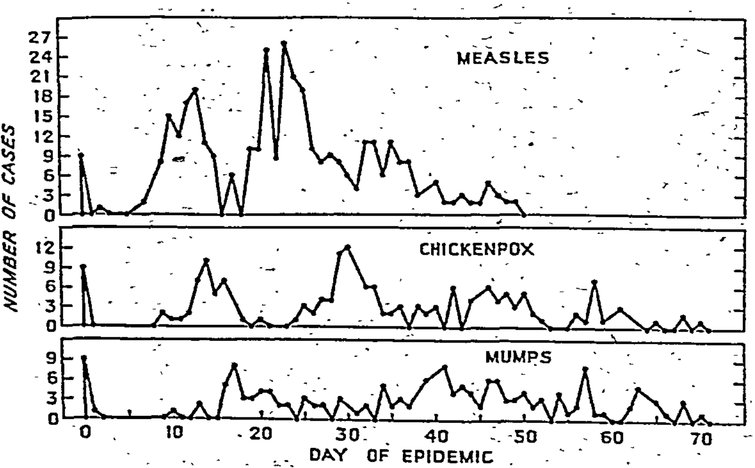

Fig. 2—First, second, and subsequent generations of cases in epidemics.

The methods used here differ from those used by Wilson et al. (1939), whose paper should be consulted for details of previous usages. The choice of method makes a considerable difference, especially when one is studying attack-rates in families with differing numbers of susceptibles at risk. To compare our figures with those of Wilson et al. we have re-analysed them in table XII by the methods which they used.

Results

Table II shows the infectiousness of the three diseases, the figures for each representing the experience of almost the same families. Measles is evidently the most infectious in the community provided by the household. Mumps is not half as infectious as measles and only just over a half as infectious as varicella. Fig. 3, based on tables VI and VII, shows the infectiousness of the three diseases throughout the seasons, a three-monthly moving average being used. Tests of significance show that the variation in each is not more than would be expected by chance. The degree of infectiousness in the three diseases is also reflected in the proportion of secondary cases that escape once or twice before finally coming down (table VIII).

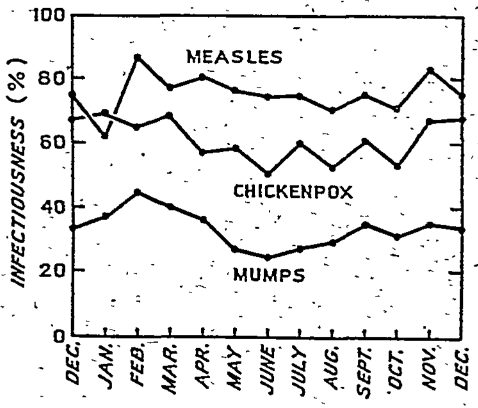

Fig. 3—Infectiousness of measles, chickenpox, and mumps in different seasons.

EFFECT OF SIZE OF FAMILY ON INFECTIOUSNESS

Table IX shows the infectiousness of the three diseases in families with 1–4 or more susceptibles at risk. The numbers of families with more than 3 susceptibles at risk are not large enough to be representative.

INFECTIOUSNESS AND AGE OF ATTACK

In diseases which confer life-long immunity the degree of infectiousness is reflected in the age at which a person is most likely to be attacked. The more infectious the disease the younger is the age at which an attack is likely to be received. Table X, which shows the age-distribution and the infectiousness of measles, varicella, and mumps, brings out the closeness of this inverse relationship.

INFECTIOUSNESS AND SEASONAL PREVALENCE IN MEASLES

During the period of this study measles in this area was mainly a disease of spring and summer, 78·6% of the 663 cases in the epidemic studies having fallen during the months from May to August (table XI). In case these figures were unrepresentative, drawn as they were largely from studies of total epidemics in various parts of the area, the fairness of the picture was tested by analysing the measles seen in the same period in a local general practice among some 4000 patients. Of the 229 cases of measles encountered in the practice more than 75% fell in the months from May to August; hence the epidemic figures may be taken as representing the local trend of measles during that period.

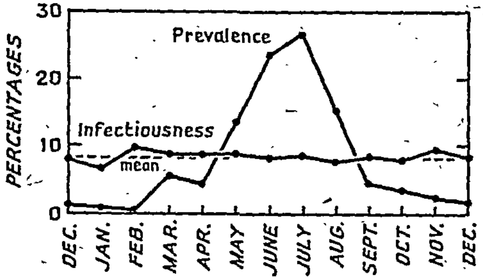

Fig. 4—Comparison of infectiousness and prevalence of measles.

Was the autumn decline in prevalence due to diminished infectiousness of the disease? Comparison of the seasonal infectiousness with the seasonal prevalence in table XI and fig. 4 shows a vivid contrast between the uniformity of the infectiousness and the variation in the prevalence. There is no seasonal waxing and waning in infectiousness such as might explain the vagaries of these epidemics.

RELIABILITY AND UTILITY OF THE PRESENT METHOD

The simple method presented here of assessing infectiousness can be adapted to the study of virus mutation and other factors involving secular changes in infectiousness. The measurement given is absolute and not merely relative, 100% infectiousness representing a disease which attacks every exposed susceptible in the home at the first opportunity. Measles approaches quite near to saturation, and experience suggests that whooping-cough will give an even higher figure. It has been shown above how the method can be used to study seasonal variation in infectiousness; and, in view of its possible usefulness in other spheres, it is well to inquire if the figures produced possess the requisite stability. Were the investigation to be repeated in another part of the country, for example, or here at another time, would different figures emerge? Although further research is needed to decide this, our experience suggests that sufficiently stable figures can be obtained. The measles cases analysed here can be arranged in a form to compare with the admirable studies of Wilson et al. (1939) at Providence, Rhode Island. Reference to table XII shows that their figures fall close to ours in both age-groups.

TABLE XI—SEASONAL PREVALENCE AND INFECTIOUSNESS IN MEASLES

(The three percentage columns show the proportion of the total occurring in each month)

—	Infectiousness in epidemic studies			Prevalence					
				In epidemic studies			In general practice		
	Infectiousness	%		Cases	%		Cases	%	
January	62·5	6·9	33·8	5	0·8	10·7	7	3·0	11·7
February	86·4	9·5		2	0·3		1	0·4	
March	77·4	8·5		36	5·4		10	4·4	
April	80·6	8·9		28	4·2		9	3·9	
May	76·9	8·5	32·7	88	13·2	78·6	27	11·7	76·1
June	74·7	8·2		156	23·6		36	15·7	
July	75·0	8·2		176	26·6		49	21·5	
August	70·6	7·8		101	15·2		62	27·2	
September	75·5	8·3	33·5	28	4·2	10·7	11	4·8	12·2
October	70·8	7·8		22	3·3		14	6·1	
November	83·3	9·2		13	2·0		1	0·4	
December	75·0	8·2		8	1·2		2	0·9	
Total	908·7	100·0		663	100·0		229	100·0	

(See also fig. 4.)

Several workers have suggested that infectiousness alters during the course of an epidemic and is at a different level in interepidemic periods. This matter can also be investigated simply and directly by the present methods: it would demand a simultaneous collection of records from a wide area and would need to be continued for several years.

Summary

It is possible to give a quantitative expression of the infectiousness of certain diseases by assessing the incidence of cases resulting from every exposure of a susceptible in the home (susceptible-exposure attack-rate). Infectiousness in the diseases studied was:

Measles: 75·6%, Varicella: 61·0%, Mumps: 31·1%.

The mean reproductive cycle of the virus of measles is twelve days, that of varicella fourteen days, and that of mumps about twenty days. Cases are reckoned as co-primary with the first case in the household if they fall within a period of half the reproductive cycle. Subsequent generations are reckoned by adding on to this half-cycle a period equal to one reproductive cycle for each generation. Details are given of the methods used.

TABLE XII—COMPARISON OF THE SECONDARY ATTACK-RATE IN MEASLES IN DIFFERENT AREAS AND AT DIFFERENT TIMES

Age-group (yr.)	Secondary attack-rate	
	Providence, U.S.A., 1929–34 (Wilson et al. 1939)	Cirencester, 1947–51
Less than 1	40·6	40·0
Less than 15	81·1	80·1
15 or more	16·7	16·3

The age-distribution of these diseases shows a close inverse relationship with the infectiousness.

The summer prevalence of measles in these areas during the period under review was not due to any increase of infectiousness that could be shown in the home attack-rate.

A numerical expression of infectiousness should prove of value in the study of various problems concerning infectious disease.

It is a pleasure to acknowledge the great help received from every member of the unit during the five years of its existence, and the grant from the Medical Research Council which made the work possible. I have also had help and advice from many people, and I wish especially to mention that received from Prof. A. Bradford Hill. I am glad also to acknowledge the willing coöperation of the school-teachers in this area, and of my general-practitioner colleagues, and the patients who form the subject of this work.

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"... The meaning of the irrational is so ambiguous in recent psychology that the man in the street, as we all know, is inclined to draw the conclusion that, being so full of irrational factors, he cannot be expected in any circumstances to behave rationally and could hardly know that he was behaving rationally even if he did so behave."—*Times Literary Supplement*, Sept. 5, 1952, p. 585.

INADVISABILITY OF GIVING A.C.T.H. TO PATIENTS WITH GASTRIC ULCER

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SINCE the advent of A.C.T.H. and cortisone reports have been published emphasising the danger of their side-effects. One of these alleged effects is the activation of healed or quiescent peptic ulcers, leading on occasion to bleeding or to perforation (Beck et al. 1950, Habif et al. 1950, Smyth 1951, Mandel et al. 1951, Sloan et al. 1951, Gray et al. 1951). Even more alarming are the records of perforation or of massive hæmorrhage in A.C.T.H.-treated patients with no previous history of ulceration (Habif et al. 1950, Gray et al. 1951). In such cases A.C.T.H. seems to have produced an ulcer.

Two explanations are offered for this untoward effect (Spiro et al. 1950, Gray et al. 1951):

(1) An increase in peptic activity as the result of administration of A.C.T.H. or of cortisone is shown both by a rise in the concentration of pepsin in the gastric juice and by increased excretion of uropepsin in the urine. The effect is not immediate but becomes manifest a few days after the start of treatment. It appears both in normal and in ulcer patients.

(2) At the same time there is a rise in gastric acidity, which is also slow, for the increase is not well marked until therapy has been given for 7–14 days. This effect also is seen in both normal and ulcer patients. When treatment is stopped, gastric acidity returns to normal.

So far Gray et al. (1951) have reported this increased gastric acidity only for A.C.T.H.; but it seems not unlikely that cortisone produces a similar effect, since it also increases peptic activity. Gray et al. comment:

> "The necrosing and erosive properties of acid-pepsin-gastric juice are well established. There is no reasonable doubt that the continuous stimulation or overproduction over a period of days or weeks of highly acid gastric juice rich in pepsin may result in a reactivation, perforation, or hæmorrhage from peptic ulcer."

They used fairly large doses, 100–160 mg. of A.C.T.H., or 250 mg. of cortisone, daily. This is more than most patients receive as a routine nowadays. However, the reported ulcer catastrophes cannot all be dismissed as due to excessive dosage; for, although one patient bled after receiving 4000 mg. of A.C.T.H. in twenty-one days, another perforated and died after having only 375 mg. in five days (Smyth 1951).

The activation of healed or of quiescent peptic ulcers, and the apparent production of ulceration in normal stomachs, are serious indictments of A.C.T.H. and cortisone—more particularly of A.C.T.H., since almost all the published reports of catastrophes refer to its use. Probably about 1 in 5 of the adult population of these islands has at one time or another had a peptic ulcer and would therefore seem to be at risk if given A.C.T.H. or cortisone. Physicians may well hesitate to administer these drugs, however pressing the indications for their use, to anyone who has a previous history of dyspepsia; they know how difficult it is to exclude the possibility of ulcer having caused the symptoms. Preliminary barium-meal radiography may show a scarred and deformed duodenal cap, but it may not reveal the scar of a healed gastric ulcer; and even when no previous ulcer exists, there is still the possibility that the treatment may cause one to appear. To make matters worse, the perforation of a peptic ulcer in a patient under treatment with A.C.T.H. or with cortisone may be attended by minimal symptoms and signs, owing to the masking effect of these drugs. The diagnosis may therefore be delayed, or even missed altogether, with fatal results (Smyth 1951).

There are indications, however, that the risk of ulcer activation is not really so great as might appear from the foregoing. Large numbers of people in Britain and elsewhere have now been treated with A.C.T.H. and with cortisone, yet the published reports of gastric accidents are relatively few. Even if the recorded catastrophes form only a small proportion of those that have taken place, there seems at present no indication that the situation is so grave as to cause widespread disquiet among those clinicians in this country who are using these drugs. Are A.C.T.H. and cortisone in fact as bad for peptic ulcers as a reading of the relevant reports might lead one to suppose? Whenever a new drug appears, the initial wave of enthusiasm is nearly always quickly succeeded by a trough of doubt. A.C.T.H. and cortisone were received initially, especially by the lay press, with even more than the usual acclaim, but a recent description of them as merely "a glorified aspirin" seems equally lacking in proportion. It would be a pity if such potentially valuable drugs were to be withheld from patients who might benefit from them, because of exaggerated fears about their toxic effects on the stomach.

The present investigation was started in the hope that it might throw some light upon the extent of this particular danger.

METHOD

Only patients with gastric ulcers have been included in this study. The healing, or otherwise, of gastric ulcers can be judged objectively by X rays, whereas that of duodenal ulcers as a rule cannot. Subjective clinical assessment of ulcer activity is notoriously unreliable.

Eighteen patients with uncomplicated gastric ulcers were divided into three groups. One group was treated with A.C.T.H. and one with cortisone, and the third was used as control. No selection was exercised, and all that the patients had in common was a chronic gastric ulcer, with a history of dyspeptic symptoms for several months or years.

As soon as the presence of an ulcer had been radiologically confirmed in the hospital outpatient department, the patient was put on the inpatient waiting-list and admitted as soon as possible. It was unfortunately impracticable to give A.C.T.H. and cortisone effectively to outpatients. However, while the patients were in hospital, no restriction was placed on their activities. They were allowed to smoke, were given no drugs other than A.C.T.H. or cortisone, and were kept on an almost normal diet. It was impossible to give a completely unlimited diet, because most patients were already accustomed to some self-imposed dietary restrictions which they were reluctant to abandon altogether; moreover the control group might well have complained that they were being kept in hospital unnecessarily. However, the diet given was merely the routine "post-ulcer régime," which consists simply of snacks between the main meals and the prohibition of grossly irritant articles of diet.

During the inpatient period A.C.T.H. and cortisone were given to patients in the appropriate groups by intramuscular injection at six-hour intervals. After two or three weeks of such treatment the patients were sent home with instructions to remain away from work and to continue the "post-ulcer" dietary régime, and were seen in the outpatient department at intervals until radiography showed complete healing of the ulcer or, in the case of those ulcers that failed to heal, until some other form of treatment was adopted.

RESULTS

The "radiological healing-time" of the ulcer has been arbitrarily assessed as the number of days which elapsed between the initial outpatient radiogram showing an ulcer and the final radiogram showing complete healing. The figure thus obtained is necessarily inexact, because

TABLE I—A.C.T.H.-TREATED PATIENTS

Case no.	Age (yr.)	Sex	History of ulcer (yr.)	Total dose of A.C.T.H. (mg.)	Period of administration (days)	Symptomatic improvement under treatment	Radiological healing-time	Remarks
1	45	M	20	980	15	Worse	..	Gastrectomy
2	55	F	3	440	12	Moderate	..	Eventually healed on routine treatment
3	55	M	2	980	27	Well marked	..	,,

radiography could only be done relatively infrequently (usually about once a fortnight). However, this is unimportant when dealing, as here, with a chronic lesion taking several weeks to heal, because differences of a few days one way or the other are of minor consequence.

The results in the three groups are summarised in tables I–III.

A.C.T.H.

There were originally five patients in this group, but one has been excluded because of doubt about whether the original radiogram did in fact show an ulcer. A second patient refused, for irrelevant reasons, to continue the injections after the first three days. As will be seen from table I, two of the remaining three patients said they felt better after the course of injections, but their radiograms showed no decrease in the size of the ulcer. One patient was apparently made worse:

Case 1.—*A lorry-driver, aged 45, had had intermittent* dyspepsia for twenty years. Radiography on March 22, 1951, showed a chronic gastric ulcer on the lesser curvature. He was admitted to hospital on April 25, 1951, and further radiography on May 4, 1951, still showed the ulcer, though it was smaller. A.C.T.H. 12·5 mg. six-hourly was given from May 5 to May 11, 1951, when the dose was increased to 20 mg. six-hourly. By May 17, 1951, he was complaining of increased pain; so the dose was reduced to 10 mg. six-hourly, and A.C.T.H. was finally omitted two days later. The patient was then put to bed on a light gastric diet, but despite this he continued to complain of severe pain and asked for operation. On May 28, 1951, a partial gastrectomy was done. The ulcer, which was simple and surrounded by considerable scar tissue, adhered to but did not actually penetrate the pancreas. Uneventful recovery followed.

There seems to be little doubt that this man's ulcer, which appeared to be healing before he came into hospital, was made worse by the A.C.T.H. and might well have perforated had the injections been continued.

In view of the uniformly poor results in these three patients, and the reported catastrophes after the use of A.C.T.H., it seemed unjustifiable to submit any more patients with gastric ulcers to the risk of A.C.T.H. injections.

TABLE II—CORTISONE-TREATED PATIENTS

Case no.	Age (yr.)	Sex	History of ulcer (yr.)	Total dose of cortisone (mg.)	Period of administration (days)	Symptomatic improvement under treatment	Radiological healing-time (days)	Remarks
4	51	M	5	300.	24	Well marked	48	..
5	41	M	10	2200	23	,,	26	Relapsed 2 mos. later
6	41	M	5	1850	20	,,	55	..
7	50	M	$^{3}/_{12}$	2250	23	Moderate	57	..
8	66	F	10	1650	17	Well marked	..	Gastrectomy
9	50	M	3	2650	28	,,	33	..
10	50	F	1	2450	25	,,	..	Gastrectomy
11	44	M	$^{3}/_{12}$	2150	23	,,	51	..

Cortisone

By contrast, this group of eight patients did unexpectedly well. With two exceptions the patients showed progressive clinical and radiological improvement, both during the period of cortisone injections and afterwards, to the point of complete healing of their ulcers. Two patients, however, failed to get radiological healing.

Case 8.—A married woman, aged 66, had had intermittent dyspepsia for many years. Radiography on Dec. 12, 1951, showed a deep chronic gastric ulcer on the lesser curvature. She was admitted to hospital on Dec. 13, 1951, and cortisone 25 mg. was given six-hourly between Dec. 13 and Dec. 27, 1951. Then the dosage was tapered off and the drug finally discontinued on Dec. 30, 1951. During this period the patient gradually lost all her symptoms, but radiography on Dec. [illegible], 1951, showed no diminution in the size of the ulcer. She was discharged from hospital and observed at outpatients. Two months later the ulcer was still present; so in March, 1952, a successful partial gastrectomy was done. The ulcer was simple, but associated with much scarring and adherent to the pancreas.

Case 10.—A married woman, aged 50, had had dyspepsia for a year. Radiography on Jan. 14, 1952, showed a chronic gastric ulcer on the lesser curvature. She was admitted to hospital on Jan. 19 and given cortisone 25 mg. six-hourly from Jan. 22 to Feb. 13. Then the dosage was tapered off and the drug finally discontinued on Feb. 16. During this time the patient became symptomless, but radiography on Feb. [illegible] and 21 showed no change in the size of the ulcer. A month later a partial gastrectomy was done because malignancy was suspected. The patient died shortly after operation. The ulcer was simple.

TABLE III—CONTROLS

Case no.	Age (yr.)	Sex	History of ulcer (yr.)	Symptomatic improvement in hospital	Radiological healing-time (days)	Remarks
12	45	M	10	Well marked	63	..
13	24	M	3	,,	35	..
14	61	F	10	Moderate	..	Gastrectomy
15	37	M	5	Well marked	48	..
16	41	F	2	,,	31	..
17	36	F	1	,,	53	..
18	73	F	$^{3}/_{12}$	,,	19	..

Although both these patients became symptom-free while on cortisone, their ulcers did not show radiological improvement. It is therefore possible that the cortisone may have delayed healing; it did not, however, seem to make the ulcers any worse.

Controls

All but one of these seven patients showed progressive clinical and radiological improvement to the point of complete healing, although they received no treatment other than the "post-ulcer régime." The exception was an elderly lady with a large ulcer on the lesser curvature. Although her symptoms improved and the ulcer decreased in size, after four months it was still visible on radiography. Gastrectomy was successfully done. The ulcer was simple.

DISCUSSION

The good results obtained in the controls confirm the experience of previous observers that gastric ulcers have a strong tendency to heal spontaneously, though the healing may only be temporary. Stolte (1950), for example, obtained radiological healing, usually in about [illegible] weeks, in twenty-one of twenty-four gastric-ulcer [illegible] patients treated only with placebos. It therefore follows that, if a drug is given to such patients, and if as a result some of them show appreciable delay in the progressive healing of their ulcers, it must be assumed that the drug is doing harm, even though there is no actual worsening of the condition.

The three A.C.T.H.-treated patients were all radiologically unimproved after the drug had been given, and one of them was symptomatically worse. A case against A.C.T.H. has already been made by three recorded episodes in which a gastric ulcer was made worse by the administration of A.C.T.H. (Sandweiss et al. 1950, Smyth 1951, Gray et al. 1951), and this case seems to be strengthened by the present findings. It would be foolhardy to persist in using A.C.T.H. for patients with active, or even quiescent, gastric ulcers.

The case against cortisone, however, does not seem so strong. There is no published record of a gastric ulcer having been made worse by cortisone, and in fact there is only one report of such deterioration in a duodenal ulcer (Lubin et al. 1951). It is also worth noting that the gastric-ulcer patient recorded by Smyth (1951) as having been made worse by A.C.T.H. subsequently received a course of cortisone without ill effect. On the other hand, S. J. Gray (personal communication) has had a patient who, after several months of cortisone treatment in fairly heavy dosage, developed a gastric ulcer for the first time.

In the present series six of eight cortisone-treated patients progressively healed their ulcers in an average time of 45 days. This compares favourably with the six similar controls, whose ulcers healed in an average time of $41\frac{1}{2}$ days. It therefore does not seem that cortisone, in contrast to A.C.T.H., materially interferes with healing in most gastric ulcers.

This apparent difference between the effect of cortisone and that of A.C.T.H. on gastric ulceration is perhaps less surprising than might appear at first sight. Copeman (1952) says:

> "Twenty-six different steroid substances have been isolated by Kendall from the adrenal cortex, one of which is cortisone. The administration of corticotropin to a patient stimulates the production of all twenty-six substances, and more side-effects are therefore to be expected than after cortisone alone."

Perhaps the malign effect of A.C.T.H. on gastric ulceration is in part due to the action of one or more of the other twenty-five cortical steroids; but it would be unwise to assume, on the present available evidence, that cortisone itself is entirely blameless.

It must be emphasised that any tentative conclusions to be drawn from the data presented here apply only to *gastric* ulcers. Many workers believe that gastric ulcer and duodenal ulcer are different diseases; the evidence has recently been summarised by James and Pickering (1949). So perhaps they react differently to A.C.T.H. and cortisone. Certainly reports of activation of duodenal ulcers by A.C.T.H. are far more numerous than reports of activation of gastric ulcers. This may simply be due to the fact that duodenal ulcers are more common, but it might also be that duodenal ulcers are more likely to be adversely affected by A.C.T.H. There are some theoretical grounds for believing that this is so. If, as seems probable, both A.C.T.H. and cortisone increase pepsin and acid secretion in the stomach, this may do less harm to gastric than to duodenal ulcers. Hollander (1938) and Hunt (1950) suggest that there is a hypothetical alkaline, as well as an acid, component in the gastric juice of patients with peptic ulcer. Hunt further believes that gastric-ulcer patients have a supernormal central reactivity in the secretory mechanism of this hypothetical alkaline component. Without stretching hypothesis too far, it might be conjectured that gastric-ulcer patients can therefore more easily than duodenal-ulcer patients compensate, to some extent, drug-induced increases in the acidity and peptic activity of their gastric juices.

CONCLUSION

On the evidence presented here, and in the light of previously published work, it seems reasonable to suggest that patients with active gastric ulcers, or with a past history of gastric ulcer, should not be given A.C.T.H. The administration of cortisone to such patients may be justifiable if it is strongly indicated for some concomitant disease, provided that the risk of possible ulcer activation is borne in mind. The appearance or worsening of gastric symptoms would be an imperative signal to discontinue the drug, or at least to reduce the dosage.

SUMMARY

The alleged activation of peptic ulcers by A.C.T.H. and by cortisone has been recorded. This effect has been attributed to the fact that these drugs increase the acidity and peptic activity of gastric juice.

Three hospital patients with active uncomplicated gastric ulcers were given A.C.T.H., eight were given cortisone, and seven were used as controls. No other significant treatment was given to any of the patients.

All three A.C.T.H.-treated patients failed to improve radiologically while on this treatment, and one of them became symptomatically worse. In contrast, six of the eight cortisone-treated patients progressively improved radiologically, and their ulcers healed; none of them was made worse. Six of the seven controls progressively improved and their ulcers healed radiologically. In the cortisone-treated and controls the rates of healing in the successful cases did not differ much.

It is suggested that this apparent difference between the effect of A.C.T.H. and that of cortisone on active gastric ulceration may be due to the fact that A.C.T.H. stimulates the secretion of adrenal cortical steroids other than cortisone.

It is inadvisable to give A.C.T.H. to patients with active or healed gastric ulcers, but it may be justifiable to administer cortisone, provided that a careful watch is kept for signs of ulcer activation. This conclusion applies only to gastric ulceration, and it would be unwise to assume that it is equally true for duodenal ulceration.

I am grateful to my colleagues, Dr. P. R. C. Evans and Mr. R. S. Ninian, for allowing me to treat some patients under their care, and to Dr. J. N. Hunt for his helpful advice in the preparation of this paper.

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"... Even as threatening an incident as hospitalization and surgery is merely another feeling-experience. It is the combined responsibility of parents, physicians, and hospital personnel to make it a constructive experience or at least to keep its emotional damage to a minimum. . . . The parent should explain honestly and simply what is going to happen and why. The child's questions should be answered patiently and reassuringly. It is important that the parents avoid communicating to the child any apprehension that they may have. On the other hand, the child's fear should be accepted as normal and be neither denied nor ridiculed. In other words, the child should be allowed to be frightened but should be able to look to the adults and find them adequate and unafraid."—KATHERINE JACKSON, RUTH WINDLEY, OTTO FAUST, ETHEL CERMAK, *J. Amer. med. Ass.* Aug. 23, 1952, p. 1536.

C-REACTIVE PROTEIN IN RHEUMATIC FEVER

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IN many cases the activity of rheumatic fever can be readily established on purely clinical grounds; in others, however, the situation is less clear, and assistance is sought from laboratory findings, particularly the erythrocyte-sedimentation rate (E.S.R.). Among such findings the presence of C-reactive protein in the blood has been said to provide "probably the most sensitive test for the presence of rheumatic activity that we now possess" (Anderson and McCarty 1950).

C-reactive protein is an abnormal constituent of the blood and other body-fluids, and can be detected during the acute stages of many infective and non-infective conditions. It forms a precipitate with the C, or somatic, polysaccharide of the pneumococcus, a reaction first observed by Tillett and Francis (1930). In investigating the value of determination of C-reactive protein in rheumatic fever Anderson and McCarty (1950) used as their test reagent a specific antiserum prepared in rabbits by immunisation with purified human C-reactive protein. Wood and McCarty (1951) compared the sensitivity of such an antiserum with that of C polysaccharide in detecting the C-reactive protein, and concluded that the antiserum was more efficient and was the reagent of choice in assessing rheumatic activity.

As it is difficult to obtain enough material containing C-reactive protein in sufficient concentration to produce an antiserum, the present investigation was planned to explore the value of the less sensitive C-polysaccharide test in rheumatic fever. Single or multiple determinations of C-reactive protein were made in 15 cases. The main objects were to correlate fluctuations in the concentration of C-reactive protein with changes in the clinical condition and E.S.R., and to investigate the relation of such fluctuations to treatment with salicylate.

METHODS

The technique used in testing serum for C-reactive protein (hereafter called C protein) has been described by Hill (1951). Briefly, it involves a ring test in which a 1 in 10,000 dilution of C polysaccharide, prepared by the method of Goebel et al. (1943), is layered over undiluted serum, cleared when necessary by Seitz filtration. To enable results to be recorded in a roughly quantitative way an arbitrary grading of reactions from +4 downwards is used.

Experience in applying this test to rheumatoid arthritis has shown that precipitation due to C-polysaccharide antibody can sometimes lead to confusion; such reactions can be differentiated from those produced by C protein by repeating the test with citrated serum; there is no precipitation in the absence of calcium ion when C protein is the reactive agent, but there is precipitation when C-polysaccharide antibody is responsible (Abernethy and Avery 1941).

The E.S.R. was measured in Westergren tubes and read at the end of 1 hour.

RESULTS

The accompanying table summarises the results of the initial tests for C protein in 13 cases of rheumatic fever. All 6 of the acute febrile cases had a very strong (+4) reaction. In the subacute cases the reactions were +2, +3, and +4. C protein could not be detected in serum from any of the 4 convalescent patients. The relation of C protein to rheumatic activity illustrated by these initial tests was studied in more detail in several cases, the patient's serum being retested at intervals throughout the illness.

REPRESENTATIVE CASES

Case 1.—A woman, aged 45, was admitted eight days after the onset of acute rheumatic fever. She had acute febrile polyarthritis and gave a history of a previous attack of rheumatic fever at the age of 25. She was treated with salicylate and became afebrile after two days. Fig. 1 shows that C protein, initially present in high concentration, disappeared between the third and fifth days after clinical recovery. Convalescence was uneventful and C protein remained absent. The E.S.R. fell to normal rather more slowly.

Case 2.—A man, aged 25, was admitted with acute febrile polyarthritis on the fourth day of his illness. He had no history of a previous attack of rheumatic fever. C protein was present in high concentration in the initial specimen of serum. Treatment with salicylate was started on the day after admission but was interrupted after six days. Fig. 2 shows that a clinical relapse followed the withdrawal of salicylate, and that the fall in C-protein titre which had already started was quickly reversed, a new peak being reached three days after the return of symptoms. Fever and joint pain were again controlled when treatment was started again, and the fall in C-protein titre was resumed, the tests finally becoming negative. A second interruption of treatment was again followed by a relapse, mild on this occasion, and by a return of C protein. Changes in E.S.R. followed a similar trend but tended to lag behind those in C-protein concentration.

RESULTS OF TESTS FOR C PROTEIN IN 13 CASES OF RHEUMATIC FEVER

Clinical condition	No. of cases	C protein	
		Present	Absent
Acute febrile	6	6	0
Subacute—			
Occasional mild fever	1	1	0
Afebrile	2	2	0
Convalescent	4	0	4
Total	13	9	4

Case 3.—A boy, aged 13, had an attack of tonsillitis six weeks before admission. Flitting joint pains started two or three weeks later but seem to have been only moderately severe. The boy had no history of a previous attack of rheumatic fever. On admission he was afebrile and his only complaint was of slight pain and stiffness in the hands and elbows. C protein was not detected in serum taken on the

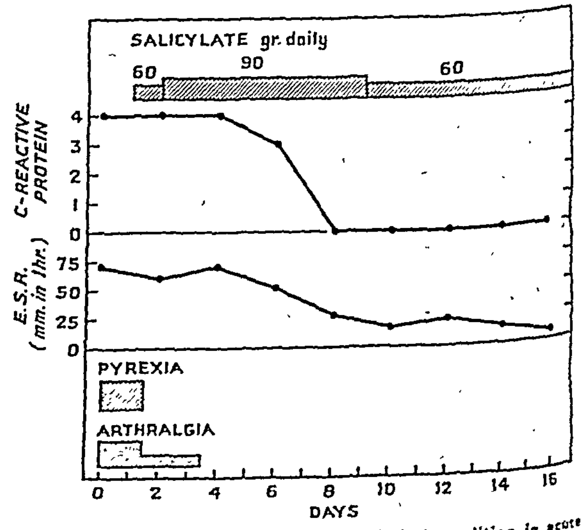

Fig. 1—Changes in C protein, E.S.R., and clinical condition in acute rheumatic fever in which recovery was prompt and uneventful (case 1).

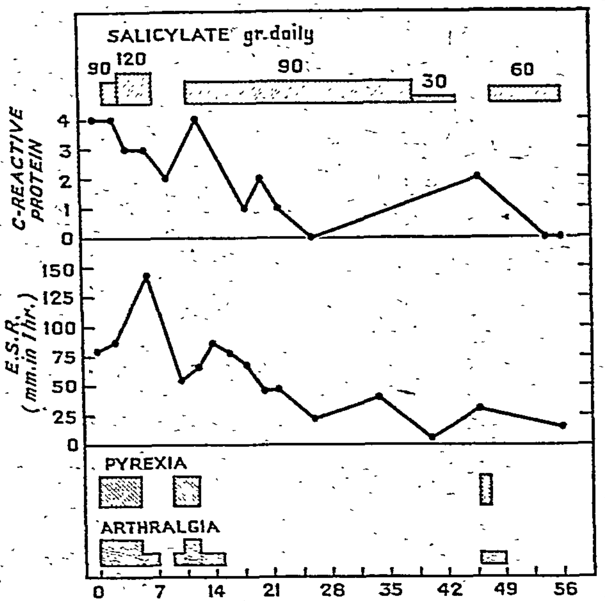

Fig. 2—Changes in C protein, E.S.R., and clinical condition in acute rheumatic fever in which withdrawal of salicylate was followed on two occasions by clinical relapse (case 2).

first day in hospital, though the E.S.R. was raised (47 mm. in 1 hr.). He was given a small daily dose of salicylate for eleven days. Two days after this had been stopped there was a recurrence of joint pain with swelling. C protein was found in serum collected three days later (fig. 3). A further rise in E.S.R., presumably related to this relapse, was recorded a few days after the first appearance of C protein. Treatment with salicylate was restarted on the third day of the relapse, and C protein disappeared, but it subsequently reappeared in low concentration in a single specimen. This brief reappearance remained unexplained: there were no clinical signs of renewed rheumatic activity at the time, and salicylate was still being administered.

Case 4.—A boy, aged 14, had subacute rheumatic fever pursuing a protracted course and showing only occasional mild pyrexia, but with persistent evidence of carditis. The continuation of activity despite treatment with high doses of salicylate was further emphasised by the appearance of periodical crops of nodules. C protein remained present for many months (fig. 4) but in a concentration lower than that encountered in the more acute cases, providing evidence of its value as a sensitive index of rheumatic activity.

The results of E.S.R. and C-protein determinations were most often divergent in early convalescence. In one case, for example, the E.S.R. six weeks after clinical recovery was 73 mm. in 1 hr., though clinical evidence of residual activity was lacking and C protein was not detected. A month later the E.S.R. was 19 mm. in 1 hr., and after a further month it had fallen to 1 mm. in 1 hr. In most cases, however, the interval between the first negative test for C protein and the first normal E.S.R. did not exceed a few days.

A strongly positive test for C protein in the absence of rheumatic activity was encountered in one case only:

The patient, a man aged 41, had a typical attack of acute rheumatic fever, during which his serum gave a strong reaction for C protein. As the symptoms subsided, C protein disappeared. The E.S.R. remained rapid, however, and C protein reappeared after having remained absent for seven weeks. This reappearance could not be explained by any obvious recrudescence of rheumatic activity, and further investigation revealed a bronchial carcinoma.

In testing for C protein by the method used in this investigation it is necessary, as we have said, to consider C-polysaccharide antibody as an alternative cause of precipitation with the test solution. Weak reactions persisting after treatment of the serum with citrate, and accordingly attributed to antibody, were observed in two cases of rheumatic fever: (1) serum from one patient, collected during an acute attack, contained both C protein and antibody, the reaction being reduced in intensity but not wholly inhibited by citration; and (2) in the second case a reaction uninfluenced by citrate first appeared several weeks after the end of an acute attack. Only one case (not included in the table) gave a strong (+3) reaction of the antibody type; the patient had old-established rheumatic heart-disease, and there was no suggestion of current or recent acute rheumatic activity.

Though the number of cases in the present series is small, the incidence of strong antibody reactions was substantially lower than that we encountered in rheumatoid arthritis.

DISCUSSION

The first detailed study of C protein in rheumatic fever was made by Rothbard et al. (1948) in the course of an investigation of the immunological changes in patients with infections due to hæmolytic streptococci. Using the C-polysaccharide test they detected C protein in 97·6% of their patients in whom rheumatic fever developed.

Anderson and McCarty (1950) tested for the presence of C protein with specific antiserum in 45 cases of rheumatic fever and found that the test provided the most consistently positive laboratory finding in the presence of rheumatic activity. Though changes in the amount of C protein present tended roughly to parallel changes in the E.S.R., the E.S.R. often remained raised during the early recovery period after C protein had disappeared. The total leucocyte-count was not an accurate guide.

In the present series a similar rough parallelism was found between C-protein titres and the E.S.R., but again there was a tendency for the E.S.R. to remain above normal during early convalescence after the C protein had disappeared. The combination of a normal E.S.R. with a positive C-protein reaction, which Anderson and McCarty (1950) occasionally found, was not encountered, but the persistence of C protein for long periods in cases of smouldering rheumatic activity was exemplified by case 4. The reaction for C protein was always positive when the rheumatism was active. In the closeness of this relationship rheumatic fever differs from rheumatoid arthritis: occasional undoubtedly active cases of rheumatoid arthritis do not give a positive reaction (Hill 1951).

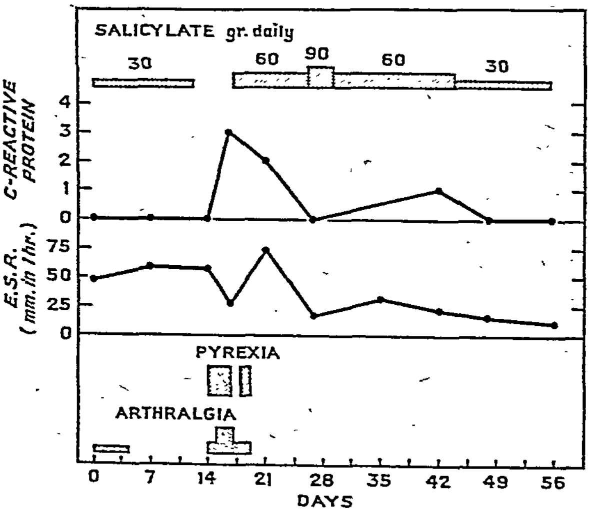

Fig. 3—Changes in C protein, E.S.R., and clinical condition in rheumatic fever, quiescent when first observed but relapsing on withdrawal of salicylate (case 3).

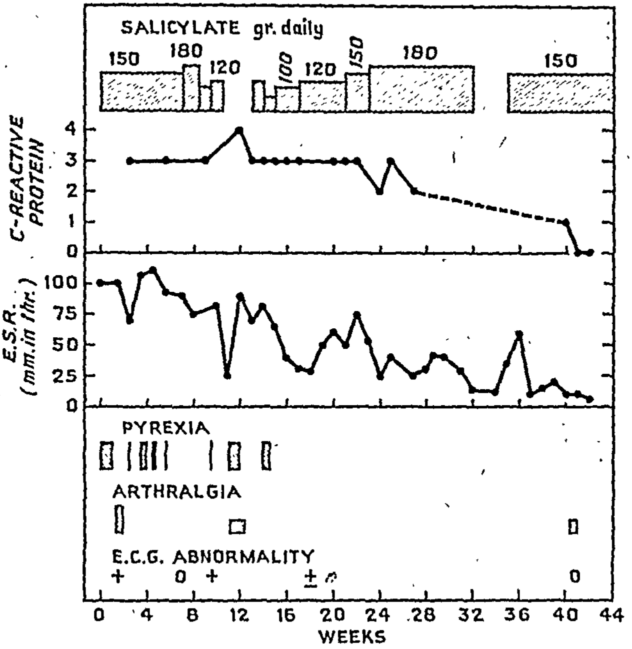

Fig. 4—Changes in C protein, E.S.R., and clinical condition in subacute rheumatic fever pursuing a protracted course with persistent evidence of carditis and showing no apparent response to salicylate (case 4).

The value of tests for C protein in rheumatic fever lies particularly in the characteristic rapidity with which this abnormal substance can appear in or disappear from the blood, and in the close correlation of such changes with variations in the patient's clinical state. This lability was clearly evident in some cases of rheumatoid arthritis, particularly where the disease was temporarily modified by a course of A.C.T.H. or of cortisone. In such cases C protein disappeared soon after the symptoms had been suppressed, and reappeared equally promptly when treatment was stopped (Hill 1951). The influence of these hormones on C-reactive protein in rheumatic fever has been reported by McEwen et al. (1950). Suppression of the clinical manifestations of rheumatic fever by salicylate seems to be regularly accompanied by the disappearance of C protein; when salicylate was clinically ineffective (case 4), C protein was, however, uninfluenced.

In using the C-polysaccharide test for detecting C protein the possible introduction of false positive results by C-polysaccharide antibody must be considered, but this difficulty is likely to be encountered less often in rheumatic fever than in rheumatoid arthritis. As a test reagent C-protein antiserum is preferable to C polysaccharide not only because it avoids this difficulty but also by virtue of its greater sensitivity. Wood and McCarty (1951) showed that antiserum can detect C protein in a concentration less than a tenth of that required to produce a visible reaction with the polysaccharide. The greater sensitivity of the antiserum test is likely to prove of particular value in helping to establish the existence of smouldering rheumatic activity when the clinical signs are equivocal. Despite these considerations the technique which uses the more readily available polysaccharide can provide useful information: the sensitivity of the test is enhanced by careful clarification of each serum before testing, and the specificity of a positive reaction can be confirmed by a control test with citrated serum.

SUMMARY

The presence of C-reactive protein in the serum of 13 cases of rheumatic fever has been studied, the C polysaccharide of the pneumococcus being used as the test reagent.

Positive reactions were obtained in all active cases, and changes in the concentration of C-reactive protein faithfully mirrored fluctuations in the activity of the disease. Though these changes tended to parallel variations in the E.S.R., the E.S.R. often remained high during early convalescence after C protein had disappeared. A clinical response to treatment with salicylate was closely followed by the disappearance of C-reactive protein.

I should like to express my thanks to Dr. J. J. R. Duthie for advice and encouragement during this investigation, and to Dr. J. A. Strong for permission to study cases under his charge. Part of the work was done during tenure of a Nuffield fellowship in rheumatic diseases.

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SHOCK IN BOTULISM TREATED WITH DEXTRAN AND BLOOD

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BOTULISM is a type of food-poisoning caused by the toxin of *Clostridium botulinum*. Under normal conditions it is rare, but it might be used in biological warfare.

The *mortality* from botulism is high, averaging 50% according to published reports, but it varies. In the U.S.A. there have been some very severe poisonings due to *Cl. botulinum* type A (Hall 1936). In France, on the other hand, about 1000 cases, mainly due to type B, were reported during the occupation, with a mortality of about 2% (Legroux et al. 1947).

The principal *symptoms* are general weakness, abdominal pain, vomiting, internal and external ophthalmoplegia, dryness of mucosæ, paralysis of the pharyngeal muscles, and, finally, respiratory and cardiac paralysis.

The *treatment* consists in the injection of the type-specific antitoxic serum: the administration of antibiotics; feeding through a *duodenal tube*; the parenteral administration of fluid, glucose, and electrolytes; and the administration of oxygen, clearing of the pharynx and bronchi, tracheotomy, and treatment with a mechanical respirator as the case indicates.

Treating a small family epidemic in the autumn of 1951, we noticed that 4 of our 6 patients were in a state of severe shock on admission. These 4 patients received dextran and blood-transfusions, apparently with a favourable result. Since shock does not seem to have been emphasised previously as a sign in this disease, we report our experience here.

THE OUTBREAK

Our 6 patients had luncheon together on Oct. 21, 1951, at noon; 5 were admitted in the afternoon or evening of Oct. 22, and 1 on the morning of Oct. 23. The poisoning was due to home-made pickled herrings, no doubt infected with *Cl. botulinum* by contact with earthy potato peel at an early stage of the preparation. The herrings ontained botulinus toxin type B. Of the 6 patients were fairly weak, 1 slightly, and 1 not at all.

ILLUSTRATIVE CASE-RECORD

Case 1.—A man, aged 43, was admitted at 4 P.M. on Oct. 22. eneral malaise had come on in the late evening of Oct. 21, welve hours after the luncheon. About 6.30 A.M. on Oct. 22 e felt ill, dizzy, and nauseated, and vomited eight times. e then had blurred vision, and later diplopia and much ryness of buccal and pharyngeal mucosa. The symptoms rew worse during the day, and shortly before admission he as feeling very ill, and dizziness and vomiting came on when e tried to get up.

On examination he was weak and pale, with a small soft ulse. On sitting up for auscultation he became still paler nd his pulse small, rapid, and almost imperceptible. This tate was relieved by lying down. Examination of his eyes y Dr. H. Skydsgaard showed loss of accommodation and iplopia due to paresis of the external ocular muscles. No ther signs of cranial nerve pareses were seen, particularly o ptosis, nasal tone, hoarseness, or dysphagia. His faucial ucosa was dry. His heart beat was regular, pulse-rate 100, eart sounds normal, and blood-pressure 85/50 mm. Hg. His ngs were normal on auscultation, and his respirations were 6 per minute. His abdomen was diffusely tender, with some uscular guarding. The reflexes of the arms were normal, and hose of the legs too brisk, if anything.

Treatment and Progress.—Shortly after admission the atient received carbon and magnesium sulphate by mouth nd botulinus antitoxin (types A and B) 50 ml. intramuscuarly. The antitoxin was repeated next morning. The patient as made to lie flat, and his pulse-rate and blood-pressure ere observed for a few hours. When the pulse became faster, he blood-pressure fell, and the patient grew cool, dextran litre was administered by intravenous drip, followed by a lood-transfusion of 500 ml. He then improved somewhat, nd at 9 P.M. his blood-pressure was 110/80 mm. Hg and pulse-ate 100. Seven times in the night the patient vomited copious atery matter and complained of an uncomfortable feeling n the abdomen. Next morning his general condition was fair, ut his blood-pressure had again dropped somewhat; so nother blood-transfusion of 500 ml. was given. During the ext few days, the condition was characterised by slight espiratory difficulty, but not actual paralysis; much dryness f the mouth and pharynx; and mydriasis, diplopia, and cular fatigue. On Oct. 24 the patient was too ill to be further xamined for diplopia. He took ample fluid but could not wallow much food, because of the dryness of the mucosa. He was subfebrile, and from Oct. 25 received prophylactic enicillin 150,000 units twice daily for five days. His temperaure reached its peak on the evening of Oct. 26. Since his erum-potassium level was low, he was given a solution of otassium sodium chloride 250 ml. by mouth on Oct. 25 nd 500 ml. on Oct. 30 and Nov. 1. On Oct. 28 he developed n itching serum exanthem, which subsided in two days. He radually improved and was discharged on Nov. 8, feeling ather tired, and with slightly reduced vision and some ryness of the throat.

Laboratory Tests.—The patient's blood was not tested for otulinus toxin. His urine contained no albumin, blood, pus, r sugar. A white-cell count showed 6800 leucocytes per .mm., with a pronounced shift to the left, suggesting intoxiation. Radiography of the chest on Oct. 24 showed no bnormality. Electrocardiograms made daily from Oct. 24 o Nov. 2 showed slight flattening of TII. on Oct. 27 and 29 nd a constantly negative or iso-electric TIII. Examination of he blood gave the following additional information:

	Oct. 23	*Oct. 24*	*Oct. 26*	*Oct. 27*	*Oct. 29*	*Nov. 1*
Serum-chloride (m.eq.)	95	97	..	..	..	..
Serum-bicarbonate (m.eq.)	28	26	..	..	..	..
Serum-sodium (mg. per 100 ml.)	305	..	332	..	..	..
erum-potassium (mg. per 100 ml.)	14	13·2	12·9	..	..	14·4
lood-urea (mg. per 100 ml.)	79	57	56	44	44	..
b (%)	94	100	101	104	102	..
ed cells (million)..	4·59	4·61	4·52	4·81	5·20	..

DISCUSSION

The diagnosis of botulism must be considered as stablished beyond doubt. The symptoms were typical, nd botulinus toxin was found in the blood of 3 out of the 4 patients in which it was sought. No attempt at neutralisation with type-specific antitoxin was made, because not enough serum was available. As mentioned above, examination of the herrings showed that the infection was of type B.

BLOOD-PRESSURES AND PULSE-RATES BEFORE AND AFTER TREATMENT WITH DEXTRAN AND BLOOD-TRANSFUSIONS

Case no.	Age (yr.)	On admission		24 hours later		Treatment during first 24 hours	
		Blood-pressure (mm. Hg)	Pulse-rate	Blood-pressure (mm. Hg)	Pulse-rate	Dextran (ml.)	Blood (ml.)
1	43	85/50	100	110/80	90	..	1000
2	11	80/50	136	110/75	120	1000	1100
3	51	110/90*	126	130/90	92	1500	500
4	36	90/70	140	105/65	92	1000	1500
5	50	100/80	80	120/85	84	..	..
6	39	110/80	80	125/85	84	..	..

* Normally a systolic blood-pressure of about 200 mm. Hg.

The principal symptoms were severe weakness, dryness of the mucosæ, and visual disturbances. Four patients were in a state of shock on admission, 3 had dysphagia, and 2 slight air-hunger on swallowing, but none developed pharyngeal or respiratory paralysis. One patient had attacks of laryngeal spasm, and another tonic convulsions in his limb muscles, with tetany position of the hands.

Although the disease was benign in the sense that pharyngeal or respiratory paralysis did not develop, 4 patients were severely affected by the initial shock. The brief incubation periods (12, 18, 16, 19, 20, and 20 hours) also indicate severe poisoning.

The patients' shock on admission was striking. They were pale, weak, and cool, with low blood-pressure and fast pulse-rate. This is shown by the accompanying table and by the case-history, which shows also that the infusions of dextran and blood produced much improvement in blood-pressure, pulse, and general condition. We have found some published reports from which it must be presumed that the patients were in a state of shock, particularly in extremis, but we have never seen this point emphasised. Treatment by venesection, on the other hand, was not uncommon. Thomas et al. (1951) report a case in which a blood-transfusion was given to a boy, aged 13, who died of botulism after a botulinus infection in a relatively small gunshot wound of the leg. We feel that shock is rather common in severe botulism, and that it is due to direct action of the toxin on the organs regulating the circulation (cf. diphtheria). From our experience we recommend blood-transfusion and feel that the symptomatic treatment should be on the lines prevailing at present in other neurotoxic poisonings, such as barbituric-acid poisoning.

All our patients had slightly reduced serum-potassium levels, the lowest value being 11·9 mg. per 100 ml. From the second to the seventh day after admission the average serum-potassium level was 13·5 mg. per 100 ml., although 5 patients received potassium by mouth. The potassium balance does not seem to have been studied in this disease, and the cause of the reduction is unknown. It can hardly be due to loss of potassium, because it occurred also in a patient who did not vomit. Nor does a decreased intake of potassium seem to be the explanation.

Electrocardiograms were made daily from Oct. 23 to Nov. 2, and transitory changes were observed in 5 cases. These changes consisted almost exclusively in flattening to the extent of negativity of TII between the seventh and twelfth days.

A few workers—e.g., Joly (1944), Mouquin et al. (1944), and Dyggve (1946)—have previously reported electrocardiographic changes in single cases. These changes were extrasystoles, depression of the S-T segment, negative or iso-electric T waves, and splitting of